Abstracts of the 12th Edition of the Biopharmacy - Pharmacokinetics & Industrial Pharmacy Symposium

8 November 2019
Cluj-Napoca

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The authors have the responsability for the content of these paper abstracts

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Foreword

It is our pleasure to introduce the abstract book of the The 12th Edition of the Biopharmacy - Pharmacokinetics & Industrial Pharmacy Symposium, Cluj-Napoca 8 November 2019.

In 1982, Professor Sorin E. Leucuța organized the First Edition of the Symposium of Biopharmacy and Pharmacokinetics, thus promoting this new research field in Romania. Further, he worked his entire life with professionalism and dedication to develop this domain, by organizing and coordinating the next 10 editions of the mentioned scientific event and by publishing a large number of scientific articles and books.

Currently, his successors continue Professor Leucuța's work by organizing The 12th Edition of the Symposium, covering broader areas than the previous editions. This edition will comprise presentations highlighting nowadays issues in both Biopharmacy-Pharmacokinetics and Pharmaceutical Industry, being a commemorative edition dedicated to its mentor.

We wish you a good benefit from this meeting and from the abstracts published here.

The editors

In Memoriam

A Life Dedicated to Science and the Profession

Academic professors and researchers are people dedicated to pharmaceutical sciences and the Faculty of Pharmacy of Cluj ...

It is not only thought-provoking, but also significant and a duty to remember one of the professors of this Faculty, who left his mark by his love for the profession, for science, for the young researchers and students.

Professor Doctor Sorin Leucuța was indeed one of those persons one rarely encounters, a master of pharmaceutical sciences, great academic, a humanist and path opener for Biopharmacy, Pharmacokinetics and Clinical Pharmacy.

For about four decades almost every event of the Faculty of Pharmacy, be it academic, scientific or social, is linked to Professor Sorin Leucuța's presence and implication.

The generations of students and PhD candidates he guided knew him as a transmitter of knowledge and science, wise, authoritative, fair, reliable colleague, objective, honest and stable in his decisions. Beyond the art and dedication in offering knowledge, there was a deep devotion for the profession of pharmacist.

Professor Sorin Leucuța reached to the students' hearts not only through his words, but also his attitude, voice, eyes, all totally convincing.

He had a rich scientific research activity in the field of Pharmaceutical Technology, always up to date and applying modern research methods in accordance with the most recent advances in the pharmaceutical industry.

He initiated and promoted the introduction of Biopharmacy, Pharmacokinetics and Clinical Pharmacy into the curriculum of the Faculty of Pharmacy. In the research activity he tackled current issues in collaboration with his doctoral students (32), being highly appreciated and acknowledged by the scientific community. He founded and led the Center of Biopharmaceutical and Pharmacokinetic research and the Bioequivalence Laboratory of the University.

He conducted and participated in numerous research projects and grantss.

As President of SSFR (Romanian Society of Pharmaceutical Sciences) during 2002-2010, he coordinated and guided pharmaceutical scientific research and organized the national congresses of SSFR.

The curtain has fallen, there is no way to know what is beyond, but what remained is a model of a life devoted to the pharmaceutical profession and Romanian community.

He is so far above that our eyes cannot contemplate his face, but we can open our minds and enjoy the wisdom he gave us.

The passage of time did not erase Professor Sorin Leucuța from our memory, on the contrary, he is more present than ever in the mind and hearts of generations of pharmacists.

Prof. Dr. Marius Bojiță
Rector of the University of Medicine and Pharmacy Cluj-Napoca (2000-2008)

Sorin, around his biography and beyond

(I. A Dream. II. How we met. III. First steps into scientific research. IV. The Scientist.)

I. A dream. An annotation of 2 September 2016: "This beautiful morning on the threshold of autumn I suddenly woke up from a dream at 5.40. I had dreamt I was with my friend and colleague Sorin Leucuța, who had passed away, unexpectedly, on the 24th of June this year. Not three months have passed and I don't much care about dreams, either I don't dream at all, or I forget everything I dream.

In the dream, Sorin and I were still young. We lived on the first floor of a building that seemed to be a hostel. At one point we were in the large courtyard of that building.

A woman passed us, heading toward the entrance, and I took out of my pocket a handful of gold and silver chains, like twisted wires, 30-40 cm long, like a diadem. I gave them to Sorin, who took them.

In that courtyard, at about a hundred feet behind me, there was a small white building, in which a contest examination was about to start.

We were both sitting the exam, as pharmacists (the term consultant pharmacist came later). We were not competing for the same position, but in my dream it was a contest.

All of a sudden I decided to withdraw from the competition, I hadn't studied anything. So I told him:

'Sorin, I changed my mind, I am not going.'

'Are you sure about this?' he asked.

'Absolutely, Sorin, good luck!'

And we parted. He walked toward the small white building and I woke up because my wife was moving, getting up to go to the bathroom."

I opened my eyes. My lady had gone out, and a thought crossed my mind, that I wasn't ready for the exam to which Sorin had gone on 24 June 2016.

II. How we met. Since 1956 I had worked as a practicing pharmacist. On the 1st of September I transferred from Deva to the Faculty of Pharmacy of Cluj. Following a contest I became assistant lecturer at the Department of Pharmaceutical Technique headed by Professor Victor Ciocănelea.

On the morning of my first day of work in the assistants' laboratory I found Sorin there, alone. We did not know each other, we had not met before. He had entered university in 1956, about 6 weeks after my graduation.

I introduced myself and he said:

'Courses start on the 1st of October. The Professor and the staff will come later. I am a doctoral student.

Nice boy, agile, spontaneous, very intelligent. We got on friendly terms, talked a little, he showed me the laboratories.

The next day Sorin suggested that we go together to Pasteur Institute. In front of the Neurology Hospital we met a friend of his, also young, blond hair. Sorin introduced me:

'My colleague Honorius Popescu.'

'Oh, it's you?' Dr. Octavian Bârzu was surprised. He was the successor of Ion Manta, my great professor of Biochemistry.

'Why are you surprised?' I asked him.

'Simiti has told me you are the best of the first 20 graduate years.

My family had remained in the rented apartment in Orăştie. Professor Ioan Simiti, the Dean, had managed to find me a room in the Victor Babeş students hostel. This is where Sorin also lived, we shared the 5-bed dormitory for assistants for 2 years.

Destiny had tied me to Sorin very closely, we breathed the same air in the hostel, at the canteen and between 8-13, 14-19 şi 20-22 in the laboratory. Indeed, we worked 12 hours a day in the 6 days of the week.

In the evening we were working on the dissertations. In those times there was no copying, no plagiarism.

We had very few exceptions from the evening routine, but I remember one, suggested by Sorin. We were four, the other two were Polinicencu and Bojiţă. Sorin said:

'Let's go downtown. Near Mathew Corvin's statue there was a bar.

'Let's go in here' Sorin decided.

We sat on the high chairs, asked for a brandy, and we were just warming up when the Dean, Professor Simiti, came in:

'What are you doing here?'

'We were waiting for you' Sorin laughed and ordered a brandy for the Dean.

"I was looking for you in the lab' the Dean said with a smile.

On other evenings we went to a series of lectures on the History of Art. They were delivered by a reader of the Fine Arts School, his name was Deák, if I remember rightly.

After one year I was transferred to the department of Pharmacognosy.

After two years the Rector stopped approving lodging for academic staff in hostels. It was the autumn of

1970 when we split. For another 2 years I slept on a folding bed in the laboratory.

III. The first steps into scientific research. At least half of the work of an academic is devoted to research. How to become a researcher? This is a tough question!

During our working hours in the laboratory, late in the evenings. We talked about this. In November our colleague Polinicencu joined us. One day Sorin confessed:

'I really don't know what to do regarding my doctoral subject.'

'What is your subject again?'

'Contributions to the study of drug substances interaction with macromolecular excipients … etc.

'Want some advice? Ask for a documentation visit to Bucharest from the Rectorate, stay for a month, go to ICSMCF and do as I did.

When he returned to Cluj he laughed while telling me:

'I did as you told me. With a bunch of roses in one hand and a box of chocolates in the other I entered the Library through the door used only by Mrs. Ionescu, the librarian. When she took the gifts she asked me laughing: Mr. Popescu taught you?'

This is what I had done in May 1968.

The lady was the widow of the great Professor C.N. Ionescu of Pharmaceutical Chemistry (1905-1956). I had asked her to let me study in the library storeroom in order to have direct access to the shelves and the books and journals, from which I collected a wealth of information.

Sorin returned to Cluj. He had brought the documentation. Following that effort, he finished his dissertation, which he maintained in 1970, becoming a Ph.D. In 1975 he published the book "Introduction to Biopharmacy". The reference list at the end of the book includes 524 items and may serve as example for any doctoral student.

When they read the titles of my doctoral students dissertations, a few members of the faculty, appointed by political criteria, objected to the wording "Research into…". They were convinced, as they are nowadays, that a doctoral thesis can be copied!

Nevertheless, the doctorate represents an introduction to scientific research, the dissertation being the result of an effort that qualifies a specialist for scientific research.

Around 1977, a position of associate professor opened at the Department of Pharmaceutical Technique in Bucharest. Sorin asked me:

'Should I go for it? I know I don't stand a chance, as they want Mrs. Lucreţia Istrătescu-Guţi.'

'Go, Sorin, go and show them, until you don't show what you are capable of, nobody will know.'

He went, but the people in Bucharest did not care very much.

Shortly Sorin was promoted associate professor in Cluj, he was the first of us to gain this position.

At the end of December 1989 the young Romanians turned over communism. Associate professor Sorin Leucuța became Dean of the Faculty of Pharmacy of Cluj in the first days of 1990. He was spontaneously elected, not appointed at any political orders.

IV. The scientist. In the eulogy for Sorin I wrote he was a scientist.

Those from Bucharest asked me to account for it.

His distinguished wife, Mrs. Mariana Leucuța, asked me to confirm it was true and I assured her it was, though I think she already knew.

Once someone said:

"A scientist is not someone who knows, nor someone who seeks, but the one who finds."

Sorin, the scientist, seeked, knew and found.

- For himself, he found the path of research and pharmaceutical sciences.

- For the specialists in our country he found Biopharmacy, Pharmacokinetics, Pharmaceutical Nanotechnology etc.

It is surprising, but not too much, that the pharmacists in Romania had not published anything in these domains.

As a proof, in 1977, when he was lecturer, the scientist Sorin Leucuța went to Bucharest regularly, invited to teach the researchers of ICSMCF (Institute of Drug Control and Pharmaceutical Research).

I cannot forget that one or two of the politically appointed faculty staff tried to study Sorin's books and then deliver lectures in Sibiu, Bistrița, Alba Iulia.

The numerous books of my scientist together with the 380 journal articles published in Romanian and international journals reinforce all the above.

To conclude, I would like to ask Mrs. Mariana Leucuța to accept my admiration and thanks for keeping Sorin's place, supporting the friendship and meetings of our old "gang": Leucuța, Polinicencu, Rotaru, Popescu.

Prof. Dr. Honorius Popescu

Half a century in the company of a great professor and scientist Pharmacist Dr. Sorin E. Leucuţa

Speaking about the emblematic personalities of Romanian pharmacy, Professor Sorin Emilian Leucuța stated: "*Remembering the names and facts, we honor their memory and bring our homage of esteem, consideration and gratitude*".

Now it is his turn to be remembered and that we pay our homage of esteem, consideration and gratitude.

An insight into Professor Leucuța's statement shows us that it comes from a man of value who did not hesitate to highlight the others' merits for fear that he might remain in their shadow. His achievements guaranteed such attitude.

His whole life was under the auspices of Fortuna the goddess, who helped him overcome all obstacles and conquer.

The "Merit Diploma" at the graduation of a high school that gave 21 famous academy members, provides the measure of his intellectual abilities.

The fact that he was denied entrance to the Faculty of Medicine did not stop him. He found the way to a related field – Pharmacy, in which Fortune paved the path to a health profession and science, in which he obtained national and international recognition.

Among the first credits he received at a national level, we mention the one from the reputed Professor of Pharmaceutical Technique, V. Ciocănelea, who, speaking at a scientific event, called him "**the prodigious child of Romanian pharmaceutical research**".

Professor Ciocănelea's assertion was proved by the achievements of the one we honor today. If we mention only the introduction and the development of biopharmaceutical and pharmacokinetic research in Romania, a domain in which he had 37 personal initiatives of national importance, we can realize his outstanding contribution to the development of new pharmaceutical fields.

The establishment in Cluj of the Bioequivalence Laboratory coordinated by Professor Leucuța was a big progress for Romanian pharmaceutical science. Complex studies were performed here, with top quality equipment and highly specialized staff. The bioequivalence of Romanian and foreign generic drugs was performed under the supervision of the Professor, an activity of utmost importance for the drug companies.

Scientific research in Biopharmacy based on professor Leucuța's studies and publications progressed at a level that required the introduction of this domain into the academic curriculum. He may be called the father of this discipline in Romania, along with other two: Industrial pharmaceutical technology and Clinical pharmacy.

The results of his scientific work gained international acknowledgement in Europe, Asia and the USA. He was included as member of numerous international pharmaceutical scientific societies. He was Board member of international congresses, holding highly responsible positions. He was also member of editorial boards of Romanian and international journals.

He had very clear thinking, well structured and organized, which allowed him to have an insight into the biological mechanisms that remained inaccessible for many. This facilitated his path toward clinical pharmacy.

I remember our conversations at the end of the day, when we were young, about some biological mechanisms, both of us with our medical or pharmaceutical viewpoint respectively. Thus the idea of bioadhesive medicines for the humid environment of the oral cavity developed, they were unknown till then. This was also the start for the bioadhesive ointment as substitute of the blood clot in the dental alveoli after tooth extraction on the antitumoral radiated bone. An invention that helped us solve difficult cases in those years.

Looking at Professor Leucuța's prodigious scientific activity one might have the impression that his main work at the University of Medicine and Pharmacy was research. Totally wrong! He was first of all a teacher, a position he honored and which included him in the gallery of famous professors of our school. His achievements in this field were also outstanding. He modernized pharmaceutical education by updating the curriculum, first in Cluj-Napoca, then in other faculties in the country. He introduced 14 new disciplines, at the level with the education in Europe. He established many exchanges with European universities.

His teaching abilities were recognized internationally, being invited to lecture in many universities in France.

We have mentioned his well organized thinking – for 19 years he was member of the Senate of the University of Medicine and Pharmacy of Cluj-Napoca.

His activity in the academic governing bodies was guided by high ethical principles, sometimes at the cost of being alone to defend his opinions. He introduced rigor not only in teaching and research, but also in academic management and the meetings of the scientific societies.

At the Senate meetings he spoke only to present valuable ideas, he had great respect for this academic forum. He was also a great enemy of decisions based on personal interests that were not serving the whole community.

In recognition of his high moral status, the Senate entrusted him with editing the University **Code of Professional Ethics,** which was adopted as written by the one who we honour today.

His moral qualities were manifest also in his personal and social relationships, we had a friendship that lasted half a century, until fate took him from among us.

Prof. Dr. Alexandru Rotaru

Professor Dr. Sorin E. Leucuța

Landmarks of Life and Professional Career

Professor Dr. Sorin Emilian Leucuța was born on the 7th of December 1939 in Oradea.

Education

Graduated from the George Coșbuc Național College (former 10-Year High School 1) of Năsăud.

In 1956 he gained free admission, based on his high school merit grades and Diploma, to the Faculty of Pharmacy of the Institute of Medicine and Pharmacy of Cluj-Napoca.

Professional activity as pharmacist

In 1961, after faculty graduation, he was allocated the position of probation pharmacist in the village of Cefa, Bihor county, then at the Bihor County Pharmaceutical Distribution Office in Oradea.

In 1965 he passed the assessment test for urban pharmacists, coming 7th in the national contest, and chose a position at the Pharmacy Store no. 1 in Cluj-Napoca.

In 1967 he enrolled for Doctoral Studies, under the guidance of Professor V. Ciocănelea, the head of the Department of Pharmaceutical Technique of the Faculty of Pharmacy, Cluj Inst. of Medicine and Pharmacy.

Teaching and research activity

In 1969 he was appointed temporary assistant lecturer at the Department of Pharmaceutical Technique.

In 1970 he defended his Doctoral Thesis "Contributions to the study of physico-chemical interactions between drug substances and macromolecular and tensoactive excipients in aquaeous solutions and suspensions".

In 1970 he published his first scientific article in the journal Clujul Medical: S. E. Leucuța, M. Kory. Modification of the absorption speed of drug substances in the presence of tensoactive and macromolecular excipients.

In 1972 he gained permanent position as assistant lecturer at the Department of Pharmaceutical Technique.

Between 1972-1973 he presented the first scientific communications at the national level regarding the pharmaceutical principles and the factors influencing the bioavailability of drugs, thus opening a new research direction in medical sciences.

The academic year 1973-1974 marked the introduction of the optional course of Biophamacy and Pharmacokinetics in the 4th study year of the Faculty of Pharmacy of Cluj-Napoca (subsequently also in other faculties of pharmacy in the country), thus becoming the founder of this field in Romania (since 1990 an integrant part of the core curriculum).

In 1975 he published the first book "Introduction to Biopharmacy" – Dacia Publisher.

In 1975 he became lecturer and in 1980 promoted to the position of associate professor.

In the beginning of the 1980s he became acquainted with the concept of clinical pharmacy and in 1984 he co-authored, with other faculty members, the monograph "Elements of clinical pharmacy".

In 1982 he organized the first edition of the National Symposium of Biopharmacy-Pharmacokinetics, which continued to its tenth edition over the years.

In 1987 he published the monograph "Pharmaceutical systems of controlled release and targeted transportation", thus marking the start of new research lines.

In 1989 he published "Pharmacokinetics in drug therapy", dedicated specially for practitioner physicians.

In 1990 he gained the position of professor, and thus the status of doctoral supervisor.

Academic career

During 1990-1992 he was Dean of the Faculty of Pharmacy, playing a major role in the modernization of the curriculum. In 1990 he introduced the studies of Industrial Pharmaceutical Technology and Clinical Pharmacy.

Starting with 1990 till retirement he was member of the University Senate and Council of the Faculty of Pharmacy.

In 1992 he was head of department, which he renamed in 1991 as Pharmaceutical Technology and Biopharmacy.

In 1992 he became a member of the Romanian Academy of Medical Sciences, being secretary of the Cluj branch between 1992-2009.

Impact and recognition of scientific work

During 1992-2000 he had an intense teaching and research activity at international level, he participated in research programs and was invited as visiting professor to pharmaceutical faculties in Paris, Grenoble, Brussels, Strasbourg, Rouen.

He founded the scientific research center "Biopharmaceutical and pharmacokinetic drug research" officially established in 2002.

He organized the Bioequivalence Laboratory of the Cluj U.M.Ph, authorized by the Ministry of Health in 2002; he was director till he retired. The laboratory had over 50 research contracts, whose objective was the assessment of bioequivalence of Romanian generic drugs.

Between 1991-2003 he was President of the Cluj Branch of the Romanian Society of Pharmaceutical Sciences (SSFR).

During the period 1999-2011 he was President of SSFR (three mandates) and succeeded in 2002 to make SSFR a member of the European Federation for Pharmaceutical Sciences. He also played a major role in promoting the journal Farmacia to be indexed in Web of Science and Journal Citation Reports starting with 2009.

He was member of numerous national and international scientific organizations and editorial boards of prestigious journals. He participated in the organization of many national scientific events.

He conducted 5 research grants attributed by international and national competition. He obtained 35 patents as author and co-author. He supervised and finalized 31 PhD dissertations.

He published 27 books as unique author or first author, and 15 as co-author. He published 405 scientific articles, 138 of them indexed in Web of Science.

Owing to these remarkable results and his passion and devotion for the pharmaceutical profession, as well as his outstanding contribution to the development of pharmaceutical education, he was awarded many a prize and diplomas. We select only a few: Victor Babeş Prize of the Romanian Academy (1990), Opera Omnia Prize from CNCSIS (2002), Iuliu Haţieganu Prize of the Cluj U.M.Ph. (2004), Professor Emeritus Diploma of the U.M.Ph. Cluj-Napoca (2015) and the Order and Medal "Educational Merit, Officer Grade" by a Decree of the Romanian President (2004).

Retirement

He retired in 2009, at the end of the 2008-2009 academic year.

During 2009-2015 he was consulting professor and continued to write and publish books (5 books on the concept of subcellular bioavailability) and journal articles (n=56), as well as supervise PhD dissertations (there were 7 doctoral dissertations defended in this period of time).

Professor Dr. Sorin E. Leucuţa passed away on the 24th of June 2016.

Prof. Dr. Marcela Achim

Conferences

C1. The bioequivalence study design of highly variable drugs

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Introduction. The scope of bioequivalence studies is to demonstrate that the bioavailability of developed generics is comparable with the one of the original drug from the market after administration in the same molar dose, to ensure comparable *in vivo* performance in respect to safety and efficacy. Establishing the adequate design of the bioequivalence studies ensures that the formulation effect can be distinguished from other effects. In this presentation, through "design" are understood key aspects of the bioequivalence studies: crossover/parallel/ replicate, single dose/multiple dose, number of subjects, sampling time points, washout period. All these can be challenging to be established for highly variable drugs. "Highly variable drugs" are defined as drugs that present the within-subject variability (S_{WR}) equals or exceeds 30% of the maximum concentration (C_{max}) and/or the area under the concentration versus time curve (AUC). Mesalamine (mesalazine) that is available in different formulations is considered a highly variable drug as its variability is strongly influenced by the mechanism of action and pH dependent release of the molecule from the formulation.

Material and methods. There were conducted multiple bioequivalence studies on healthy Caucasian volunteers in fasting and fed conditions to evaluate the bioavailability of different delayed release formulations of Mesalamine 1.2 g and Mesalamine 800 mg generics and reference listed drugs.

Results. The data obtained from the bioequivalence studies were used to establish the most relevant design to minimize the variability effect of the investigated medicinal products: locally acting gastrointestinal drugs, minimum number of the subjects to be included and the best sampling schedule for the studies.

Conclusions. This most relevant design was used for the studies conducted and information obtained were relevant to conclude over the bioavailability/ bioequivalence of the investigated products. In the same time, the design selected ensured the well-being and safety of the healthy volunteers' participants at the studies.

Keywords: pharmacokinetics, bioequivalence, Mesalamine, delayed release tablets

Acknowledgments. The studies have been performed at the Clinical Pharmacology and Pharmacokinetics Terapia S.A and the Sponsor of the studies agreed to disclose the study results for publication.

C2. Clinical relevance of pharmacokinetic-based drug-drug interactions

Corina Briciu

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Introduction. The term drug-drug interaction (DDI) is used when the effects of one drug (victim) are altered by the co-administration of another (perpetrator). Several studies have shown that the probability of DDIs increases with the number of medications being taken and due to the fact that polypharmacy is common in elderly patients, this special population is particularly prone to drug interactions. DDIs are generally classified in terms of proposed mechanism as pharmacodynamic or pharmacokinetic. Pharmacokinetic DDIs can involve changes in absorption, distribution, metabolism and elimination. Examples of mechanisms responsible for pharmacokinetic-related drug interactions include the following: reduction of absorption by concurrent drugs, displacement from protein-binding sites, inhibition or induction of drug-metabolizing enzymes or transporters and competition for active transport during elimination. The aim of this selective literature review was to

connect theory to practice by discussing several pharmacokinetic drug interactions and their real clinical impact.

Material and methods. Selected examples of clinically significant pharmacokinetic DDIs were chosen from the scientific literature and information such as drug interaction mechanisms, clinical consequences and management were documented.

Results. The clinical relevance of an interaction can depend on several factors like the therapeutic index of the victim drug, the potency and concentration of the inhibitor/inducer, the baseline bioavailability of the victim drug, whether the latter is a prodrug or an active drug and pharmacogenomics. Pharmacokinetic DDIs may lead to drug therapy problems such as adverse effects or reduced therapeutic effects of some drugs. Nonetheless, not all interactions are harmful. There are some pharmacokinetic drug interactions that can contribute to positive clinical outcomes and therefore, can be viewed as beneficial. A number of strategies for screening and minimizing exposure to DDIs can be considered in order to enhance medication effectiveness and reduce safety concerns.

Conclusions. A better understanding of the mechanisms and consequences of pharmacokinetic DDIs is essential in order to make informed and rational decisions on drug selection, and to ensure an effective and safe disease management.

Keywords: pharmacokinetic drug-drug interactions, drug interaction mechanism, clinical relevance

C3. Using nanosuspension in traditional and alternative drug formulation

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Introduction. Nanoparticle engineering has been developed and reported for pharmaceutical applications. In this approach, poorly water-soluble compounds are formulated as nanometer-sized (100-1000 nm) drug particles. Nanoparticulate technology offers increased bioavailability, improved absorption, and the potential for drug targeting. During our work the prepared nanosized systems (as pre-dispersions) were applied in drug formulation (to reach local or systemic effect) to get effective therapies in different diseases. Therefore we should find cost-effective production by new technological processes containing the most important technological and material parameters.

Materials and methods. Meloxicam (MX) (Egis Plc., Budapest, Hungary) was used as a model active ingredient for preparation of nanosuspension using different kind of polymer as stabilizer. Pre-suspension were produced by wet-dispersion technologies (planetary ball milling, laser ablation, high pressure homogenization and high intensity ultrasound). The particle size distribution and morphology were determined with laser diffraction (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd.) and scanning electron microscopy (Hitachi S4700, Hitachi Scientific Ltd.). The surface adhesion was analyzed using contact angle system (OCA, Dataphysics Inc). Physico-chemical properties analyzed with differential scanning calorimetry (Mettler Inc.) and X-ray powder diffraction (Bruker D8 Advance). In vitro drug release was carried out by modified paddle method in different media. Aerodynamic properties have been tested in vitro using Andersen Cascade Impactor (Copley Scientific Ltd.)

Results and discussion. The presentation will introduce our applied material and technological parameters during the preformulation of nanosuspension containing meloxicam. Per os, intranasal and pulmonar formulation aspects of prepared systems will be also summarized focusing on structural, micrometric and in vitro investigations.

Keywords: particle engineering, nanosuspension, formulation, pulmonary administration, intranasal delivery

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C4. The functionality of lipid-based excipients

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Lipid-based excipients (LBE) are attractive compounds for drug delivery, because they are naturally occurring materials with "Generally Recognized as Safe" (GRAS) status. Their potential application covers a broad range from nanoparticles to multiparticulate systems and tablets with controlled release properties for oral, pulmonary, dermal, transdermal, and injectable formulations. The application of LBEs, however, is not always straighforward. The main challenge is the propensity of LBEs to time-dependent solid state transformations at any hierarchical level of structure which leads to instability of the final dosage form during storage. To overcome this, the most addressed strategy is by far polymorphism control either by tempering the product during or after manufacturing process, or by addition of modifiers to induce the stable polymorphic form and thus to avoid the final product instability. However, application of such strategies is not always successful and requires a mechanistic understanding of the relation between the molecular structure of solid lipids and their macroscopic properties and the effect on the performance of final product.

The next generation of LBEs are polyglycerol esters of fatty acids (PGFAs) (WITEPSOL PMF®), which are oligomeric hydroxyethers of glycerol fully or partially esterified with fatty acids. Tuning the number of polyglycerol moieties, fatty acids chain length and free hydroxyl groups per molecule results in diverse physicochemical properties, e.g. HLB, melting point, and wettability, which makes these molecules attractive candidates as novel LBE for different pharmaceutical applications. Moreover, these compound possess an extraordinary stable solid state due to the lack of polymorphism. This stable solid state was confirmed by investigation of the every hierarchical level of structure, namely molecular, nano-, and microstructure and the resulting physicochemical properties relevant for a LBE, which results in an advanced and stable performance of the formulations developed with these compounds. Examples are hot melt coated multiparticulate systems and matrix tablets for oral delivery and nanosuspensions for pulmonary application.

Keywords: lipid-based excipients; polyglycerol esters of fatty acids; solid state, stability, drug delivery

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C5. Development of innovative continuous technologies for the pharmaceutical industry

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Introduction. By the advent of continuous pharmaceutical manufacturing, development of new methods and approaches for real-time prediction of critical quality attributes of the product is more and more important. In vitro dissolution testing is one of the most substantial analytical methods in the pharmaceutical industry, however, it is a destructive, labor-intensive and time-consuming measurement. Over the last years, a clear need for real-time assessment and modeling of dissolution behavior has emerged. The aim of this work is the prediction of the dissolution of extended-release tablet formulations from their NIR and Raman spectra using artificial neural networks.

Materials and methods. Extended release matrix tablets were prepared with the variables being the drug content, the retarding polymer content and the tableting compression force. Then, Raman and NIR spectra were measured and artificial neural networks were used to mathematically

model the relationship between the spectra and the dissolution.

Results. The developed surrogate model-based methods were applicable to non-destructively predict the dissolution of extended release tablets using the measured vibrational spectra.

Conclusion. The obtained results imply that utilizing the proper data processing methods enables us to replace some of the most cumbersome analytical techniques with ones that require a minimal amount of human labor, yet can characterize a much larger fraction of the product. These solutions, when adopted by the pharmaceutical industry, can lead to well controlled technologies where the quality of the product is understood to a much deeper extent, and thus it can be assured that the patient will receive a treatment of the desired quality.

Keywords: continuous pharmaceutical manufacturing, process analytical technology, dissolution prediction, artificial intelligence

C6. Whatever is in a name, it should be standardized – a formal analysis of the active substances in the human MRIndex

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Introduction. The European regulatory framework in force provides three distinct procedural ways for the authorization of medicinal products within the EU, with different degrees of complexity and freedom of choice for the applicants, although the set of substantial rules applying in each one is essentially the same. Mutual recognition (MRP) and decentralized procedures (DCP) are the middle option, being used for a variety of pharmaceutical products and legal bases. All products authorized through MRP and DCP in Europe should be, in principle, accessible through the Human MRIndex, available online on the website of the HMA website. The analysis of the active substances as reported in the Human MRIndex shows that there is a need for standardization, as is the case for other drug databases.

Materials and methods. The publicly available data in the Human MRIndex (http://mri.cts-mrp.eu/Human) were downloaded and subject to data mining in the R language and environment for statistical computing (v. 3.6.1). We were interested to find how many active substances have been authorized through these procedures, which of them were most often used, what was the evolution across time etc. Although apparently a simple exercise, its performance needed considerable data mining techniques because of the lack of any standardization

Results and discussion. The MRIndex is not a proper relational database; therefore mining the relevant information is challenging and requires extensive use of regular expressions. Analyzing active substances in the MRIndex is particularly challenging because of multiple typing errors and a lack of standardized approach (e.g. “acetylcystein” and “acetylcysteine”; “acetyl salicylic acid”, “acetylsalicyclic acid” and “acetylsalicylic acid”; “albumin human”, “human albumin”, “human serum albumin”, “humanalbumin”, are spelling variants for one and same substance). Different strengths are treated as different active substances, which further complicates the analysis of both single substance products and fixed dose combinations (FDC). Certain herbal substances are described only by the herbal part (e.g. “agnus castus fruit 10 mg”, although the official name in one RMS states “Agni casti fructus extractum siccum”, i.e. a dry extract); both “folium” and “leaf” are found in different products. The name of the salts may is written in a plurality of ways: “ibuprofen lysidin salt”, “ibuprofen lysine salt”, “ibuprofen lysine” and, rather surprisingly, “ibuprofen lysate”, or “sulphate” and “sulfate”. Azelastine may be found as “azelastine hydrcochloride”, “azelastine hydrochloride”, and “azelastine hypochloride” (the trouble is that “hypochloride” is chemically quite different from “hydrochloride”, and pharmacists are the first to know it; but most likely the collective product that is MRIndex is not in the charge of pharmacists). This somewhat reflects the high volume of work in which competent authorities are involved each year in the MRP and DCP procedures, leaving no time such “trivial” matters as the name of an active substance.

The number of active substances (moieties) in MRIndex as of August 2018 is 1016.

Conclusions. Ironically, EU manages to harmonize product labelling for many products, but is not (yet) able to harmonize the names of the products in one of its most important databases. It is still more ironical when one thinks that for the pharmaceutical forms a standard terminology has been adopted and is enforced at European level; in theory, using a standard terminology for active substances should not be more difficult. It seems that only in theory, though.

C7. Building microbiological quality into drugs

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The microbiological quality of pharmaceutical products is influenced by the environment in which they are manufactured and by the materials used in their formulation. With the exception of preparations which are terminally sterilized in their final container, the microflora of the final product may represent the contaminants from the raw materials, from the equipment with which it was made, from the atmosphere, from the person operating the process or from the final container into which it was packed. Some of the contaminants may be pathogenic while others may grow even in the presence of preservatives and spoil the product. Any microorganisms that are destroyed by in-process heat treatment may still leave cell residues which may be toxic or pyrogenic.

Additionally, microbes can alter the chemistry and pharmacology of drugs, with a potential adverse impact on their effectiveness due to the breakdown of the active ingredients as well as on their safety due to the toxicity of potential degradant products. Therefore, control of microbes in drugs is essential, either by assuring absence of microbes in sterile drugs that are administered parenterally and applied to sensitive tissues or by controlling microbial bioburden to appropriate levels for nonsterile drugs that are administered to regions rich in microbial flora with physical or immunological barriers to infections.

Oral presentations

OP1. Quality by Design (QbD) in pharmaceutical industry - Design of Experiments (DoE) tool in drug development

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Introduction. Quality is of paramount importance for the pharmaceutical industry. Drug manufacturing was led by a strategy to control the intermediate and the end-products and never intervene into an authorized product recipe or a validated process. Over the years, this approach has showed its weaknesses in lost batches, process errors, "out of the specification" products. The Quality by Design (QbD) concept offers as an alternative, a flexible process and product, with the guarantee of constant quality. In the QbD paradigm, Design of Experiments methodology is a statistical tool used in several industries in order to study or to optimize products or technological processes. It is based on the thorough selection of variables that impact the quality attributes of the output and on performing the least number of experiments needed to cover the entire variation range. The aim of this work is to summarize the most important aspects of DoE use in different pharmaceutical products development.

Material and methods. The first step in drug development is to establish the Quality Target Product Profile (QTPP), out of which the Critical Quality Attributes (CQAs) can be identified. A risk assessment analysis usually precedes the experimental stage to rank the Critical Process Parameters (CPPs) and Formulation Variables. Those who get the highest risk scores, thus impact on the CQAs are further included as independent variables into the DoEs. A DoE can be developed for an intermediate product (e.g. granules) or for the final pharmaceutical product (e.g. oral lyophilisate, prolonged release tablet or ointment), and depending on the number of studied variables it can be designed for screening or optimization purposes. The CQAs for granules are mean particle size, polydispersity index, moisture content, while those for oral solid dosage forms are disintegration time, in vitro dissolution profile and mechanical strength. The CPPs for topical preparations are usually related their rheological properties and texture, as well as to their API release profile.

Results. The results of the statistical analysis are interpreted to assess the quality of fit, meaning the way the dependent variables can be connected to the independent variables. The effects of formulation factors and process parameters on the responses are presented as histograms of the regression coefficients as a function of the response or as response surfaces which allow an easier interpretation of the interactions. Finally, out of the experimental domain, a Design Space can be obtained, by imposing the constraints of the quality target product profile. The resulting Design Space is the sum of factor combinations that lead to products with CQA within the QTPP.

Keywords: design of experiments, design space, quality target product profile, critical quality attributes, critical process parameters

OP2. Quality by Design (QbD) in pharmaceutical industry - NIR spectroscopy as Process Analytical Technology (PAT) tool for the real-time monitoring of solid oral dosage forms manufacturing processes

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The modern drug manufacturing is expected to be controlled and monitored in real time, by implementing Process Analytical Technology (PAT), as an integrated part of the Quality by Design (QbD) concept. Lately, the near-infrared (NIR) spectroscopy, especially combined with chemometric algorithms, has become an extensively used PAT tool due to its fast, non-destructive and low-cost characteristics, being widely applied in several pharmaceutical manufacturing operations. The following works aim to exemplify the successful development of in-line NIR methods for the analysis and control of several manufacturing processes of solid dosage forms.

The first study describes an innovative in-line method for the quantification of the total polyphenolic content (TPC) of *Ajuga genevensis* dry extracts, obtained by spraying and adsorbing a liquid extract onto an inert powder support. The second study focuses on the monitoring of the granulation of two APIs, by the real time assessment of water content during the fluid bed granulation process. The last work presents the monitoring of an industrial scale pan coating process, through the real-time evaluation of the tablets' weight gain.

The real-time monitoring of the three manufacturing processes has been performed by operating an in-process integrated MicroNIR Pat-U spectrometer. In the case of the fluid bed processes, the apparatus was attached on the expansion vessel, at the same height as the sampling port found on the vessel's wall. In order to monitor the film coating process, the spectrometer was mounted inside the coating pan, with the detector at a close range of the tablet bed and out of the way of the spraying gun. Spectra of the moving powder, respectively tablet bed were recorded continuously, over the whole range of the spectrometer, 950 to 1650 nm. In order to develop the monitoring methods, the multivariate analysis of the recorded spectral data has been performed using the SIMCA 14.0 software. Thus, orthogonal partial least squares (OPLS) models for the prediction of the properties of interest have been developed.

Finally, the new developed techniques were applied for the process monitoring, the average recovered values of the NIR in-line predictions, compared to the ones obtained after performing the traditional reference methods, were 98.7% for the TPC content, 101.7% for the moisture content of the granules and 95.8% of the tablets weight gain.

As a conclusion, one can state that the described approaches allow the development of robust, fully controlled processes, offering valuable information regarding the successful implementation of NIR spectroscopic techniques as reliable PAT tools for the manufacturing of solid oral dosage forms.

Keywords: process analytical technology, near infra-red, real-time monitoring, granulation, coating

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Conclusions. The investigated products are bioequivalent under fasting and fed condition thus the newly developed modified release product could be registered for obtaining the marketing authorization. Moreover, the product proved a favourable safety profile. Food intake did not have a major impact on gliclazide's disposition in the body, so the product can be administered irrespective to food intake, hence increasing the patients' compliance and adherence to treatment. By registration of the generic product, the economical burden could be reduced for patients under medical treatment for type 2 diabetes. In addition, more patients would have access to appropriate treatment and the compliance to treatment could be increased due to the simplicity of the dosing regimen and a good tolerance profile of Glizlacide 60 mg modified release tablets.

Keywords: pharmacokinetics, bioequivalence, gliclazide, modified release tablets
Acknowledgments. The studies have been performed at the Clinical Pharmacology and Pharmacokinetics Terapia S.A and the Sponsor of the studies agreed to disclose the study results for publication.

OP7. Continuous manufacturing of pharmaceutical semi-solid dosage forms with drug-loaded nanoparticles

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Introduction. For decades, the pharmaceutical and cosmetics industries are mainly producing semi-solids via batch-wise processes which are often time-consuming, expensive and irreproducible between batches. On the other hand, recent advances show that continuous manufacturing processes have win the race for higher productivity, efficiency and product quality against the traditional methods. At the same time, developments in nanotechnology offers the opportunity to produce superior topical dosage forms with advanced drug delivery compared to conventional products. The aim of this study is to investigate the applicability of a continuous manufacturing system for semi-solid dosage forms with drug-loaded nanoparticles. Moreover, a QbD approach was applied to study the impact of several formulation and process parameters on the quality of the topical nano-gel.

Materials. As a semi-solid pharmaceutical dosage form, a gel was initially selected. As nano-drug delivery vesicles, liposomes and ethosomes were chosen, formulated from egg or soy lecithins, containing 0.1% (w/w) Hydrocortisone Acetate as active substance.

Methods. To produce a topical pharmaceutical gel with nano-drug delivery vesicles, two different preparation techniques were developed. In a first step, the processability of the gel with the continuous production system (Contimix, Hebold systems, Cuxhaven, Germany) was investigated. The raw materials of the semi-solid base were premixed and dosed separately via peristaltic pumps to the mixing compartments, which consists of two consecutive mixing units. In the second step, liposomes and ethosomes were prepared via ethanol injection method which was used initially as batch and then as a continuous process. Practically, premixes of ethanol with the dissolved lipid were prepared and injected directly into the aqueous phase leading to the formation of nano-systems. Prior to any experiments, the critical material attributes (CMAs) and process parameters (CPPs) from each of the continuous processes were identified though risk assessment tools such as Ishikawa diagrams and failure mode effect analysis (FMEA) charts. Furthermore, the influence of the formulation and process parameters on the product quality of the gel and nano-systems was studied separately through statistical Design of Experiments (DoE).

Results. The active pharmaceutical ingredient (API) concentration, yield point, viscosity and pH were identified as the critical quality attributes (DOE responses) of the gel agent. In case of the nano-carrier devices. The particle size and percent drug entrapment (lipophilic drug) were found

as the most critical. Furthermore, liposomes were found to be more suitable as nano-carrier devices compared to ethosomes since the former achieved up to 60% (w/w) encapsulation efficiency while the latter almost 50% (w/w).

Conclusions. Combining risk management tools and DoE was achieved a better insight on the formulation and process parameters in both continuous processes. Whereas, the application of a continuous manufacturing process provides a better control of nano-particles characteristics, semi-solids quality, easy automation and cost-effectiveness compared to the expensive batch production of semi-solids with pharmaceutical nano-delivery devices.

OP8. Development of a prolonged release tablet formulation containing as active substance fampridine based on risk assessment and the principles of Quality by Design

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Introduction. Used in the treatment of multiple sclerosis (MS), fampridine (4-amino-pyridine) is presently the only active substance approved for the advancement of walking disability in patients with MS. The limelight of current research trends often focus on the computational aided development and validation of both analytical methods and technological processes. In this context, defining the quality target product profile and subsequently the critical quality attributes for QbD analysis demands a risk assessment based evaluation.

Material and methods. Based on the preliminary risk assessment, tablet composition and manufacturing technology was evaluated applying a full factorial experimental design using MODDE 12.1 software (Umetrics, Sartorius Stedim Biotech, Umea, Sweden). The type of matrix former excipient (HPMC type K100LV, K4M, K15M and K100M), diluent/filler (Cellulose, microcrystalline type 102 and 112, MCC), homogenization time (2 to 10 minutes) and lubrication time (2 to 10 minutes) were defined as factors. Besides final powder blend in-process control parameters (e.g. flow-out time, bulk density), dissolution profiles were documented as responses and were recorded according to FDA requirements (phosphate buffer, pH = 6.8 and 50 rpm paddle rotation speed) modifying only the sampling intervals to 1, 2, 4, 8 and 12 hours. For the optimized composition and manufacturing technology a separate experimental design was implemented for tablet compression.

Results. After model fitting and refinement acceptable results were obtained for the model performance indicators. Optimal tablet composition and manufacturing technology was acquired using the optimizer function of the software. The set point selected according to the lowest DPMO (defects per million opportunities) was using HPMC K100LV and MCC type 112 in the composition and a homogenization and lubrication time of 2 and 10 minutes, respectively. The optimizer batch showed good correlation in comparison to the predicted results for both the in-process control results and release kinetics, the latter being confirmed by a substantially greater similarity factor result when compared to the acceptance threshold of 50 (f_2 = 80).

Conclusions. The study proposed the development of an extended release tablet formulation for fampridine using risk assessment and design of experiments as joined methods in QbD approach. The selected computational design proved to be adequate to reveal important response to factor interactions and returned a tablet composition and manufacturing technology suitable to ensure a dissolution of fampridine similar to the originator product.

Keywords: fampridine, quality by design, risk assessment, extended release

OP9. Polymer-based micro/nanofibers as pharmaceutical carrier systems obtained by electrospinning method

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Introduction. Micro/nanofibers formed with polymers into which low solubility active substances are embedded provide the opportunity to increase the solubility of these active substances, both as a result of size reduction and amorphization. Our research team used electrospinning to produce micro /nanofibers.

Material and methods. Active substances: levofloxacin, nebivolol, fenofibrate, aceclofenac etc. Used polymers: poly(ε-caprolactane) (50kDa); poly(vinyl-pyrrolidone) (PVP K90, Kollidon K90); poly(vinyl alcohol) (PVA Emprove 18-88) etc. Nanofibres were produced by electrospinning, in each case using various parameters. The basis of the method is that electrostatic force produces solid thin polymer fibers from a polymer dispersion containing an active ingredient. Fibers were analyzed with in vitro physical and physico-chemical tests: optical and scanning microscopy, thermoanalysis (DSC), FTIR (Fourier transform infrared spectroscopy), PALS (positron annihilation lifetime spectroscopy), and drug dissolution.

Results. In every study after a preliminary optimization of the composition, the morphology of the produced fibres was examined and compared.The SEM photos of the placebo and the drug-loaded fibers indicate that the fiber diameter is in both cases in a nanometer range. DSC curves confirm the crystalline amorphous transition of active substances due to fiber formation. Changes in the supramolecular structure are also indicated by the results of PALS analysis, where significant difference was found in the o-Ps lifetime values between the nanofibers and the drug-loaded nanofibers.The results of the FTIR measurements were also in good agreement with the PALS results. With respect to the microfibers, merging and broadening of the peaks were detected. It is in good agreement with the results of previous studies that the lack of an ordered crystalline structure, such as an amorphous dispersion allows numerous types of conformations, which can result in the widening and merging of the expected peaks. Dissolution studies were performed in a low-volume setup.

Conclusions. Our studies demonstrated that the nanofiber forming process is influenced by multiple parameters such as the composition of the active substance-containing viscous solution and the electrospinning parameters. The SEM studies confirmed the nanofibrous structure, while the FT-IR and DSC tests proved the amorphous state of different active substance in the formulations. The dissolution from the polymer matrix was fast and complete.

Keywords: electrospinning, nanofiber, polymer, pharmaceutical carrier

OP10. Integration of continuous filtration into a continuous pharmaceutical production line

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Introduction. Continuous manufacturing (CM) gained notable interest in the pharmaceutical industry in the past decade. Continuous technologies have numerous advantages over traditional batch processes: lower investment and operational costs, easier scale-up, and improved process control providing constant product quality. Accordingly, main regulatory bodies encouraging pharma companies to develop continuous processes. Many research papers can be found in the literature dealing with continuous pharmaceutical techniques, including flow synthesis,

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continuous crystallization, filtration, homogenization, granulation and tableting. However, the integration of the individual technological steps still seems to be challenging. Crystallization is a key purification and separation technique in the pharma industry. More than 90% of the currently marketed drugs are crystallized during their production. Therefore, continuous crystallization is a widely discussed topic in the literature. As the inseparable counterpart of crystallization, filtration is also an important step of drug manufacturing. A few examples already can be found about continuous filtration, in some cases together with crystallization. Nevertheless, these studies do not delve into detail regarding how the product quality is affected by the direct connection of these two steps.

In this work we attempted to directly connect the continuous crystallization of acetylsalicylic acid (ASA) from a flow synthesis reaction mixture and the continuous filtration of the suspension. Additionally, the impact of the crystallization setup on the quality of the filtered was aimed to be investigated.

Material and methods. The reaction mixture of ASA was crystallized in a mixed suspension mixed product removal (MSMPR) crystallizer. Heptane was used as antisolvent. A continuous filtration carousel, a prototype unit designed by Alconbury Weston Ltd. was applied for the downstream processing of the suspension. The inlet tubing in the CFC was directly inserted into the MSPMPR reactor and used as outlet of the crystallization. During the experiments samples were taken after filtration to analyze moisture content, recovered mass and particle size distribution (PSD) in the case of different process parameters in the MSMPR reactor.

Results. A design of experiment study was conducted to investigate how the filtered product quality changes in the case of different MSMPR process setups. Direct correlation was found between the temperature and the residence time of the continuous crystallization and the moisture content of the filtered crystals. The yield of the 2-step process was similar to the standalone MSMPR experiments. The PSD of the product was not affected by the CFC process when washing was turned off. The purity of the crystals was acceptable even without washing.

Conclusions. The direct connection of a continuous MSMPR crystallization process to the continuous filtration of the suspension was carried out in this work. The impact of the process parameters of the first step on the final product quality was investigated by a design of experiment study. In conclusion continuous filtration was successfully integrated into a continuous production line starting from the flow synthesis of ASA.

Keywords: continuous manufacturing, crystallization, filtration, integrated technologies
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OP11. Development and validation of a comprehensive Extractables and Leachables testing protocol

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Introduction. Extractables from Pharmaceutical Packaging Systems are compounds that can be solvent extracted from the packaging material. Extractable studies identify all compounds that have the potential to leach into the product. Leachables are the compounds that migrate from the packaging into the product under intended use conditions. Extractables and leachables (E&L) testing is a complex analytical study involving several analytical techniques: HeadSpace and liquid GC-MS, LC-MS, ICP-MS. Rompharm Company and Scient have collaborated to develop, implement and validate a comprehensive analytical methodology for E&L testing of packaging materials used in new parenteral drug products. The validated testing protocol has been successfully used to obtain market approval for several new parenteral drug products.

Materials and methods. GC-MS: Perkin Elmer Clarus 680 Gas Chromatograph / Clarus SQ8T Mass Spectrometer operated in full scan over 33 – 620 m/z; Elite-5MS chromatographic column, L 30 m, ID 0.25 mm, 0.25 µm film thickness. GC-MS-HS: For HeadSpace injection, a TurboMatrix 40 incubator/injector was used; compounds were separated on an Elite-Volatile L 30 m, ID 0.25 mm, 1.4 µm capillary column. The mass spectrometer was operated in full-scan over 25 – 200 m/z. LCMS: Perkin Elmer Flexar UHPLC / Sciex QTRAP 5500 Tiple Quadrupole system operated in full-scan in the range 80 – 1250 m/z in both positive and negative ionization; sepparation was made on a Phenomenex Synergi 4u Fusion-RP chromatographic column. ICP-MS: Perkin Elmer NexION 300S.

Results. GC-MS method validation involved chromatographic separation of Grob mix components, a mix comonly used in chromatography as a benchmark for the evaluated method's ability to accurately detect non-polar, polar, basic and acidic compounds. The detected extractables / leachables compounds' concentrations are estimated using an internal standard area ratio, and is based on an average response factor calculated for the Grob mix components. A method detection limit was estimated with the Signal-to-Noise approach using the poorest sensitivity from the Grob mix components. The validated detection limit was 0.708 µg/mL. For the GC-MS-HS method a similar approach was taken; since a benchmark mixture similar to the Grob mix is not available for volatile compounds, a custom mix was developed, a similar approach to Jenke et al. The headspace method detection limit was 0.607 µg/mL. For the LC-MS screening method, reference standards of the identified extractables were used to calibrate the full-scan method, in both positive and negative ionization, and an internal standard was also used. A method reporting limit of 0.500 µg/mL was validated. The elemental impurities were identified and monitored using validated ICP-MS methods. For extractables testing, the packaging material was subjected to solvent reflux extractions, with hexane and isopropyl alcohol used as non-polar and polar solvents, respectively. The developed method was successfully employed to identify the extractable compounds and estimate their concentrations. New drug products using packaging made with the tested material were screened for leachables based on the information gathered in the extractables study.

Conclusions. The developed Extractables and Leachables methodology is a useful tool in the parenteral and ophthalmic drug development and approval process.

Keywords: Extractables and Leachables, pharmaceutical packaging, drug approval

OP12. Software-assisted development of a liquid chromatographic method for the simultaneous determination of related substances of paracetamol, acetylsalicylic acid and caffeine

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Introduction. Simultaneous determination of related substances in case of combination tablets is often challenging due to the high number and heterogeneity of analytes. In these cases, the classical intuitive or trial-and-error method development approach takes tremendous amount of time and often fails in identifying optimal selectivity. Thus, in case of these complex mixtures, software-assisted chromatographic modelling softwares offer a more efficient method development process with significant time and cost savings. Taking into account these considerations, when faced with the challenge of the simultaneous determination of related substances of paracetamol, acetylsalicylic acid and caffeine from a combination tablet, the new version of the fully QbD compatible Drylab (ver. 4.3.3) software was selected to aid the method development and optimization process.

Materials and methods. 12 analytes were identified and selected for the present study, including paracetamol and its related substances (4-aminophenol, 4-nitrophenol and

4-chloroacetanilide), caffeine and its related substances (caffeidine nitrate, caffeine impurity B, theobromine, theophylline and isocaffeine), acetylsalicylic acid and salicylic acid. Separations were performed on a Kinetex Biphenyl column (250x4.6 mm, 5 µm), employing a quality by design approach, using design of experiments, with three experimental factors: gradient time (*tG*, 20 min and 60 min), temperature (*T,* 20°C and 40°C) and pH of mobile phase A (*pH*, 3.2/3.8/4.4) and 12 experimental runs. Mobile phase A consisted of aqueous solution of 10 mM ammonium formiate set to the desired pH value by formic acid, while mobile phase B was methanol. Chromatographic analysis was performed on a Hitachi Chromaster HPLC system.

Results. Apart from 4-aminophenol, all analytes could be retained on the column. Critical pairs of analytes, with low resolution values included theobromine and theophylline, 4-nitrophenol and caffeine, acetylsalicylic acid and 4-chloroacetanilide. Based on the design space provided by the modelling software, a robust setpoint was selected (mobile phase A pH=3.2, *tG* 40 min, 0 to 35 min, 5% to 40% B, 35 to 40 min, 40% B; *T*=35°C), which predicted baseline separation of all analytes. Upon application of the recommended settings, excellent correlations were found between predicted and experimentally obtained retention times and resolution values, which further proved the reliability of the predictions.

Conclusions. Software-assisted method development and optimization was undertaken for the simultaneous determination of related substances of paracetamol, acetylsalicylic acid and caffeine using a multivariate, gradient-temperature-pH mode. The experimental design-based approach yielded a design space, from which a robust setpoint was selected, predicting baseline separation of all analytes. Predicted vs. experimental runs showed excellent correlation providing further proof for the applicability of this approach. The developed method was applied for the impurity analysis of fixed-dose combinational tablets containing paracetamol, acetylsalicylic acid and caffeine.

Keywords: Drylab, quality by design, experimental design, HPLC

Posters

P1. Cyclodextrin complexes of some chiral nonsteroidal anti-inflammatory drugs – molecular modelling study

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Cyclodextrins are widely used auxiliary substances in biopharmaceutical studies and in capillary electrophoresis. The aim of this work was to evaluate the affinity of four cyclodextrins (β-CD, TM-β-CD, RAMEB and HP-β-CD) to six acidic nonsteroidal anti-inflammatory drug (NSAID) enantiomers (ibuprofen, IBU; ketoprofen, KETO; fenoprofen, FENO; flurbiprofen, FLU, naproxen, NAP, indoprofen, IND), in order to assess the difference in the binding energy to the R(-) and S(+) configurations.

Molecular mechanics calculations, using the HyperChem 8.0 software, were employed to study the inclusion of the NSAIDs in the CDs. The structures of the NSAIDs, the CDs and the 1:1 binary host-guest complexes were geometrically optimized using the MM+ force field, Polak-Ribière algorithm, until 0.01 kcal/(molÅ) RMS gradient was achieved. The optimization of the complexes was repeated at least sixty times, till the most stable (the lowest energy) complex was found.

Regarding the results shows that IBU S(+), KETO R(-), FLU S(+), and NAP S(+), form the most stable complex with TM-β-CD; FENO R(-) with the β-CD and IND S(+) with the RAMEB, respectively. The binding energies in the above cases are: 32.7 kcal/mol, 47.1 kcal/mol, 30.9 kcal/mol, 22.7 kcal/mol, 32.9 kcal/mol and 18.6 kcal/mol, respectively. Regarding the geometry of the complexes, the guest molecules enter totally in the cavity of the CD. Concerning the difference between the enantiomers: RAMEB and HP-β-CD have higher affinity to the S(+) isomers and the difference is statistically significant (p=0.04 and 0.01); β-CD and TM-β-CD show similar affinity to both enantiomers.

The presented results can be valuable in selection of the appropriate type of CD: in chiral separation is advantageous if there is high difference between the affinities of the enantiomers to CD, if CDs are used to increase water solubility the opposite is valid.

Keywords: molecular mechanics, nonsteroidal anti-inflammatory drugs, cyclodextrins

P2. Improved pharmacokinetics and reduced side effects of doxorubicin therapy by liposomal co-encapsulation with curcumin

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Introduction. Doxorubicin is an effective antracyclin antibiotic which is being used alone or in combination with other drugs to treat a broad spectrum of solid tumors (breast, bladder, ovaries, stomach, lung, thyroid) as well as hematological malignancies (Hodgkin′s lymphoma) and soft tissue sarcomas. To maximize the therapeutic efficacy of doxorubicin and minimize its side effects, it was encapsulated in various nanoformulations among which liposomes, that have the advantage of being the least toxic for *in vivo* applications. The goal of the current study was to investigate the pharmacokinetic profile, tissue distribution and adverse effects of co-encapsulated long-circulating liposomes *in vivo*, which should supply evidence for its enhanced antitumor efficacy, previously demonstrated by our group.

Material and methods. Pharmacokinetic studies were carried out in non-tumor bearing rats following i.v. injection of a single dose of liposomes (1 mg/kg doxorubicin). Doxorubicin

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concentration in tumors, hearts and livers were measured after administration of two i.v. doses of liposomes (2.5 mg/kg doxorubicin) to Balb/c mice bearing C26 colon tumors. Markers of murine cardiac and hepatic oxidative status were determined to provide additional insights regarding the beneficial effects of curcumin when co-encapsulated with doxorubicin in liposomes over doxorubicin-induced adverse reactions in these organs.

Results. Consistent with other studies showing improvement of doxorubicin pharmacokinetics by nanoencapsulation, our results clearly indicated that when co-delivered with doxorubicin in long-circulating liposomes, curcumin modulated the pharmacokinetic properties of doxorubicin by prolonging its plasma half-life ($t_{1/2}$, $p<0.0001$) in comparison with free doxorubicin, and thereby increasing the exposure of doxorubicin in the blood (AUC, T_{max}, K_{el}, $p<0.0001$).

Conclusions. The current study demonstrated that *in vivo* administration of doxorubicin together with curcumin in long-circulating liposomes effectively modulated the pharmacokinetics and specific tissue distribution of doxorubicin, limiting its side effects, via curcumin-dependent antioxidant actions.

Keywords: liposomes, curcumin, doxorubicin, pharmacokinetics, colon cancer

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P3. The pharmacokinetics comparison of two formulations containing 10 mg Dapagliflozin under fed condition in a randomized crossover study in healthy caucasian subjects

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Introduction. In the past years SGLT2 inhibitors, such as dapagliflozin were demonstrated to improve the control of blood glucose in patients with Type 2 Diabetes Mellitus following a mechanism which is independent from the insulin process. A new immediate release formulation containing 10 mg dapagliflozin was developed and its pharmacokinetics was assessed in comparison with a reference product under fed condition.

Material and methods. The present study was open and design as crossover, balanced, randomized, with two periods, two treatments and two sequences. 44 healthy adult volunteers were included out of which 33 subjects completed both periods of the study. After having the recommended high fat, high-calorie test meal the subjects were administered either test or reference drug product with 240 mL of a 20% glucose solution in water at ambient temperature. Washout period was 7 days. 48 blood samples were taken during each period. A validated HPLC method coupled with mass spectrometry was used for determination of dapagliflozin concentrations in plasma. Non-compartmental pharmacokinetic analysis was performed using Pheonix® WinNonlin® version 6.3. Calculated pharmacokinetic parameters were C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{1/2}$, T_{max} and K_{el}. Statistical analysis was performed using SAS version 9.3.1 Type III ANOVA for calculating the least square means.

Results. Ratios of least square means for ln- transformed pharmacokinetic parameters for dapagliflozin using 90% Confidence Interval were calculated. The results obtained for ln C_{max} was 103.66% (95.93% – 112.01%), for ln AUC_{0-t} was 101.35% (98.84% – 103.93%) and for ln $AUC_{0-\infty}$ 101.48% (99.05% - 103.96%). The mean T_{max} values for dapagliflozin under fed condition from the test formulation was 3.14 hours and 3.62 hours from the reference formulation, respectively.

Conclusion. Based on these results, the two formulations containing 10 mg of dapagliflozin were determined to be bioequivalent in healthy, adult, human subjects under fed condition as the 90% confidence intervals for the ratio of test and reference product averages of the pharmacokinetic parameters were within 80.00-125.00% acceptance range.

Keywords: bioequivalence, dapagliflozin, diabetes mellitus, fed

P4. *In vitro* release study of tenoxicam from hydrogels based on carbomer

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Introduction. Tenoxicam is a nonsteroidal anti-inflammatory agent of the oxicam group, with anti-inflammatory, analgesic, and antipyretic properties, often used in the treatment of rheumatic, arthritic diseases and very little soluble in water. The experimental study followed the *in vitro* release of tenoxicam from Carbopol Ultrez 10-based hydrogels, as well as the assessment of the effect of formulation variables on the diffusion profile of tenoxicam through synthetic membranes.

Material and methods. Seven hydrogels were performed based on carbomer 1% (Carbopol Ultrez 10), containing 1% tenoxicam, the neutralizing agents used were monoethanolamine (formulations T1, T2, T3, T4, T5a, T6) and triethanolamine (formulation T5b). The study of *in vitro* release through synthetic membrane was conducted with the help of the Franz diffusion cell, the reception environment was represented by the phosphate buffer solution (pH 7,4). The hydrogels were assessed according to viscosity, pH, spreadability, consistency and rheological behaviour.

Results. All hydrogels displayed appropriate consistency and spreadability, thixotropic pseudoplastic character, whereas pH values were situated within the limits imposed by the pharmacopoeia. The *in vitro* release study has emphasized that tenoxicam was released in the greatest proportion in the codified T4 formulation, following neutralization with monoethanolamine, while the slowest release was realised in the codified T1 formulation.

Conclusions. The release of tenoxicam from hydrogels was influenced by the type of salt which was formed following neutralization, but the decisive role on the release was played by the presence of β-cyclodextrin in the formulation. Tenoxicam was released at approximately equal speeds from the other formulations, without significant differences due to formulation variables.

Keywords: tenoxicam, hydrogel, carbomer, cyclodextrin

P5. Importance of phenotyping based on a pharmacokinetic study of atomoxetine

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Introduction. Atomoxetine is a potent and selective norepinephrine reuptake inhibitor and is the first nonstimulant medication approved in the United States for the treatment of attention deficit hyperactivity disorder (ADHD) in adults, adolescents and children. The metabolism of this drug is mediated by CYP2D6 and leads to the formation of its main metabolite, 4-hydroxyatomoxetine, which has similar pharmacological activity with that of atomoxetine. Considering that CYP2D6 is a polymorphic enzyme, between phenotypic groups were noted differences in the bioavailability of poor metabolizers (PMs) (94%) and extensive metabolizers (EMs) (63%). Thus, the aim of this study was to analyze a potential phenotypic variation within the studied group based on the pharmacokinetic profile of atomoxetine and its active metabolite and to evaluate the impact of CYP2D6 phenotype on atomoxetine pharmacokinetics.

Material and methods. The study was designed as an open-label, non-randomized clinical trial that included 43 Caucasian healthy volunteers. Each subject was given a single oral dose of 25 mg atomoxetine. Atomoxetine and 4-hydroxyatomoxetine-O-glucuronide (glucuronidated active metabolite) plasma concentrations were further determined. A noncompartmental method was used for determination of the main pharmacokinetic parameters of both compounds. Further on, the CYP2D6 metabolic phenotype was assessed using the area under the curve (AUC) metabolic ratio (atomoxetine/ 4-hydroxyatomoxetine-O-glucuronide) and specific statistical tests (Lilliefors (Kolgomorov-Smirnov) and Anderson-Darling test). The phenotypic differences in atomoxetine disposition were identified based on the pharmacokinetic profile of the parent drug and its metabolite.

Results. The statistical analysis revealed that the AUC metabolic ratio data set did not follow a normal distribution. Therefore, two different phenotypes were identified, respectively the poor metabolizer (PM) group which included 3 individuals and the extensive metabolizer (EM) group which comprised the remaining 40 subjects. Also, it was proved that the metabolic phenotype significantly influenced atomoxetine pharmacokinetics, as PMs presented a 4.5-fold higher exposure to the parent drug and a 3.2-fold lower exposure to its metabolite in comparison to EMs.

Conclusions. The pharmacokinetic and statistical analysis emphasized the existence of 2 metabolic phenotypes: EMs and PMs. Furthermore, it was demonstrated that the interphenotype variability had a marked influence on atomoxetine pharmacokinetic profile.

Keywords: atomoxetine, CYP2D6, polymorphism, bioavailability

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P6. Improving the release of polyphenols by encapsulation in nanostructured systems

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Introduction. Polyphenols are bioactive compounds with beneficial effects for health, cosmetics or food industry. However, after being extracted from medicinal plants, polyphenols present several shortcomings: poor physicochemical stability, low water solubility which will lead to poor bioavailability, bitter and astringent taste. In the present study we encapsulated polyphenols from Calendullae flos in nanostructured liposomal systems in order to improve their characteristics. Liposome vesicles are colloidal nanoparticles composed of phospholipids with unique features: biocompatibility, biodegradation, non-toxicity. These shall provide polyphenols with a range of benefits - better absorption, reduced incidence of adverse reactions, masked unpleasant taste, and better compliance with treatment.

Material and methods. To develop liposome vesicular systems we used flowers of Calendula officinalis L. harvested from the Crişana region, Bihor County. The flowers were carefully selected as to obtain an alcoholic extract by maceration with 30% (v/v) alcohol, plant-to-solvent ratio 1: 5. The liposomes loaded with polyphenols from the Calendullae flos extract were prepared by the hydration method from phosphatidylcholine (50 mg), dipalmitoyl phosphatidylcholine (50 mg), cholesterol (2.5 mg). DLS (Dynamic Light Scattering) and ZP (zeta potential) measurements were carried out to determine the physicochemical and morphological properties of the nanoparticles. The entrapment efficiency was determined immediately after preparation, after 30 days and after 60 days. The Folin - Ciocâlteu test using gallic acid as a standard was used for evaluation. A testing system of six Franz diffusion cells and the UV spectrophotometric method were used to determine the release of the polyphenolic complex from the liposomal nanoparticles.

Results and discussion. The size and polydispersity index of the liposomes was performed at 25°C, with nanometric dimensions less than 500 nm.The obtained liposomal systems showed high entrapment efficiency of 81.02±0.42% and stability at 25°C for at least 60 days.

Several kinetic models (order zero, order I, Higuchi) were used to investigate the mechanism of in vitro release of polyphenols. All the entrapped polyphenols were released in 24 hours (98.15 ± 0.22%).

Conclusions. The evaluation of the liposomal systems loaded with polyphenols extracted from Calendullae flos demonstrated good entrapment efficiency (~80%), small sizes (less than 500 nm), low polydispersity index and good stability after 60 days at 25°C.

P7. Wet milling of a prolonged release suspension for injection: influence of process parameters on particle size distribution and drug substance dissolution

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Introduction. Wet milling is used in the pharmaceutical industry to obtain nanosuspensions of poorly soluble drug substances and thus to increase their bioavailability by enhanced dissolution rate. Stability of particles in suspension is achieved with different stabilizers (surfactants, polymers etc.). Critical process parameters for media milling are drug concentration, amount and size of milling beads, milling speed and milling time.

Materials and methods. Initial suspension was obtained by mixing the insoluble drug

substance with an aqueous solution of polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, monosodium dihydrogen phosphate monohydrate and disodic hydrogen phosphate anhydrous. Wet milling was performed on a DeltaVita 50 mill from Netzsch (Germany) with the aid of yttria-stabilized zirconia grinding beads. Process parameters (beads filling volume percentage of the milling chamber, beads diameter and milling time) were variated in order to assess their impact on particle size distribution (PSD). Three milling tests with a total duration of 80 minutes were done with: T1) 85% filling volume and 0.3 mm diameter beads T2) 60% filling volume and 0.3 mm diameter beads and T3) 60% filling volume and 0.5 mm diameter beads. The rest of milling parameters (suspension volume and concentration, feed pump flow and milling rotatory speed) were kept constant. Samples were taken after different periods of milling time and PSD was measured with the aid of a laser diffraction analyzer Mastersizer 3000 from Malvern Panalytical (UK). Dissolution tests of final milled suspensions were performed according to the FDA dissolution methods database.

Results. PSD analysis of final suspensions resulted after milling showed a decrease of d10 value of 54% for T1, 46% for T2 and 38% for T3 when compared with the suspension before milling. d50 value decreased with 67% for T1, 63% for T2 and 53% for T3. d90 value decreased with 49% for T1, 48% for T2 and 40% for T3. Dissolution of the 3 suspensions were correlated with the PSD results. After 45 minutes dissolution time, dissolution percentages were the following: 83% for T1, 81% for T2 and 70% for T3.

Conclusions. After this study, we confirmed that diameter of beads and their filling percentage in the milling chamber are critical process parameters which impact the milling time and yield: smaller the bead particles, higher the efficiency of the attrition process and higher the filling volume of the wet mill, higher the efficiency of the attrition process.

Keywords: wet milling, injectable suspension, particle size distribution

P8. EGCG liposomes: formulation development and *in vivo* antioxidant potential evaluation

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Introduction. (-)-Epigallocatechin gallate (EGCG) is the most abundant catechin from green tea with antioxidant properties. Due to its polyphenol chemical structure, it is characterized by low stability and consequently, low bioavailability. To overcome these problems, liposomes are proposed for EGCG targeted delivery. Liposomes are composed of the main components of the cellular membrane namely phospholipids and cholesterol. The main objective of this study was to develop liposomes with EGCG for intravenous administration by using the concept of Quality by Design (QbD), and to evaluate the antioxidant potential of the optimized formulation in migraine and diabetes.

Material and methods. All the QbD steps were performed in accordance with the International Conference on Harmonization (ICH) guide ICH Q8 (R2). By using an Ishikawa diagram for risk assessment, three factors were identified as potential critical for EGCG liposomes development, namely phospholipids concentration, EGCG concentration and phospholipids to cholesterol molar ratio. Identified critical quality attributes of the liposomes were liposomal size, EGCG liposomal content, encapsulation efficiency (EE%) and zeta potential. Taking into consideration all these factors, an experimental design with 14 experiments was performed. *In vivo* studies were carried out in order to study the antioxidant potential of EGCG liposomes in comparison with EGCG solution in conditions like diabetes and migraine.

Results. The liposomes prepared according to the experimental design had the following

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quality attributes: the size varied between 157.36 and 202.83 nm, zeta potential between -80.23 and -8.56 mV, EGCG concentration between 36.7 and 249.8 µg/ml and EE% between 26.71 and 76.7%. All the results were fitted by using multiple linear regression (MLR). The two statistical parameters, namely R2 and Q2, showed that all the results fitted well with the proposed model since their values are greater than 0.6 for all responses and the difference between them for each answer is not greater than 0.3. The responses were influenced the most by EGCG concentration and phospholipids to cholesterol molar ratio. The QbD approach allowed the determination of an optimized formulation, with enhanced EGCG EE% and minimized size. The *in vivo* studies revealed that liposomal EGCG has a significant potential to reduce the oxidative stress associated with conditions like migraine or diabetes.

Conclusions: In conclusion, the QbD concept was successfully implemented in the development of EGCG liposomes, allowing a better understanding of the factors influencing product quality, and the preparation of a product meeting the targeted quality profile.

Keywords: EGCG, liposomes, antioxidant properties

P9. Doxorubicin and simvastatin co-encapsulation in long-circulating liposomes for increased efficiency of colon cancer therapy

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Introduction. Doxorubicin (DOX), a chemotherapeutic drug, is widely used in different types of cancer. Its great disadvantage is its cardiotoxicity and other side effects that decrease patient compliance. First liposomal formulation with DOX was Doxil® in USA. The most important features of this product are that liposomes are pegylated to ensure long circulation in blood, DOX is incorporated through active loading, for higher encapsulation efficiency (EE%) and liposomal size is smaller than 200 nm, preventing clearance by the reticuloendothelial system (RES). Simvastatin (SIM) is a cholesterol-lowering drug with antioxidative properties. In the recent studies, SIM encapsulated in long-circulating liposomes (LCL) has been shown to inhibit C26 colon carcinoma growth via supression of tumor angiogenesis and inflammation, and through direct cytotoxic effects on carcinoma cells. The aim of this study was to develop LCL in which DOX and SIM are co-encapsulated, for improved inhibition of C26 colon cancer growth.

Materials and methods. Liposomes were prepared through film hydration method and doxorubicin was encapsulated through an ammonium sulphate gradient. For formulation development, the following factors were taken into consideration: phospholipids concentration, DOX concentration, SIM concentration, ammonium sulphate pH and incubation time with DOX. For liposomes characterization, liposomal size, polydispersity index (PDI), drugs' encapsulated concentration, drugs' encapsulation efficiency (EE%) and zeta potential were determined. The *in vitro* antiproliferative effects of the drug combination was studied on C26 murine colon cancer cells co-cultured with macrophages and drugs' combination index was determined.

Results. Preliminary studies showed that DOX EE% is higher than 50% and SIM EE% is strongly dependent on the formulation factors. Liposomal size and PDI were determined before and after incubation of SIM liposomes with DOX in order to monitor if the incubation conditions may influence liposomal critical quality attributes like the aforementioned parameters. *In vitro* studies showed a strong inhibitory activity of the combination of drugs co-encapsulated in liposomes, against C26 murine colon cancer cells proliferation when co-cultured with primary macrophages.
Conclusions. In conclusion, the co-encapsulation of DOX and SIM in LCL is a promissing strategy which should be further evaluated in vivo for the treatment of C26 colon cancer.

Keywords: Doxorubicin, Simvastatin, LCL, colon cancer

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P10. Formulation of co-loaded fluconazole/benzocaine cubosomes

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Introduction. Topical delivery of fluconazole is still a major limitation due to problems related to controlled drug release and achieving therapeutic efficacy. Literature review has revealed that cubosomal systems can serve as an ideal vehicle for drugs with poor loading and permeability for the treatment of topical fungal infections. The aim of this work was the development and characterization of a novel nanoparticulate system, based on cubosomes loaded with benzocaine (BZ) and fluconazole (FL), as model drugs for topical mucosal treatment of mycosis.

Material and methods. The production of cubosomal dispersions was based on the emulsification method. A D-optimal design was used to study the influence of the formulation and process parameters (such as the type and method of incorporating the drug substance, homogenization speed and time of the preparation of co-loaded FL-BZ cubosomes) on the studied responses, namely particle size, polydispersity index (by dynamic light scattering, Nano-ZS90, Zetasizer, Malvern Instruments, UK) and entrapment efficiency, calculated as the difference between the total amount used in the preparation of the cubosomes and the amount in the filtrate, (Amicon Ultra 10 kDa, Millipore, centrifugation at 14000 rpm, 4°C, 30 min.) as determined by HPLC validated methods (Agilent, 1100, USA). BZ analysis: analytical column Gemini C18 (100 mm x 3 mm, 3 µm), at 240 nm. FL analysis: analytical column Zorbax C18 (100 mm x 3 mm, 3.5 µm), at 260 nm. The morphological aspects of FL-BZ loaded cubosomes was evaluated by using transmission electron microscopy (TEM) (JEOL Model, 70 kV transmission electron microscope (JEM 1400, USA). The construction and fitting of the experimental data followed by the calculation of the statistical parameters to validate the experimental design was achieved using Modde 11.0 (Umetrics, Sweden) statistical software, Partial Least Squares (PLS) method.

Results and discussion. The initial model was refined by excluding the terms insignificant for responses ($p>0.05$). The obtained results revealed that as the rotation speed and time speed increased, there was a decrease in the mean diameter of the cubosomes. The influence of active substances on the studied responses was qualitatively assessed. The entrapment efficiency in the case of BZ varied between the 72.77 - 78.12%, and in the case of FL, a more hydrophilic substance, in the range of 10.48 - 15.87%. The optimal formulation predicted in the optimization process was prepared and studied and the obtained experimental data were very close to the predicted ones.

Conclusions. Homogeneous co-loaded FL-BZ cubosomes were obtained using a D-optimal design. Further studies are needed to identify an appropriate regression model, to improve the FL entrapment efficiency.

Keywords: cubosomes, fluconazole, benzocaine, nanoformulation

P11. Formulation of curcumin loaded polymeric microspheres for colon-specific delivery

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Introduction. Curcumin is a diphenolic compound extracted from the rhizome of the perennial herb *Curcuma longa* (turmeric), mostly used as a spice, coloring agent and flavoring agent, but also in traditional Asian medicine to treat a series of diseases. The therapeutic activities of curcumin include antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, hepatoprotective and neuroprotective properties. Recently, it has attracted increasing attention in inflammatory bowel diseases and colon cancer treatment, because it can scavenge free radicals, reduce inflammatory cytokine production and inhibit tumor growth. Besides its multiple biological properties, studies also demonstrated a very low toxicity in animals or humans. Up to the present, several studies have shown the efficacy of curcumin by various nanoparticulate systems to different colon diseases. However, the studies which present the development of microparticulate systems encapsulating curcumin are limited, and no study with a curcumin loaded Eudragit® FS-polycaprolactone microparticulate system has been performed. Therefore, the aim of this work was to develop curcumin loaded microspheres through the Design of Experiments approach, in order to establish the influence of formulation factors on the characteristics of the obtained delivery system.

Materials and methods. Microspheres were prepared by oil/water emulsion technique and solvent evaporation, using Eudragit® FS and polycaprolactone as polymers for colon-specific delivery. For formulation development, the following factors were taken into consideration: Eudragit® FS proportion (0-25-50%), curcumin concentration (6.5-9.75-13 mg/ml) and polymer (mixture Eudragit® FS-polycaprolactone) concentration (130-195-260 mg/6.5 ml). All formulations were prepared according to the experimental design matrix consisting of 17 experiments. For the characterization of microspheres, the following properties were determined: particle size, drug loading, encapsulation efficiency, particle size distribution, yield and drug released over 24 hours in environments that simulated the gastric (pH 1.2) and intestinal (pH 6.8) fluids.

Results. Curcumin encapsulation ranged between 56% and 82%, drug loading was between 1.3 and 6.9 mg curcumin/100 mg polymer and yield varied between 76% and 94%. *In vitro* dissolution studies indicated that the pH-dependent polymer, Eudragit® FS had an important influence on curcumin release, especially in the acidic environment. Thus, formulations containing the highest Eudragit® FS proportion (50%) led to low curcumin release in the gastric simulated fluid after 2 h, less than the maximum release required for colonic drug delivery systems (10%).

Conclusions. In conclusion, the polymeric microspheres, obtained using a mixture of Eudragit® FS and polycaprolactone, are a promising colon-specific delivery system for the encapsulation of curcumin and should be further evaluated.

Keywords: curcumin, Eudragit® FS, polycaprolactone, colon-specific delivery system

P12. Preliminary evaluation of solid state stability of promestriene

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Introduction. Promestriene is a synthetic oestrogen derivative, currently used in topical estrogen therapy. Promestriene is used for treating vaginal atrophy symptoms, but also has been studied in phase IV of the clinical trial on improvement of hormonal cytology. Promestriene was also investigated as topical treatment in order to improve surgical healing of infants suffering of hypospadias. Since no published data were found in literature regarding the solid-state stability of promestriene during thermal treatment, in this study we set our goal in the investigation of degradative mechanism of promestriene in inert atmosphere.

Material and methods. Promestriene (CAS 39219-28-8) as certified reference material was stored according to supplier request and used as received. The solid-state stability of was evaluated using a Perkin Elmer Diamond thermobalance. The obtained data was collected using five different heating rates β = 5, 7, 10, 12 and 15°C·min-1 in dynamic nitrogen atmosphere and was later analyzed as to determine the values of the apparent activation energies. Two isoconversional methods were used for this purpose, namely Kissinger–Akahira–Sunose and Flynn-Wall-Ozawa, while the NPK method was afterwards employed to differentiate the chemical and physical processes that occur during thermal treatment.

Results. It was shown that promestriene has a good thermal stability, associated with the presence in its structure of the steroidal moiety. For the main decomposition step, the kinetic study based on isoconversional methods suggested a multi-step process of degradation, which was confirmed by the results obtained by using the non-parametric kinetics (NPK) method, since the observed variation of apparent activation energy (Ea) vs. conversion degree was out of the 10% confidence interval.

Conclusions. It was possible to estimate kinetic parameters by using three different kinetic methods for promestriene. This allowed us to compare the apparent activation energy values obtained for the analyzed compound. Only the modified NPK method allowed an objective separation of the temperature, respective conversion influence on the reaction rate and in the same time to ascertain the existence of two simultaneous steps, both associated with physical and chemical transformations.

Keywords: degradation, kinetic analysis, promestriene stability

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P13. Formulation of orodispersible tablets containing paracetamol and their *in vitro* characterization – a QbD approach

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Introduction. Quality by Design (QbD) concept in drug formulation and development was introduced in order to achieve and ensure a proper product quality through a good process understanding. By identifying the variability sources that influence the product characteristics, the product quality can be built from the development phase. By applying this concept, in the present experimental work was intended to develop and evaluate orodispersible tablets (ODTs) with paracetamol.

Material and methods. In order to reach a good balance between their properties: quick disintegration, convenient hardness and a fast drug release, a statistical method was used. 36 formulations were prepared according to a D-optimal experimental design. The formulation factors used in the design were: the type of the diluent agent, the type of disintegrate agent, and the percentages of the disintegrant, sweetener and flavor. The tablets obtained were analyzed *in vitro* for their friability, disintegration time, wetting time and dissolution profile.

Results. During this experiment it was observed that the mechanical properties were mainly influenced by the type of diluent agent used, the disintegrant agent and it's ratio in each formulation. The percentage of sweetener and flavor also influenced the dissolution profile, beside the other formulation variables.

Conclusion. QbD approach was successfully applied within this study and the ODTs with paracetamol that have desired pharmaceutical characteristics may be successfully prepared.

Keywords: orodispersible tablets, paracetamol, quality by design, experimental design

P14. Co-solvent system freezedrying: tert-butanol – water mixture used in the formulation of ademetionine 1,4-butandisulfonate drug product

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Introduction. The use of co-solvents in freeze-drying of pharmaceutical products may overcome some issues that can appear during drug product development: low aqueous solubility of the drug substance, low chemical stability of drug substance in aqueous solution etc. Tert-butanol (TBA) is one of the preferred co-solvents used in freeze-drying due to its' miscibility with water and due to high freezing point of mixtures water/TBA. The presence of TBA in the bulk solution alters the crystal size and shape of ice, therefore TBA affects the primary drying period and the final cake properties. The main drawback when TBA is used in freeze-drying is its' residual presence in the final drug product. Lyophilization cycle must be developed in such way that residual TBA in drug product is at acceptable level. Ademetionine (or S-adenosyl methionine) is very hygroscopic and chemical unstable, especially in the presence of water, therefore the manufacturing as a powder for solution for injection is the best way to ensure quality of the drug product for a longer period of time.

Materials and methods. Ademetionine 1,4-butandisulfonate was dissolved in water or in water/TBA mixtures before freeze drying. TBA/water ratios (V/V) used were 5/95, 10/90 and 20/80. Ademetionine concentrations used were set to allow a filling volume of 3 mL or 4 mL for a final amount of 950 mg ademetionine 1,4-butandisulfonate (500 mg ademetionine) per vial. Freeze-dryer

used was Lyofast Mini 1.6 manufactured by IMA Life. Shelves temperature during primary drying was set at -10°C based on results obtained from differential scanning calorimetry analysis. Freeze-dried vials were checked for appearance. Water was analyzed by Karl-Fischer titration and residual t-butanol was analyzed by Gas Chromatography with Flame Ionization Detector.

Results. Freeze-dried vials from solutions without TBA presented melt back of cake powder. Water percentage found by Karl-Fischer titration was 2.2%. Freeze-dried vials from solutions with 10% TBA presented an elegant cake powder. Water percentage found by Karl-Fischer titration was 1.0%. Freeze-dried vials from solutions with 20% TBA presented also an elegant cake powder. Water percentage found by Karl-Fischer titration was 0.6%. Vials obtained by freeze-drying solution with 10% TBA and solution with 20% TBA showed similar residual TBA, around 1%.

Conclusions. Presence of TBA in the bulk solution resulted in cake powder with enhanced properties in comparison with vials freeze-dried from aqueous solution without TBA. Optimum TBA/water ratio in the bulk solution is 10/90. At 5% TBA concentration, cake powders presented a small degree of melt back, while lyophilizing a solution with 20% TBA did not have a better influence in terms of cake appearance or residual TBA.

Keywords: freeze-drying, lyophilization, t-butanol, ademetionine

P15. Preparation and evaluation of aceclofenac-loaded rotary-spun microfibers

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Introduction. Aceclofenac is a potent NSAID with significant anti-inflammatory and analgesic properties. It presents a better gastric tolerance, which explains its safety compared to traditional NSAIDs. Aceclofenac is practically insoluble in water, belongs to Biopharmaceutical Classification System (BCS) Class II. After oral administration it is well absorbed, but its bioavailability is reduced due to high first pass metabolism and poor aqueous solubility. Among the myriad of techniques intended for solubility enhancement, incorporation of drugs in fibrous formulations have gained increased interest in the recent years. The present study aimed at the high-yield preparation and evaluation of a rotary spun, aceclofenac-loaded fibrous formulation as orally dissolving webs for improving solubility and dissolution rate of the active.

Material and methods. Rotary spinning of ethanolic, poly(vinyl-pyrrolidone)-based viscous polymeric solutions, containing aceclofenac was performed on an in-house built centrifugal spinning device. The final solution contained 25% (w/w) PVP K90 and 5% aceclofenac, dissolved in ethanol. A rotation speed of 3800 rpm was found to be optimal, when used with two, 0.6 mm internal diameter needles. The needle to collector distance was set to 12 cm. The obtained fibers were subjected to scanning electron microscopy imaging, thermal analysis, drug content determination and *in vitro* dissolution studies.

Results. Rotary spinning of the prepared viscous solutions was achievable with the in-house prepared device at a production rate of around 1.5 g/min. Morphological analysis of the obtained mats revealed uniform fibers with smooth surfaces, with an average diameter of 8.9 ± 3.1 µm. Differential scanning calorimetry revealed the disappearance of the melting endotherm of aceclofenac in the fibrous sample, indicating a possible crystalline-amorphous transition of the active. UV spectroscopic determinations confirmed the presence of aceclofenac in the fibers, while drug-content determinations showed excellent loading efficacy (96.10%). Dissolution studies revealed a rapid disintegration of the nanofibrous samples with an immediate release of the active substance.

Conclusions. High-yield production of microfibrous, aceclofenac-loaded, PVP-based mats were obtained by centrifugal spinning. Smooth surfaced, uniform fibers were obtained with

diameters in the micrometer domain. The spinning process resulted in the amorphous to crystalline transition of the active substance, which, together with the large surface-to-volume area and high porosity of the microfibers, improved the dissolution rate of the active.

Keywords: centrifugal spinning, rotary spinning, aceclofenac, microfibers

P16. Combining curcumin-cyclodextrin inclusion complexes with chemotherapy: a feasible way of improving doxorubicin anticancer efficacy

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Introduction. Curcumin (CURC), a natural compound found in *Curcuma longa*, has shown various pharmacological properties, including good antitumor effects. However, its low aqueous solubility hinders its clinical applications. One particular method to overcome this limitation is by forming inclusion complexes with cyclodextrins (CD). The classical therapeutic approach in cancer is chemotherapy, doxorubicin (DOX) being a widely used anticancer agent. Despite its potency, DOX is fairly toxic and its efficacy is achieved at high doses which usually cause severe side effects. The co-administration of chemotherapeutic agents and natural compounds may overcome chemotherapy limitations, by decreasing the administered dose. It has been shown that CURC can enhance DOX efficiency when associated. The purpose of this study was to increase the aqueous solubility of CURC by complexation with CD, and evaluate the anticancer efficacy *in vitro* of a combination of DOX and CURC-CD complex.

Material and methods. The effect of 2 types of CD, namely β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) on CURC solubility was investigated by phase solubility studies to determine the CD with the highest solubilizing effect. The phase solubility diagrams were obtained by plotting the dissolved CURC concentrations against CD concentrations (0-1% for β-CD and 0-15% for HP-β-CD, respectively), followed by calculating the stability constant (Ks) and complexation efficiency (CE). CURC-CD complexes were prepared using HP-β-CD and CURC in a molar ratio of 1:1 and 3:1, respectively by 2 methods, namely solvent evaporation and freeze-dying. The complexes were characterized by differential scanning calorimetry (DSC). The CURC-CD complex (0-100 μM) was tested in combination with DOX (0-10 μM) *in vitro* on C26 murine colon cancer cells co-cultured with macrophages, by using an ELISA BrdU proliferation assay.

Results. The phase solubility studies indicated an increase in CURC solubility with the CD concentration. However, HP-β-CD showed the highest solubilizing effect (Ks=2645.8 M-1, CE=0.0055) compared to β-CD (Ks=1446.8 M-1, CE=0.0030), and was considered the most suitable for preparing the inclusion complexes. The formation of CURC-CD complexes by the 2 investigated preparation methods was confirmed by DSC analysis. However, the solvent evaporation method assured a higher concentration of entrapped CURC. Therefore, the proliferation study was performed on the complex obtained by the latter method which had the highest complexation yield. The cytotoxicity assay showed moderate inhibitory effects on the C26 cancer cells co-cultured with macrophages for the CURC-CD and DOX combination (IC_{50}=0.16 μM for DOX) than DOX alone (IC_{50}=0.29 μM). However, based on the combination index value (1.06) the effect of the combined administration of the 2 agents on the co-cultured cells is additive.

Conclusions. This study concluded that the formation of CD complexes is a suitable method of increasing the solubility of CURC. The CURC-CD-DOX association showed good efficacy in inhibiting the proliferation of C26 murine cancer cells co-cultivated with murine

macrophages compared to DOX alone. However, an adjustment in the administered doses of the 2 agents is needed to obtain a synergistic effect. Overall, this combination therapy could be a potential approach in reducing the necessary DOX dose and associated toxicity.

Keywords: doxorubicin, curcumin, cyclodextrin, inclusion complex, cancer

P17. Quantitative characterization of sustained release tablets with diclofenac by means of near-infrared spectroscopy and chemometry

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Introduction. NIR is a useful tool of Process Analytical Technology (PAT) used for easy and rapid pharmaceutical processes monitoring and non-destructive chemical and physical characterization of pharmaceutical finished products and intermediate products. A NIR-chemometric method, for direct and simultaneous quantification of diclofenac sodium, Kollidon® SR and lactose DC in sustained release matrix tablets, was developed and validated.

Materials and methods. In order to develop NIR-chemometric methods for quantitative characterization of sustained release inert matrix tablets, an experimental design with two factors (diclofenac sodium and Kollidon® SR) and five levels (80%-90%-100%-110%-120%) was used. Multiple batches were manufactured in order to perform calibration (15) and validation (36) of NIR-chemometrics methods in order to ensure representative samples for every formulation, every level of concentration and to simulate routine analysis. NIR spectra were recorded by means of an MPA FT-NIRS analyser (Brucker Optics, Germany) in Transmittance Sampling Mode.

Results. Calibration models were developed (based on partial least squares regression – PLS) considering various spectral ranges and different pre-processing modes (single or in combinations) for spectra: first derivative (FD), second derivative (SD), multiplicative scattering correction (MSC) and standard normal variate (SNV). Recoveries over 98% were obtained for all analytes at all concentration levels. Developed models are linear and have satisfactory precision and accuracy and are suitable for direct and simultaneous assay of diclofenac sodium, Kollidon® SR and lactose DC in sustained release, inert-matrix tablets. Linearity and accuracy profiles showed acceptance limits of ±10% for diclofenac sodium and ±5% for Kollidon® SR and lactose DC.

Conclusions. A NIR-chemometric method was developed for direct quantification of diclofenac sodium and two major excipients: matrix-forming excipient Kollidon® SR and lactose (diluent). The developed and validated methods can be used routinely for monitoring of manufacturing process of diclofenac sustained release tablets.

Keywords: chemometrics, near infrared spectroscopy, diclofenac assay, DoE

P18. Shelf-life evaluation of a synthetic progestogen derivative in binary mixtures

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Introduction. Desogestrel (DSGS) is a third-generation synthetic progestogen derivative, commonly used in various pharmaceutical formulations for hormonal contraception including combinations with ethinylestradiol (EE), progestin-only pill and subdermal implants. DSGS is also used in hormone replacement therapy (HRT) in menopausal women. Following a previous study regarding the compatibility of DSGS with pharmaceutical excipients in solid state, in oxidative atmosphere, we set our goal in evaluation of over-the-time occurring interactions in solid-state in binary mixtures, in inert atmosphere.

Since oral formulations contain low dose of DSGS (generally under 125 μg per tablet), over-the-time interactions can drastically affect the biodisponibility and therapeutic effect of drug after administration, taking into account that "reactive" functional moieties of excipients can interact with the ones of the active pharmaceutical ingredient.

Material and methods. Desogestrel (CAS Number 54024-22-5) was a Sigma Aldrich commercial product, sold as United States Pharmacopeia (USP) Reference Standard. Binary mixtures of DSGS and selected excipients were previously prepared, six months' prior shelf-life evaluation, and consisted in sodium carboxymethyl-cellulose, tylose, methocel, talc, magnesium citrate, mannitol, starch, calcium lactate, magnesium stearate, colloidal silica and PVP. After preparation and preliminary investigations, samples were kept in sealed vials under ambient conditions (25 ± 2°C, closed desiccator with $CaCl_2$, ambient light). Thermoanalytical data (TG/DTG/HF) were collected using 8-10 mg of samples in open crucibles in dynamic inert atmosphere on a Perkin Elmer Diamond device, at a heating rate of 10°C/min.

Results. The dynamic inert atmosphere was chosen for the analysis of the shelf-stored samples, since thermal induced interactions may be associated with the presence of dioxygen in synthetic air. Since dinitrogen is inert, thermoanalytical changes revealed by the curves are solely due to interactions between the components in the mixture.

Conclusions. It was possible to carry on a comparative discussion regarding the compatibility of DSGS and each excipient in dynamic oxidative atmosphere vs. dynamic inert atmosphere. The study revealed that DSGS presents interactions during shelf storage with two excipients.

Keywords: desogestrel, preformulation study, solid mixtures

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P19. Preformulation studies of clopidogrel containing polymer based microfibers

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Introduction. Clopidogrel bisulfate is antiplatelet drug used in the treatment and management of prevention of heart attacks and strokes. Belongs to class II according to BCS classification, having pour aqueous solubility and good permeability. Our study aims the formulation and characterization of clopidogrel containing polymer based fibers obtained by electrospinning.

Material and methods. Clopidogrel was used as active substance, poly(vinyl-pyrrolidone) (PVP K90), ethanol. Dispersion of 7, 8, 9, 10, 12% (w/w) polymer were prepared. Clopidogrel content of the dispersions was 4%. Fibers were obtained by electrospinning using an eSpin laboratory electrospinning apparatus with tube chamber, at 20 kV voltage, 10 cm distance, 0.2 µl/sec flow rate. The obtained fibers were studied by optical microscopy to measure fiber diameter, by thermoanalysis (DSC). Drug content determination and comparative dissolution studies were performed. Similarity and difference factors were calculated.

Results. Polymer based fibers containing clopidogrel within a diameter range of 0.810-1.205 µm were prepared. Drug content variated between 28-34%. The dissolution of active substance from the hydrophilic matrix was compared to an industrial clopidogrel containing solid pharmaceutical form. A complete drug dissolution was achieved under the used experimental conditions. Clopidogrel melts with a sharp endotherm peak at 185°C, physical mixture of clodipogrel and PVP shows a melting endotherm at the same temperature. Thermograms of fibers present an endotherm peak at 155°C.

Conclusions. Optical microscopy demonstrated the fibrous structure of the polymer based carriers. Due to the increased specific surface area dissolution was complete.

Keywords: clopidogrel, polymer, electrospinning, fiber

P20. Electrochemical analysis of doxorubicin loaded targeted drug delivery systems

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Even though chemotherapy is a promising type of cancer treatment, there are still some problems regarding the non-selectivity of the molecules and the ratio of the administrated dose and the in situ concentration of the drug. Considering this, targeted drug delivery systems became an intensively studied subject, the interest in the development of new methods of evaluating the efficacy of them increasing also.

The aim of this study was to develop and optimize an electrochemical method to evaluate the loading and release processes of doxorubicin from polysaccharide based microcapsules. The encapsulation of the anti-tumor drug into the particles as well as the release of the substance were realized under different conditions of pH considering the efficiency of the process in the first case, and the in situ conditions of the tumor's tissue in the second case.

The particles involved in this study were made from chitosan and hyaluronic acid and were obtained by layer-by-layer deposition technique. These natural polymers have the advantage of being biocompatible and biodegradable unlike synthetic components.

The electrochemical detection method was elaborated starting with the electrochemical characterization of doxorubicin from standard solutions. This step included the evaluation of the

impact of the following parameters on the detection of the drug: electrode material, electrolyte type other parameters related to the electrochemical technique chosen (e.g. scan rate, amplitude, interval time, etc.). The developed method was used to evaluate the success of the loading and release processes and the results were compared with the ones obtained by UV-Vis spectrophotometry.

Keywords: doxorubicin, drug delivery systems, electrochemical analysis, UV-Vis detection

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P21. The impact of API particle size on the freeze-dried filler structures

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Introduction. Building quality from the development phase is a modern global desire in the entire pharmaceutical industry. The implementation of the Quality by Design concept allowed the achievement of a good process understanding emphasizing the variability sources that impact the final product characteristics. In this respect, the current work had the purpose to evaluate and characterize lyophilized structures obtained by compounding an active ingredient with a bulking agent.

Material and methods. A D-Optimal screening experimental design, with three independent variables and three variation levels was conceived. According to the experimental plan, 18 runs and 3 replicates center points were developed in order to evaluate the formulation factors influence on the features of the lyophilised structures. The formulation factors selected were API particles (X1), the type of the bulking agent (X2) and the ratio of the bulking agent (X3). The parameters determined and evaluated for the structures were the disintegration time, the mean dissolution time, the texture characteristics as: hardness, rigidity, fracturability, resilience and load of target. Additionally, the structures were characterized in more details using XRPD and electronic microscopy.

Results. Widely, the disintegration time of the structures was compliant with the specified limit for orodisperable forms and no significant influence of the selected factors was observed. The dissolution was influenced by all the formulation factors; the significant one is the particle size of the active ingredient (ibuprofen) and the highest and rapid dissolution was observed for the formulation were trehalose was used as bulking agent. For the texture characteristics of the structures the type and the ratio of the bulking agent had the most important effects and by increasing the ratio of the bulking agent, the effect is enhanced. Maltodextrin conducted to robust structures for which, according to the XRPD results, the particles are to a certain degree in an amorphous state.

Conclusions. Using Quality by Design tools, the present work confirms once again the benefit of this concept and the obtained results represent a contribution to the actual knowledge in this area, that can be further used in development of lyophilized pharmaceutical forms.

Keywords: freeze-dried, lyophilizate, Quality by Design

P22. Ternary systems containing naproxen, omeprazole and functionalized cyclodextrins – preformulation study

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Introduction. Omeprazole (OME) is an active pharmaceutical ingredient used as proton pump inhibitor (PPI) for treating symptoms of gastroesophageal reflux disease (GERD) and other conditions caused by excess stomach acid. OME is also used to promote healing of erosive esophagitis caused by stomach acid, as monotherapy or as combination therapy with gastroprokinetic agents. Naproxen (NAP) is a nonselective COX inhibitor belonging to propionic acid class of medications, used in the treatment of pain, menstrual cramps, inflammatory diseases such as rheumatoid arthritis and fever, in *per os* administration. Since common side effects following NAP administration include along dizziness, headache, bruising and allergic reactions also heartburn, and stomach pain, we set our goal in this study to evaluate the solid-state compatibility of binary mixture NAP+OME with functionalized cyclodextrins (CD), such as randomly methylated-beta-cyclodextrin (RAMEB), (2-Hydroxypropyl)-β-cyclodextrin (2HOPrBCD) and Heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (H236TOMBCD).

Material and methods. Omeprazole (CAS Number 73590-58-6) and naproxen (CAS Number 22204-53-1) were commercial products from Sigma-Aldrich, certified as European Pharmacopoeia (EP) Reference Standards. Cyclodextrins were acquired from Cyclolab Ltd. All the compounds were used as received. Binary and ternary mixtures were prepared in agate mortars, by trituration of the compounds in equimolar ratio, in the presence of absolute ethanol as solvent.
The thermoanalytical data were collected on a Perkin Elmer Diamond thermobalance, at a heating rate β=10°C·min^{-1} in dynamic air atmosphere, in the temperature range 40-400°C.

Results. Thermoanalytical data suggest a good thermal stability for OME, up to 156°C, when the melting of the API begins. The degradation of OME is superimposed with the melting, the HF curve suggesting an endothermal process in the 156-158°C temperature range, followed by an exothermic one, in the 158 -191°C range. The DTG curve reveal two peaks, at 171°C and 229°C. At 400°C, the mass loss is ~45%. In the case of NAP, the decomposition takes place in liquid state (temperature range 183-272°C), after the melting of the API in the interval 152-155°C. In the case of NAP, the mass loss is ~100% at 272°C. The formation of host-guest supramolecular ternary structures is confirmed by the results of thermal analysis since the melting points of NAP and OME are no longer present in the thermoanalytical HF curves of the mixtures.

Conclusions. Thermoanalytical data suggest the formation of host-guest supramolecular ternary structures of OME and NAP with randomly methylated-beta-cyclodextrin (RAMEB), (2-Hydroxypropyl)-β-cyclodextrin (2HOPrBCD) and Heptakis(2,3,6-tri-O-methyl)-beta-cyclodextrin (H236TOMBCD), and as well the improvement of the thermal stability of APIs.

Keywords: complex formation, omeprazole, naproxen, thermal analysis

P23. Multivariate data analysis for quality and manufacturing process improvement of high drug load film coated tablets obtained through wet granulation

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Introduction. One of the most widely used and challenging pharmaceutical processes is the batch-wise wet granulation of powders, with potential impact on both product quality and further processability of the product. The existing historical data from manufacturing of legacy products offer an opportunity for valuable information by applying multivariate statistical analysis tools with the aim of process modeling and prediction. Multiple input and output variables can be assessed at once, making this approach much more efficient and systematic than the traditional univariate evaluation of a data set.

Materials and methods. Historical data from 59 industrial-scale batches of an immediate release film-coated tablet with high drug load and wet granulation as intermediate step, were in scope of this multivariate data analysis study. Two outcomes were targeted: identifying variables which can explain the high variability observed for the core tablets disintegration time and possibilities for processing time reduction.The data collection plan consisted of raw material batches and their physico-chemical properties, wet granulation and tableting process parameters, in-process control testing of intermediate products and the dissolution of the active ingredient as critical quality attribute. Batch evolution models, batch level models and OPLS models were built in order to assess the evolution in time of process parameters, the correlation between process parameters or raw material attributes and intermediate or final product characteristics.

Results. The variability in the evolution of torque values during wet granulation and the raw material properties are correlated with the differences observed in the disintegration time of core tablets. Models built show decent predictabilities (Q2 values between 0.5 – 0.7) and explain most of the variation in the output variable (70 – 90%). High torque values in the dry mixing phase, lower torque values in the liquid addition phases, higher chopper speed during wet granulation and higher filter differential pressures are correlated with smaller particles sizes of the milled granules. Granulate particle size is positively correlated to the disintegration time of core tablets, which in turn is a very good predictor for the dissolution of the active ingredient and a very suitable output variable for further modeling. Disintegration time could be improved without significantly affecting the tableting process performance. Unexpectedly, no clear correlation between granulate particle size and tableting speed was found. The active product ingredient (API) particle size distribution was confirmed as one of the major contributing factors to the granulate properties and disintegration time, due to the high content in the formulation. The differences observed in the granulation and tableting steps between product batches with similar API particle sizes could be due to the properties of the other raw materials in the formulation, which need further assessments.

Conclusions. Some of the expected correlations were confirmed by this modeling exercise, but also new insights were gained, which can be used for further training of the models with the aim of discerning the practically significant correlations and causality relations.

Keywords: batch modeling, wet granulation, process improvement