

BOOK OF ABSTRACTS 39TH TECHNOLOGY DAYS 7TH AND 8TH SEPTEMBER 2023

Editorial

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Received 30 June, 2023, accepted 3 July, 2023

The Department of Galenic Pharmacy of the Faculty of Pharmacy of the Comenius University Bratislava, in cooperation with the Slovak Pharmaceutical Society of the Slovak Medical Society, hosted the symposium 39th Technology Days – an international forum for knowledge exchange among experts from several scientific disciplines such as innovative dosage forms, quality control of drugs, and dosage forms, applications in pharmacy and medicine and medical devices.

Technology Days is a traditional event hosted by our department since 1967. The first symposium was held in Smolenice in 1991. Technology Days has been since organized on a biennial basis and alternated with the Pharmaceutical Technology Conference organized by the Faculty of Pharmacy of Charles University in Hradec Králové. In 2021, for the first time in its history, the symposium was also available for online participants. We would like to continue this new trend by allowing a wide range of participants (pharmacy students, practitioners, scientific leaders in pharmaceutical technology, analytical chemistry, process engineering, and other disciplines) to attend this event.

The 39th Technology Days under the auspices of the Dean of the Pharmaceutical Faculty of the Comenius University Bratislava, Professor Ján Klimas, hosted several important guests from the Czech Republic and Hungary. The symposium covered the following topics:

- The first section called **Nanoparticulate Systems in Drug Delivery** was opened with a presentation by a prominent academic, Associate Professor Martin Pisárčik,

concerning the synthesis, properties, and applications of functionalized gold nanoparticles which are promising tools for biomedical use. Professor Pisárčik is an expert in the synthesis of metal nanoparticles and in novel approaches to nanomedicines. A further presentation on nanoparticulate drug delivery systems was delivered by Associate Professor Tamás Sovány from the University of Szeged, who discussed the preparation of titanate nanotubes and their use as drug carriers. Another topic was the use of biosynthetic silver nanoparticles to produce nanomedicine drugs and various types of nanoparticulate systems, including those that might be utilized in managing microbial resistance, discussed by the research team of Dr. Tomáš Wolaschka from the University of Veterinary Medicine and Pharmacy in Košice. The chitosan nanoparticles were the topic of the team from Comenius University represented by Dr. Jarmila Ferková and Dr. Michael Lawson. They informed their colleagues about the applications of these nanoparticles in anticancer therapy and their preparation and toxicological evaluation. Dr. Barbora Boltárová from Masaryk University gave another lecture about poly(lactic-co-glycolic acid) (PLGA) nanoparticles as carriers for corticosteroids for macrophage targeting.

New scientific approaches in the development and production processes of medicines were discussed in the section **Quality by Design**. The research team of Associate Professor Zdeňka Šklubalová presented new possibilities to improve the dissolution rate of drugs. The

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team from Masaryk University in Brno represented by Dr. Hana Hořavová presented a spray drying method to produce solid particles for pulmonary delivery, and Dr. Dagmar Blaháčková discussed inkjet print as a method for the preparation of tailor-made pharmaceuticals. A very interesting lecture was from Associate Professor Zuzana Vitková from the Slovak University of Technology about the link between pharmaceutical technology and biocybernetics. Associate Professor Juraj Piešťanský gave a lecture about the alternative delivery routes of monoclonal antibodies. Mgr. Dominika Nádaská dealt with possibilities to improve the bioavailability of stilbenoids.

- In the **Applications in Pharmacy and Medicine** section, Dr. Kristína Lajtmanová from the National Institute of Cardiovascular Diseases in Bratislava presented the practical aspects of the parenteral application of drugs. Dr. Ondrej Sukeľ representing the Slovak Chamber of Pharmacists informed the audience about the policy issues related to regulatory, funding, educational, or legislative discussions. Dr. Veronika Šimunková from Comenius University informed the audience about the formulation options for mucoadhesive dosage forms for use in the oral cavity.
- The section **Evaluation of Drugs and Medical Devices** New technologies contained a lecture from Associate Professor Miroslava Sýkorová about quality regulation policy and control of active pharmaceutical ingredient (API), excipients, and compounded medicines in Slovakia. Dr. Zima dealt with microscopic methods and their optimization of oleogels' observations. Dr. Garlík Matušková talked about the determination of catecholamines using electromigration methods. The last lecture was oriented to medical devices and Dr. Szmicseková focused on those used for parenteral and enteral application of drugs and nutrition.

The ambition of the 39th Technology Days was to bring together multiple aspects of pharmaceutical technology, as it was declared under the title "From molecule to tablet" and to facilitate discussion between pharmacists working in different environments, that is, in pharmacies, hospitals, industry, regulatory areas, and research and even students of pharmacy. The aim of bringing together their respective expertise on matters of importance to public health was successfully achieved.

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THERMOSENSITIVE *IN SITU* GEL WITH BIOSYNTHETIZED SILVER NANOPARTICLES SHOWS ANTIBACTERIAL ACTIVITY

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Abstract

The green synthesis of nanoparticles using microorganisms and plants is regarded as a preferred approach. For the synthesis of silver nanoparticles (AgNPs), we used *Agrimonia eupatoria* L., because of its suitable metabolites, cost-effectiveness, easy availability, and medicinal properties. The plant extract with AgNPs was used for the first time to prepare thermosensitive *in situ* gels (ISGs). ISGs are supposed to heal human or animal skin and mucus membranes because of their ability to change from a liquid to a solid state after application. The presence of biosynthesized AgNPs, which showed maximum absorption at 425 nm, was detected by ultraviolet-visible (UV-VIS) spectrophotometry. Using the method of transmission electron microscopy, we found that the nanoparticles had a spherical shape and a size of 20 ± 4.6 nm. Fourier transform infrared spectroscopy proved the binding of metabolites from the extract to the surface of the nanoparticles. Using a fast, inexpensive, and ecofriendly method, we created AgNPs, which contained medicinal substances from *A. eupatoria* L. These nanoparticles were incorporated into an ISG, with the critical temperature of the sol–gel transition being more than 30°C, which means that this model is suitable for application on the mucosa. Using the microdilution method, we found that ISG with nanoparticles exhibits antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. This ISG with AgNPs has the potential to be used in the therapy of wounds due to the antimicrobial properties of silver and the regenerative, anti-inflammatory effects of *A. eupatoria* L.

Keywords

silver nanoparticles – *in situ* gel – green synthesis – *Agrimonia eupatoria* L.

Acknowledgment

This work was supported by the Grant Agency of the Ministry of the Education, Science, Research, and Sport of the Slovak Republic (VEGA 1/0071/21) and the Internal Grant Agency of the University of Veterinary Medicine and Pharmacy in Košice IGA UVLF 01/2023 “Increasing the effectiveness of the treatment of oral diseases by developing a silver nanoparticle-loaded *in situ* gel based on smart polymers.”

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INNOVATIVE INKJET PRINTING TECHNIQUES FOR TAILOR-MADE PHARMACEUTICALS

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Abstract

The widespread use of mass-produced drugs, standardized for the general population, aims to achieve therapeutic effects, but results in a high prevalence of adverse drug reaction due to nonindividualized pharmacotherapy. The objective of this contribution is to explore the potential of inkjet printing in personalized patient treatment and provide an overview of the different drug forms successfully prepared using this technology. It aims to highlight the advancements made in inkjet printing-based drug delivery systems and their impact on healthcare and pharmaceutical research. A systematic literature review was conducted, covering the period of the last two decades. Relevant articles were identified through a comprehensive search in databases such as PubMed, Scopus, and Web of Science, using specific keywords related to inkjet printing and drug delivery. Inkjet printing has revolutionized the preparation of various drug forms, including solid oral dosage forms, transdermal patches, contact lenses, and inhalable formulations. The precise control offered by inkjet printing technology allows for the deposition of drug substances and excipients, enabling the creation of customized drug formulations. Furthermore, inkjet printing has shown promise in personalized treatment approaches. By tailoring the drug dosage, release profile, and formulation characteristics, inkjet printing enables the production of individualized medications. This approach has the potential to optimize therapeutic outcomes, enhance patient adherence, and minimize adverse effects. Inkjet printing has emerged as a versatile technology for fabricating drug forms with precise control over composition and design. The ability to create personalized medications through inkjet printing holds great promise for the future of health care. Integrating inkjet printing into pharmaceutical manufacturing can potentially revolutionize the field by offering tailored treatments to patients, ultimately improving therapeutic efficacy and quality of life. This abstract emphasizes the importance of inkjet printing as a promising tool for the future of personalized drug delivery systems.

Keywords

inkjet printing – drug administration – personalized treatment – tailored medicine – pharmaceutical innovation

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CORTICOSTEROID-LOADED PLGA NANOSPHERES FOR MACROPHAGES TARGETING: A TOOL FOR INFLAMMATION MANAGEMENT

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Abstract

Corticosteroids are widely used, highly potent anti-inflammatory drugs. However, corticosteroid therapy is associated with serious side effects. For safer and more effective anti-inflammatory therapy, we tried to load corticosteroids into biodegradable PLGA nanospheres (NSs) with predominant distribution into macrophages, key players in the development of inflammation. These formulations could be useful in the therapy of chronic inflammation, for example, nonalcoholic steatohepatitis – chronic liver inflammation. Using the nanoprecipitation method, we prepared dexamethasone acetate-loaded PLGA NSs. The formulations were prepared in the size range of 100–300 nm, which was proven as macrophage attractive, with a maximum encapsulation efficiency of about 20% determined by high-performance liquid chromatography (HPLC). Using the macrophage cell lines such as murine bone marrow macrophages and human macrophages (differentiated THP-1 cells), we observed effective reduction of the proinflammatory cytokine levels, for example, tumor necrosis factor-alpha (TNF- α) and interleukin (IL)-1 β by our NSs, determined by quantitative reverse transcription polymerase chain reaction (RT-qPCR). Experiments were performed in the lipopolysaccharide-induced inflammation model, and no signs of reduced viability of cells were observed. By confocal microscopy, we verified the uptake of our fluorescent dye-labeled NSs by macrophages. Furthermore, we tested our NSs labeled with fluorescent dye on *in vivo* models for accumulation studies. We observed the fluorescence intensity of prepared NSs by IVIS Imaging System and the spectral cell analyzer. We were able to confirm the specific delivery of prepared NSs into the liver and preferential accumulation in proinflammatory macrophages.

Keywords

PLGA – nanospheres – Nonalcoholic Steatohepatitis NASH – macrophages – corticosteroids

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nitrosamine impurities in the production of solid dosage forms – factors affecting their formation

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Abstract

N-nitrosamines are potent genotoxic agents, and some are classified as probable or possible human carcinogens. Since 2021, the presence of *N*-nitrosamines in human medicinal products should be mitigated as much as possible and should be at or below the acceptable intake level and calculated considering a lifetime daily exposure. The Food and Drug Administration has identified seven nitrosamine impurities that theoretically could be present in drug products. Formation of nitrosamines is possible in the presence of amines and nitrite salts under acidic reaction conditions. The limit of 32 ppb of *N*-nitrosodimethylamine (NMDA) was established in oral antidiabetic tablets. During the production campaign, several batches did not comply with this limit determined by the liquid chromatography - mass spectrometry (LC-MS) method. Investigation of the root cause of noncomplying NMDA results, was focused on the influence of the wet granulation manufacturing process, the content of reactive impurities and oxidizing agents (organic peroxides) in excipients Maize starch and Povidone and physicochemical properties of active pharmaceutical ingredient (API) such as particle size distribution (PSD) and content of dimethylamine (DMA) as the source of *N*-nitrosamines. It was found that APIs with different PSD were used in the manufacturing process. PSD of the first API lot established by the laser diffraction method showed 92 µm at d(0.9), and PSD of the second API lot was 212 µm at d(0.9). The increase of NMDA in the finished product with peroral antidiabetic was due to the larger surface area of the particles and their higher exposure to a granulation medium, which had a slightly acidic pH.

Keywords

nitrosamine impurities – NMDA – DMA – reactive impurities – wet granulation

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DELIVERY OF ANTICANCER DRUGS USING NANOPARTICLES BASED ON CHITOSAN AND ITS DERIVATIVES

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Abstract

Cancer is currently the leading cause of death worldwide. Conventional treatments suffer from low efficacy and untargeted drug administration, which often lead to severe side effects. The use of nanotechnology can potentially minimize the side effects of drugs using efficient and controlled anticancer drug delivery systems. Nanoparticles (NPs) as drug carriers offer several advantages such as variability of size and shape, formation of stable interactions with ligands, high carrying capacity, and convenience of binding of hydrophilic and hydrophobic drugs. Chitosan (CS) is a linear, positively charged polysaccharide that can serve as an ideal carrier for the delivery of anticancer drugs due to its nontoxicity and numerous enhanced modifications. CS derivatives retain the original properties of CS and exhibit new or improved properties depending on the nature of the additional functions. CS NPs are easy to prepare and can be modified to exhibit functions against specific cancer cells. NPs have been found to accumulate in tumor tissues through a passive mechanism known as the increased permeability and retention effect. To improve the selectivity of nanocarriers, several approaches have been developed, mostly including functionalization with special ligands. This work aims to summarize the latest knowledge on the delivery of antitumor drugs using NPs based on CS and its derivatives.

Keywords

chitosan – nanoparticles – anticancer drug delivery – chitosan derivatives

Acknowledgments

This work was supported by the grants VEGA 1/0146/23, VEGA 1/0514/22, and FaF/18/2023.

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PULMONARY DELIVERY OF SOLID PARTICLES AND THEIR PREPARATION WITH A FOCUS ON SPRAY DRYING TECHNOLOGY

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Abstract

Inhalation is a noninvasive route of administration that can be an alternative to oral or intravenous administration. It brings a possibility of both local and systemic effects with several advantages such as direct drug delivery to the site of action with rapid onset, bypassing the first-pass metabolism, large absorption surface with rich blood supply, reduced enzymatic activity, high bioavailability, lower effective dose needed, and so on. When it comes to dosage forms, dry powder inhalers are more beneficial in comparison to liquid forms. Solid particles have improved stability and their properties can be better controlled via particle engineering.

Among the properties that particles need to possess for deep lung deposition, their physical and, more importantly, mass median aerodynamic diameter (MMAD) is the most crucial. Particles of optimal MMAD are deposited in small airways and alveoli by different mechanisms (interception, impaction, sedimentation, and diffusion). On the other hand, bigger particles either do not enter the airways or are easily eliminated from the upper airways, and smaller ones are exhaled. The problem is that such a small physical particle size corresponds to increased cohesiveness and poor flow properties. These particles are also prone to be removed by macrophages before the drug can act. A possible way to overcome these drawbacks is by using large porous particles. By lowering the density (increasing porosity), they can reach desired aerodynamic parameters with greater physical sizes.

One of the most used methods for dry particle preparation is spray drying. It is a one-step continuous process of conversion of a liquid dispersion of active substance and other excipients to dry particles. The dispersion is atomized into a tempered chamber and as the water evaporates from the droplets, solid particles are formed and separated from the air stream. Different configurations and input parameters have different impacts on final particle properties.

Keywords

pulmonary delivery – lung deposition – microparticles – large porous particles – spray drying

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HYALURONIC ACID GRAFTED WITH CERAMIDE NP AS PROMISING MACROMOLECULES FOR SKIN APPLICATION

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Abstract

In this work, amphiphilic hyaluronan (HA) was synthesized by grafting succinylated *N*-oleoyl-phytosphingosine (sCER; known as ceramide NP) via ester bonds. sCER was first synthesized by esterification of hydroxy moieties of ceramide with succinic anhydride. Secondly, the esterification of HA was carried out using oligomeric, low, and medium molecular weight HA. The oligomeric HA-sCER derivatives exhibited a strong self-aggregation as evidenced by a very low critical aggregation concentration ($1.9 \mu\text{g mL}^{-1}$), higher pyrene binding constant, and the particle's smallest size in solution. The self-aggregation properties were demonstrated to be a function of the substitution degree, the molecular weight of HA, and the substitution pattern. The prepared derivatives were noncytotoxic toward the cell line NIH-3T3. A significant inhibition of the proinflammatory cytokine interleukin-6 was observed *in vitro* using macrophages differentiated from THP-1 cells. Regardless of their size, nanoparticles prepared using amphiphilic HA-sCER derivatives improved penetration of the hydrophobic Nile red dye through the porcine stratum corneum. Interestingly, the fluorescence intensity localized at the stratum corneum was higher for oligomeric HA-sCER. These findings showed that HA-sCER are promising vehicles for use in transdermal medical or cosmetic agents for skin drug delivery.

Keywords

Hyaluronan – ceramide – self-assembling – penetration – anti-inflammatory

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QUALITY CONTROL OF HERBAL TEA CONTAINING MELISSA LEAF

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Abstract

The dried leaf of *Melissa officinalis* L. (Lamiaceae) is used for the formulation of herbal teas of various compositions. *Melissae folium* can be used as a traditional herbal medicinal product for the relief of mild symptoms of mental stress and to aid sleep and for symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence. The determination of the content of the biologically active hydroxycinnamic derivatives is set forth by Pharmacopoeia. However, Ph. Eur. 11 does not prescribe determining the content of the essential oil, although it is responsible for the biological effect. This is caused by a high value of limit of quantification (LOQ) of the pharmacopoeial distillation method and the very low content of essential oils in the drug (ca 0.1%). The main aim of the study was to find a suitable alternative method for the determination of essential oil in monocomponent herbal tea containing the Melissa leaf. Among the several methods tested, the dichromate method applied earlier in the food industry was modified for our purpose. The method consists of distilling the drug sample with water and then oxidizing the distillate with a volumetric solution of potassium dichromate under acidic conditions. A portion of potassium dichromate oxidizes the sample's essential oil and reduces itself to a chromium salt. The nonreduced amount can be determined iodometrically and then the concentration of essential oil in the drug is calculated. The method was partially validated. The analytical method provides accurate and precise results that can be repeated and reproduced. It reliably records the growth of the concentration within the minimum limit value. It detects and quantifies low concentration levels (limit of detection LOD = 0.004% w/w; LOQ = 0.006% w/w), and the series of results bear a very low level of uncertainty. The method provides a linear calibration dependency ($R^2 = 0.9954$). An empirical formula was determined to calculate the essential oil content in the drug based on the linearity results.

Keywords

Melissa officinalis – herbal tea – essential oil – quality control – validation.

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POSSIBILITIES OF PLANT DRUGS INCORPORATION INTO THE TABLETS

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Abstract

Nutritional supplements based on natural or herbal drugs are usually associated with the modern trend of a healthy lifestyle and they are usually used as prevention or complementary therapy for many civilization diseases. Natural drugs are offered to patients in the form of teas, juices, various drinks, and extracts, but the most popular are tablets. Tablets are highly appreciated because of their high application comfort, high dosing accuracy, easy storage, good bioavailability, long-term stability, and technological possibilities of adjusting controlled release. Plant material has a high content of simple sugars, lipophilic resins, and other substances that are responsible for hygroscopicity and poor compressibility. In addition, plant extracts are chemically diverse and unstable. Thanks to these properties, it is quite difficult to prepare tablets that meet the requirements of pharmacopeia or other standards. When powdered fruits, for example, common dogwood (*Cornus mas* L.) were directly pressing, the Avicel[®] PH 101 was determined as the optimal type of filler/binder, ideally in an amount of at least 50%. The plant material should be incorporated into the tablets, so that their particle size does not exceed 800 µm. Aerosil[®] 200, in the quantity of 1%, has proven itself to be suitable in the role of a sliding and anti-plastic agent. The direct formulation of a ground plant material into tablets has several technological advantages, but a higher effectiveness of tablets can be achieved by incorporating concentrated plant extracts, which are characterized by a dominant representation of active metabolites. A modified liquisolid method accompanied by microwave or hot air drying can be applied there. The resulting physico-mechanical properties of dried liquisolid tablets are influenced by the solvent used to dilute the extract (ethanol increases the strength and prolongs the disintegration of tablets), the type of drying (microwave drying increases abrasion and prolongs disintegration, hot air drying increases strength), and drying time (longer drying time increases tablet strength and density and reduces porosity and loss on drying). However, it must be noted that the effectiveness of the plant extract can be negatively affected by the presence of water as a solvent and the subsequent drying process.

Keywords

extract – liquisolid – microcrystalline cellulose – Neusilin US2 – tablet

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EXOGENOUS ANTIOXIDANTS AS POTENTIAL THERAPEUTIC AGENTS WHEN CARRIED BY NANOPARTICLE DELIVERY SYSTEMS

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Abstract

Two common exogenous antioxidants, L-ascorbic acid, and quercetin, are often praised for their beneficial properties, which include anticancer action. Bioavailability of both these compounds is limited, however. L-ascorbic acid is unstable in aqueous solution at a pH above 3.5 and blood plasma levels are limited by rapid excretion above a certain level. Quercetin has poor water solubility, poor skin penetration, and is rapidly metabolized and excreted. Nanoparticle technology may enable these substances to be targeted to specific sites at much higher concentrations than previously achievable, however. Chitosan is a particularly popular material for nanoparticles for many reasons. Its positive charge at low pH makes it suitable for dermal application.

A brief review of some recent studies of chitosan nanoparticle drug delivery systems carrying quercetin is presented. These studies demonstrate the reality of such nanoparticles, and various tests show their improved therapeutic value in treating a number of conditions. Some results of experiments performed in our own laboratories involving chitosan nanoparticles carrying L-ascorbic acid are also presented. Although the results suggested poor encapsulation efficiency, chitosan nanoparticles were easy to manufacture. Loaded nanoparticles were larger than the unloaded nanoparticles, suggesting that encapsulation of L-ascorbic acid had occurred. The MTT test was used to assess the effect of cell proliferation of nanoparticles with and without L-ascorbic acid on cancer cell lines and one healthy cell line. The results did not suggest any significant effect of L-ascorbic acid on cell proliferation. While L-ascorbic acid appears weak in therapeutic value for cancer therapy, both quercetin and L-ascorbic acid may find a role in working alongside traditional strong anticancer drugs by interacting synergistically with them.

Keywords

antioxidant – quercetin – L-ascorbic acid – chitosan nanoparticles – cancer therapy

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THE ROLE OF HOSPITAL PHARMACIST IN THE PARENTERAL ADMINISTRATION OF MEDICINES

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Abstract

The administration of parenteral medicines is a common practice within a hospital setting, encompassing various drug forms. Before administration, preparation of parenteral medicines is typically required. In the case of a powder for injection or infusion, the initial step involves reconstitution followed by dilution into a suitable solution, if necessary. The incidence of medication errors related to the preparation and administration of parenteral medicines varies depending on the study design. As indicated by a multicenter study, the incorrect diluent was utilized in 1%–18% of cases and the wrong rate of administration was chosen in 5%–49% of cases (Cousins, 2005).

Hospital pharmacists are expected to provide valuable guidance pertaining to the selection of an appropriate solution for reconstitution and dilution, concentration, the method of administration (e.g., via a central or peripheral line), rate of administration, and any incompatibilities when administering via a Y-site. Moreover, they can offer information regarding the stability and photosensitivity of the prepared solution.

This issue will be explored further through a clinical case involving a patient who requires the administration of multiple continuous infusions, thereby posing challenges in overcoming potential incompatibilities.

Ensuring the correct administration of medicines through the parenteral route is crucial to guarantee treatment effectiveness and minimize adverse effects.

Keywords

parenteral administration – reconstitution – dilution – incompatibilities

Cousins, DH. Medication errors in intravenous drug preparation and administration: a multicentre audit in the UK, Germany and France. *Quality and Safety in Health Care*. 2005; 14: 190-195, <https://doi.org/10.1136/qshc.2003.006676>.

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IN VITRO BARRIER MODELS FOR DRUG SCREENING

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Abstract

The blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier limit the exchange of molecules between the brain and periphery. The barrier systems are semipermeable, restricting the movement of detrimental molecules and cells from the blood and allowing selective nutrients and hormones to be absorbed. BBB comprises brain microvascular endothelial cells, which are supported by astrocytes and pericytes. Blood–cerebrospinal fluid barrier (BCSFB) is formed by epithelial cells of the choroid plexus. BBB and BCSFB play a crucial role in maintaining homeostasis in the central nervous system (CNS) by restricting the transport of toxic molecules and removing metabolites from the brain. Their semipermeable nature restricts the movement of large hydrophilic molecules, that is, peptides, proteins, and gene therapies, leading to low bioavailability of drugs in CNS. The methodical and scientific interest in the physiology and pathology of BBB led to the development of numerous *in vitro* models. We set up an *in vitro* model of BBB by co-culturing primary rat glial cells and primary rat endothelial cells and a model of BCSFB composed of primary rat epithelial cells of choroid plexus. We analyzed the expression of specific epithelial and endothelial tight junction proteins as well as the permeability of different markers. The developed models were used for screening new potential neurotherapeutics.

Keywords

blood–brain barrier – blood–CSF barrier – drug transport – *in vitro* models

Acknowledgement VEGA 2/0129/21, APVV-21-0321, APVV-22-0313

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DETERMINATION OF CATECHOLAMINES IN DRUGS

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Abstract

The catecholamines epinephrine, norepinephrine, and dopamine are biologically active molecules with similar chemical structures. Nowadays, they are investigated as putative biomarkers of inflammatory diseases. The high complexity of these molecules enables their use as medicines in life-threatening situations. In the Slovak Republic, there are several drugs with catecholamine as an active ingredient for parenteral use. These medicines are intended to be applied by health professionals, but there are also suitable forms that can be directly administered by patients (pens for intramuscular application in severe allergic reactions and anaphylaxis). Two methods for the determination of catecholamines were developed based on capillary electrophoresis, both performed in hydrodynamically closed mode. The first one was simple capillary zone electrophoresis (CZE) connected with ultraviolet (UV) detection. The second one combined CZE with an isotachophoretic preseparation step (ITP). Such hyphenation allows preconcentration and heart-cut of desired compounds. Catecholamines were determined in a mixture with four other biologically active compounds. The two approaches, CZE-UV and ITP-CZE-UV, were compared. ITP-CZE-UV method was chosen as a more sensitive method with LODs of 20 ng mL⁻¹ and LOQs of 50 ng mL⁻¹. The method was applied to pharmaceutical samples – injections of epinephrine and norepinephrine. Samples after the expiration date were analyzed to test the method and stability of drugs.

Keywords

capillary electrophoresis – CZE – ITP – catecholamines – quality control

Acknowledgment

This study was supported by the projects FaF UK/4/2023 and VEGA 1/0514/22.

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INFLUENCE OF CHITOSAN LYOPHILISATES PREPARATION PROCEDURE ON LIBERATION OF IBUPROFEN

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Abstract

Chitosan (CS) is often used in novel drug delivery systems because of its beneficial properties such as safety, biocompatibility, biodegradability, and mucoadhesivity. In this work, CS was used to prepare lyophilisates for oral delivery of low-soluble drug ibuprofen (IBU) to improve its solubility and, by this, improve its potential absorption in the gastrointestinal tract. Three systems with different vehicles were proposed: two capable of maintaining IBU in a dissolved state containing ethanol or propylene glycol in combination with lactic acid and the third one was a classic suspension system in acetic acid. To evaluate differences in drug release from these CS-IBU systems, the CS-IBU hydrogels were lyophilized. The morphology of lyophilisates was studied using scanning electron microscopy (SEM). Their surface had a sponge-like structure with circular pores, with their number increasing with increasing CS concentration. In the acetic acid system, the crystals of IBU were visible. Fourier transformation infrared analysis confirmed the formation of an amidic bond between IBU and CS in all systems. Swelling of lyophilisates showed a pH-dependent behavior (it was higher at pH 6.8 than at pH 1.2). The IBU release was tested in three media: the first one at pH 1.2, the second one at pH 6.8, and the third one imitating a pH change from 1.2 to 6.8 to simulate conditions in the gastrointestinal tract. Dissolution profiles showed better release in all CS-IBU systems than in pure IBU powder, depending on the CS concentration. The polymeric lyophilized systems containing CS in the 0.2%–0.8% concentration interval showed a tendency of both faster IBU release and higher total released amount with increased CS concentration. Prepared CS-IBU lyophilisates can be proposed as innovative oral drug delivery systems with the advantages of simple preparation and improved IBU solubility, potentially leading to the reduction of dose and adverse effects.

Keywords

lyophilisates – chitosan – low-soluble drugs – dissolution testing – ibuprofen

Acknowledgment

This work was supported by research grants VEGA 1/0514/22, VEGA 1/0146/23, FaF/18/2023, and FaF/10/2023.

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BRIEF INSIGHT INTO CHEMISTRY, METABOLIC STABILITY, AND ADVANCES IN IMPROVING THE BIOAVAILABILITY OF SEVERAL STILBENOIDS

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Abstract

Phenolic compounds (polyphenols) are plant secondary metabolites, structurally defined by the presence of at least one aromatic ring with one or more OH groups. **Resveratrol (1)** and its dehydrodimers – **trans-resveratrol oligomers**, that is, **d-viniferin (2)** and **e-viniferin (3)**; Figure 1) – belong to a subclass of polyphenols, that is, **stilbenoids**, containing a typical C6–C2–C6 backbone structure. The molecules (1)–(3) show a notable range of important biological activities and currently have a high potential to be involved in preclinical and clinical trials because they provide beneficial effects for human health, including anticancer, antioxidant, anti-inflammatory, cardioprotective, antiatherosclerotic, antimicrobial, antidiabetic, and neuroprotective action. In addition, these **stilbenoids** positively mediate bone metabolism and osteoclast-related pathologies.

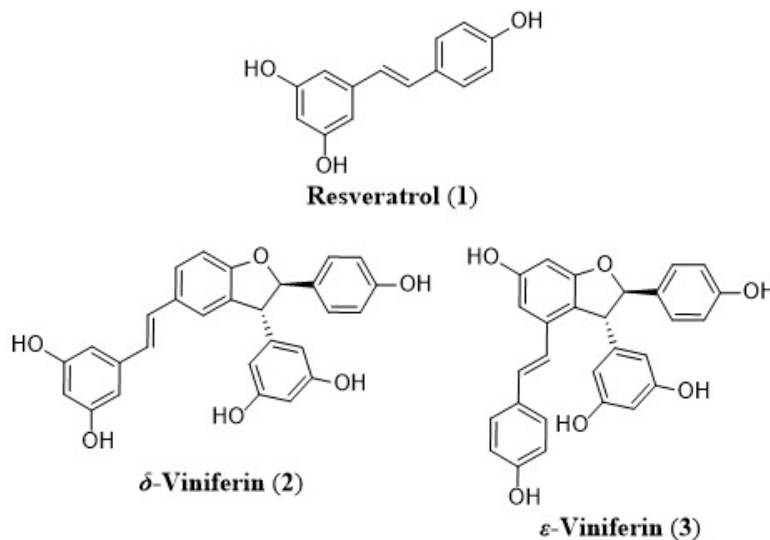


Figure 1. Structures of chosen plant secondary metabolites belonging to a **stilbenoid** class, that is, **resveratrol (1)**, **d-viniferin (2)**, and **e-viniferin (3)**.

These naturally occurring phytochemicals, however, suffer from very typical limitations; they are rapidly degraded via auto-oxidation or epimerization, for example. The molecules are also extensively biotransformed *in vivo* by the activity of various enzymes in both phase I and phase II of biotransformation. Moreover, pharmacokinetic (adsorption, distribution, metabolism, elimination (ADME)) features and physicochemical (solubility, lipophilicity) properties of the compounds (1)–(3) are not completely optimal, thus their bioavailability to a human body is limited. The lecture focuses on medicinal chemistry aspects of these molecules, especially selected structure–activity relationships, their ADME properties, and physicochemical characteristics including the descriptors generated *in silico* as well as biotransformation pathways. The increase in **resveratrol (1)** and **viniferins'** bioavailability employing several innovative delivery systems was also considered.

Keywords

resveratrol – viniferins – delivery systems

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ALTERNATIVE DELIVERY ROUTES OF MONOCLONAL ANTIBODIES

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Abstract

The use of biopharmaceuticals has been drastically expanded with the development of recombinant DNA technology. The main class of biopharmaceuticals is represented by monoclonal antibodies (mAb). Recently, increased interest has been shown on therapeutic peptides, oligonucleotides, or peptide conjugates. The typical delivery routes of innovative drugs are intravenous (i.v.), subcutaneous (s.c.), and intramuscular (i.m.) application. Alternative and more effective delivery routes of biopharmaceuticals are investigated, especially in the cases of respiratory and infectious diseases. This is due to their possibility of minimizing the dose with maintenance (or increase) of the therapeutic effect, minimization of adverse effects, and minimization of costs. Nasal and pulmonary drug delivery offers rapid and sustained drug delivery, high efficacy, no first-pass metabolism, and the achievement of local and systemic effects. Therefore, nebulization of drugs (biopharmaceuticals) represents a suitable approach for their delivery to organisms. The development of reliable and functional formulations of various biologics (including mAb) for their inhalation application demands a thorough optimization of formulation buffers designed for nebulization. Buffer composition, selection of excipients, and nebulization tools are crucial factors. The correct formulation is responsible for the creation of suitable particles during the nebulization procedure – a crucial step for the inhalation application of drugs. Stability and aggregation studies are also essential for confirmation of the prepared formulation. Modern liquid chromatography (LC) and capillary electrophoresis (CE) methodologies contribute to the appropriate evaluation of their quality control.

Keywords

monoclonal antibodies – biopharmaceuticals – formulation – nebulizers – inhalation delivery route

Acknowledgement This work was supported by research grants VEGA 1/0514/22 and APVV-21-0321.

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FUNCTIONALIZED GOLD NANOPARTICLES AS A PROMISING TOOL FOR BIOMEDICAL USE: SYNTHESIS, PROPERTIES, APPLICATIONS

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Abstract

Nanoparticles are defined as submicron particles with a typical size between 1 and 100 nm. The nanometric size provides these systems with unique physical and chemical properties that are different from their bulk materials due to their high surface area to volume ratio and special electronic effects. Along with soft nanoparticles, metal nanoparticles composed of gold and silver atoms continue to attract the interest of the scientific community as well as of industry due to their unique surface, magnetic, and plasmonic properties, and surprisingly high level of biological activity. Colloidal gold has been known for centuries for its excellent healing properties among physicians and alchemists. Gold in the form of nanoparticles (AuNPs) turned out to be a suitable platform for novel systems with distinct optical, physicochemical, and biocompatible properties and applications preferentially in biomedical and biotechnological areas. Because of the ultrasmall size of AuNPs, they can be used for targeted drug delivery and cancer treatment as well as for diagnostic and therapeutic purposes¹. One of the serious issues that prevent further development of AuNP-based applications is insufficient nanoparticle stability in aqueous nanodispersions over longer periods of time. As a promising solution to this issue, the stabilization of AuNPs by various types of chemical stabilizers such as polymers and surfactants² that form an organic capping layer on the surface of gold nanoparticle is widely investigated. The main function of these capping agents is to prevent the agglomeration of nanoparticles over time. The aim of the presented analysis of AuNPs is to show the relationship between the molecular structure of stabilizing surfactant molecule and physical properties as well as some biological activities of surfactant-capped AuNPs.

1. Anik M.I. et al. Nano Select 3 (2022) 792–828.

2. Pisárčik M. et al. J. Mol. Liq. 365 (2022) 120210.

Keywords:

gold nanoparticles – plasmon resonance – gemini surfactant – cytotoxicity – anti-inflammatory activity

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INCIDENT REPORTING OF SPECIFIC MEDICAL DEVICES IN RECENT YEARS IN SLOVAKIA

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Abstract

The safety of a medical device on the market is already estimated and calculated during manufacture. As part of safety supervision, manufacturers monitor and report the occurrence, type, and frequency of incidents to the competent authority in the country. One of the medical device types is the active implantable medical devices (AIMDs), which include defibrillators, pacemakers, neurostimulators, software, adapters, and programming devices. During the years 2020–2022, incident reports of AIMDs were monitored in cooperation with the State Institute for Drug Control in the Slovak Republic. Their occurrence was monitored and compared with the incident reports of all medical devices in the Slovak Republic during the mentioned years. The average number of all incident reports per year was 749. However, AIMD incident reports accounted for only 5.7% of the total number of medical device incident reports. There were 49 incident reports in 2020, 55 incident reports in 2021, and only 24 incident reports in 2022. This decrease in the number of reports for AIMD in 2022 was probably caused by the legislative transition from directives to regulations, in which the separate category of AIMD was canceled. Devices certified under Medical Device Directive (MDD) were reclassified as risk class III. The manufacturer began reporting the incident under class III, but this class III was not the subject of our study.

Keywords

Medical devices – AIMD – incident reporting

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EVALUATION OF *IN SITU* GELS INTENDED FOR OROMUCOSAL DELIVERY

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Abstract

Locally delivered drugs are a promising way of treating oral diseases because of reduction in dose and adverse effect occurrence. *In situ*-forming gels are liquid dosage forms that undergo a phase transition to a gel after application. This ability is useful in the oral cavity, where the dosage forms are influenced by constantly secreted saliva, speaking, and chewing movements. The evaluation process of these dosage forms is complicated because it is difficult to distinguish a gel from a highly viscous liquid. Since visual detection of gel presence is not sufficient, rheometric analysis is a preferred tool that offers determination of flow behavior, viscosity, gel presence, critical sol–gel transition temperature, gelation time, and so on. These properties of *in situ* gels were evaluated using an MCR 502 rheometer. Mechanical properties were evaluated using CT3-4500 texture analyzer. Based on the force–distance curve values, the characteristics of adhesion, back extrusion, and injectability were calculated. Formulations showed a pseudoplastic behavior at 37°C and a behavior close to a Newtonian fluid at 20°C. Gel presence was confirmed at 37°C. The critical sol–gel transition temperature of the selected formulation was 34.13°C ± 0.23°C, and the gelation process took only seconds. The viscosity of the formulation increased with temperature and reached 3597.2 ± 75.3 mPa·s (37°C, shear rate similar to speaking). According to the injection force (13.455 ± 1.973 N, 20°C), the formulation was easily injectable. Adhesion work (0.225 ± 0.025 mJ, 37°C) and adhesion force (0.203 ± 0.007 N, 37°C) increased with temperature, which indicates greater adhesion to the oral mucosa. Back extrusion work (1.03 ± 0.04 mJ, 20°C) and force (0.125 ± 0.008 N, 20°C) also increased with temperature and they are related to the firmness and consistency of the sample. Considering all preferences for local oral dosage forms, the evaluated *in situ* gel could be used for oromucosal delivery.

Keywords

rheology – texture analysis – poloxamer – carbomer – methylcellulose

Acknowledgment

This work was supported by IGA UVLF 01/2023 "Increasing the effectiveness of the treatment of oral diseases by developing a silver nanoparticle-loaded *in situ* gel based on smart polymers" and Scientific Grant Agency of the Ministry of Education, Science, Research, and Sport of the Slovak Republic and Slovak Academy of Sciences (VEGA 1/0353/22, APVV 19-324, and SK-TW Azacai).

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TITANATE NANOTUBES AS POTENTIAL PLATFORMS FOR DRUG DELIVERY

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Abstract

Naturally nanostructured carriers are of emerging interest in nanomedicine due to their better stability and excellent mechanical properties, which improve their processability compared to other nanocarriers. Titanate nanotubes (TNTs) are a novel but promising group of inorganic nanoparticles, which may be used for versatile applications in the pharmaceutical field. In an immobilized form, TNTs may be utilized to modify the surface of titanium implants to improve biocompatibility, but in a free form, it is also possible to use them as drug delivery systems. In this presentation, a general overview will be given of the properties, functionalization possibilities, and applications of these delivery systems. Hydrothermally synthesized free TNTs have similar mechanical and physicochemical properties as carbon nanotubes, but according to various studies, they may provide better biocompatibility, which makes them ideal candidates as carriers for small and macromolecular drugs. The absorption and toxicological profile of TNTs may be tailored via various routes of functionalization. It was also revealed that functionalization is succeeded only if an ionic or covalent bond was formed between the functionalizing agent and TNTs, but in case of complexation with drugs, van der Waals or weak H-bonds were more preferable because stronger bonds lead to modified drug release profile.

Keywords

titanate nanotubes – functionalization – drug delivery

Acknowledgments

Project no. TKP2021-EGA-32 has been implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme.

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REFINING ANALYTICAL TECHNIQUES FOR STRUCTURAL CHARACTERIZATION OF KEYHOLE LIMPET HEMOCYANIN (KLH)

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Abstract

Keyhole limpet hemocyanin (KLH) is a large glycoprotein composed of KLH1 and KLH2 subunits with individual molecular weights ranging around 400 kDa. These subunits assemble into massive decameric, di-decameric, and multi-decameric structures, reaching sizes of millions of daltons. Due to its strong antigenic properties, KLH represents a carrier protein that can be conjugated to nonimmunogenic peptides or other haptens to increase the immunogenicity of the preparations, mostly vaccines. KLH holds significant potential for the treatment of various cancer types, either used independently in bladder cancer treatment or as a carrier in vaccines against breast cancer or skin melanoma. In articles published to date, KLH has only been analyzed using standard liquid chromatography methods and is not sufficiently characterized in quality control laboratories. This study aimed to develop modern, reliable, and comprehensive analytical methods for the assessment of KLH. These methods could be used in the quality control process of biopharmaceuticals containing KLH. Three approaches were successfully employed: protein aggregate analysis using size exclusion chromatography, peptide mapping using LC-MS, and top-down, intact protein analysis with quadrupole time-of-flight mass spectrometry (MS-Q-TOF).

Keywords

keyhole limpet hemocyanin – carrier protein – biopharmaceuticals – proteomics – quality control

Acknowledgments

This work was supported by the projects UK/53/2023, VEGA 1/0514/22, VEGA 2/0129/21, and APVV-21-0321.

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QUALITY ASSESSMENT OF ACTIVE PHARMACEUTICAL SUBSTANCES, EXCIPIENTS, AND INDIVIDUALLY PREPARED MEDICINES IN PHARMACIES ACCORDING TO THE REGULATIONS IN FORCE IN THE SLOVAK REPUBLIC

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Abstract

Quality assessment of active pharmaceutical substances (APIs), excipients, and drugs in pharmacies in the Slovak Republic (SR) is regulated by Act No. 362/2011 **Coll. on Drugs and Medical Devices**, which defines the obligation of quality control according to the valid European Pharmacopoeia (Ph. Eur.) and the Slovak Pharmaceutical Codex (SFK). Ph. Eur. is available at the website of the European Directorate for the Quality of Medicines and Health Care <https://www.edqm.eu/>. **SFK** defines the technical requirements for the preparation, quality assessment, labeling, storage, prescription, and dispensation of extemporaneous preparations and stock preparations, and intermediate products in SR. The State Institute for Drug Control (SUKL) Pharmacopoeia Department updates the content of SFK in accordance with the Act after surveys in pharmacies. SFK contains methodologies for secondary identification testing of active substances and excipients used in pharmacies for extemporaneous and stock preparations. Monographs of extemporaneous and stock preparations presented in the SFK, are prepared in accordance with the requirements of the Pharmacopoeia, article Pharmaceutical preparations and follow the Technical Guide for Elaboration of Monographs approved by the European Pharmacopoeia by European Directorate for the Quality of Medicines and HealthCare (EDQM). For the forthcoming edition of SFK 3, we have been involved in the development of methods for the determination of API content in drugs and their validation, secondary identity tests, which are suitable for execution in pharmacies with available instrumentation and reagent apparatus, in collaboration with SUKL. For the determination of API content in the new monographs, namely Solutio coffeini 1%, Solutio levomentholi ethanolica 1%, 10%, Solutio sacchari 24%, Solutio natrii citrici 0.3 mol/l, and Solutio kalii dihydrogenophosphas 13.6% the methods from general part of the Pharmacopoeia: Absorption spectrophotometry, ultraviolet and visible, Optical rotation, Refractive index, Relative density, Potentiometric titration, Assays (Volumetric analysis), were used. The developed methods for monographs of pharmaceutical preparation were validated using the following parameters: precision, repeatability, intermediate precision, reproducibility, accuracy, and linearity. The monographs have been approved by the Pharmacopoeia Committee in Slovakia and will be published in SFK 3.

Keywords

Active pharmaceutical substance – Caffeine – Levomenthol – Spectrophotometry UV-VIS – Optical rotation

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MECHANICAL AND DISSOLUTION PROPERTIES OF TABLETS PREPARED FROM SPRAY-DRIED MATERIALS DIFFERING IN PARTICLE SIZE

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Abstract

The present work investigates the influence of spray-dried powders differing in particle size on the mechanical and dissolution properties of tablets. Aprepitant, a model active pharmaceutical ingredient (API), was spray dried with hypromellose phtalate - HP55 (HPMCP-HP55) in a ratio of 1:2. Atomization gas rate was chosen as a variable parameter to achieve batches with three different particle size distributions. The spray-dried products were subsequently subjected to tableting through dry granulation and direct compression.

Scanning electron microscopy revealed all particles were of spherical and hollow shape. In addition, the particle size significantly affected the bulk density, which increased with decreasing particle size due to a lower content of the air trapped inside. Tablet tensile strength decreased with decreasing particle size of the contained spray-dried powder. The friability values decreased as the tablet's tensile strength increased. Faster disintegration time was observed for tablets containing granulated material. Moreover, the tablet disintegration time increased with increasing powder particle size. Dissolution studies revealed no difference in the release behavior of spray-dried powders and granules. However, once the spray-dried powders were directly compressed into tablets, different release profiles were observed depending on the particle size. The tablets with the smallest particle size showed immediate release, whereas the medium and the largest particle showed prolonged release. However, all granule-based tablets exhibited an immediate release profile.

Keywords

spray drying – particle size – tablets – tensile strength – dissolution

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IMPROVING OF MELOXICAM DISSOLUTION RATE BY SPRAY DRYING FROM ETHANOLIC SOLUTION

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Abstract

The aim of this work is to increase the dissolution rate of a poorly water-soluble drug meloxicam by preparation of the co-processed product by spray drying. The mixture of meloxicam (0.31% w/w) in the presence of a surfactant sodium lauryl sulfate (62.31% w/w) and a natural polysaccharide carrier chitosan (37.38% w/w) was prepared as follows. Firstly, meloxicam was dissolved in ethanol (96% v/v, technical grade), then sodium lauryl sulfate was added and, finally, chitosan was suspended in the mixture. The mixture was spray dried by Mini Büchi spray dryer B-290 with inert loop B-295 and dehumidifier B-296 at a temperature of 85°C.

The obtained particles were characterized for particle size (laser diffraction analyzer), shape and morphology (scanning electron microscope including energy dispersive spectroscopy), and crystallinity/polymorphism (X-ray diffraction, [modulated] differential scanning calorimetry). Carrier/meloxicam interactions were further characterized via Fourier transform infrared spectroscopy. Using a flow-through cell, the dissolution rate of meloxicam from the spray-dried products was determined. A significant increase in the amount of dissolved meloxicam and increased dissolution rate of meloxicam from the product spray dried from ethanol was observed within 5 min of the dissolution test compared to raw meloxicam and the product spray dried from ethanol. The higher dissolution rate was particularly observed within the first 60 s of the dissolution test due to the improved meloxicam particle deagglomeration and better availability/wettability for the liquid medium. Formation of meloxicam polymorph I and III and partial amorphization were detected. In conclusion, co-processing by spray drying of meloxicam with sodium lauryl sulfate in chitosan dispersion resulted in improvement of the meloxicam dissolution rate.

Keywords

Spray drying – meloxicam – chitosan – sodium lauryl sulfate

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PHARMACEUTICAL TECHNOLOGY AND BIOCYBERNETICS

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Abstract

Development of sophisticated dosage forms is very topical in the theory of pharmaceutical technology. Various drug carriers and technological devices have been developed so far, for instance, intelligent polymers, micropumps, micro/nano drug carriers, and so on. The corresponding theory has the potential to revolutionize the development of dosage forms while reflecting the current conditions of the patient. Other issues are related to optimal drug delivery. Probably, the best representative example is optimization of the dosing protocols for chemotherapy in treatment of a tumor. There is no doubt that without an application of cybernetic principles, these problems will hardly be fully resolved. The problem also consists of using combined pharmacokinetic–pharmacodynamic models with the incorporated mechanism to solve the *in vitro*–*in vivo* correlations. The solutions to these problems yield the knowledge, which supports the drug designer in making decisions on whether an *in vitro* experiment can be used as a substitute for the *in vivo* study. Therefore, the goal of this presentation is to provide the audience with an insight into the philosophy of biocybernetics and how it can be incorporated into the methodology of advanced drug design. The following topics will be presented:

- The ways of building pharmacokinetic–pharmacodynamic models
- The basic mathematical models of drug release, absorption, distribution, metabolism, and elimination and their inclusion into a complex model. Based on this, the influence of auxiliary substances on pharmacokinetic parameters will be analyzed.
- Model validation based on parametric sensitivities
- Incorporation of the results of biocybernetics into the design of an automatic observer, which, based on the “observation” of an unprecise pharmacokinetic model, can predict whether the drug concentration in any compartment will be maintained within a given therapeutic range despite the fact that the samples will be sensed solely from the peripheral compartment.

Keywords

compartmental models – *in vitro*/*in vivo* correlation – sensitivity analysis – state bounding observer

Acknowledgments

The research is supported by the grant VEGA 1/0049/20 – Modelling and control of bio-systems, granted by the Ministry of Education, Science, Development, and Sport of the Slovak Republic.

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