

## SOUHRNY PŘEDNÁŠEK

## Pokroky ve farmaceutické technologii

### Pracovní den sekce technologie léků

Brno, 4. září 2019

Na Veterinární a farmaceutické univerzitě se 4. září 2019 konal již pátý „brněnský“ ročník tradiční konference s názvem Pokroky ve farmaceutické technologii (akce ohodnocena v rámci systému kontinuálního vzdělávání ČLnK 14 body), kterou pořádaly Sekce technologie léků České farmaceutické společnosti ČLS JEP a Ústav technologie léků Farmaceutické fakulty VFU Brno. Druhým rokem byla akce přesunuta na odpolední hodiny s cílem přilákat co největší počet lékárníků. Současně byly na program zařazeny přednášky, které by jejich zájem mohly podpořit. Jednalo se zejména o přednášku *Lékové formy pro dětského pacienta* (doc. PharmDr. Jan Gajdziok, Ph.D. – ÚTL FaF VFU Brno) a přednášku *Biologická léčba v revmatologii* (MUDr. Eva Dokoupilová – vedoucí lékařka soukromé revmatologické kliniky MEDICAL PLUS v Uherském Hradišti).

Letošní ročník navštívilo rekordních 125 účastníků a většina z nich byli právě lékárníci z nemocničních a veřejných lékáren. Jen namátkou jsme přivítali lékárníky z Brna, Zlína, Velkých Pavlovic, Olomouce, Broumova, Třebíče, Prahy, Kroměříže, Havlíčkova Brodu, Hustopečí, Prostějova, Karviné, Rožnova pod Radhoštěm, Vyškova a dalších měst ze všech koutů České republiky. Mezi další tradiční účastníky patří kolegové z Farmaceutické fakulty VFU Brno, Farmaceutické fakulty UK Hradec Králové, Vysoké školy chemicko-technologické v Praze, z Univerzity Pardubice, z Vysokého učení technického v Brně, Státního ústavu pro kontrolu léčiv a další. Konference se účastnili také zaměstnanci Výzkumného ústavu veterinárního lékařství Brno.

Z farmaceutických firem přijali pozvání zástupci SOTAX Pharmaceutical Testing s.r.o., ZENTIVA, k. s., TECHNOPROCUR CZ, BIOVETA a.s., PRO.MED.CS Praha a.s., TEKRO s.r.o. a ROSEPHARMA a.s.

Na konferenci zazněly mimo výše zmíněných zajímavé přednášky z oblasti farmaceutické technologie, a to

konkrétně *Půlitelnost tablet – vliv formulačních a technologických parametrů na obsahovou stejnoměrnost polovin tablet získaných rozlomením tablety s půlicí rýhou* (prof. Ing. Petr Zámstný, Ph.D. – Vysoká škola chemicko-technologická Praha), dále *Může dynamika konsolidace pomoci v odhadu úhlu vnitřního tření?* (Mgr. Žofie Trpělková – Katedra farmaceutické technologie, FaF UK, Hradec Králové), *Průtočná disoluce* (RNDr. Ludmila Butzková, Ing. Iva Martincová – Zentiva k.s., SOTAX Pharmaceutical Testing s.r.o.) a *Filmové krytí na rány s dexpanthenolem* (PharmDr. Kateřina Tenorová – Ústav technologie léků, FaF VFU, Brno). Unikátní přednáška Ing. Františka Lízala, Ph.D. (Odbor termomechaniky a techniky prostředí, Fakulta strojního inženýrství, VUT Brno) představila účastníkům možnost *Modelování dýchacích cest jako nástroje pro účinnější inhalační léčbu*.

Za organizační výbor (doc. PharmDr. Kateřina Kubová, Ph.D., doc. PharmDr. Jan Gajdziok, Ph.D., doc. PharmDr. et Mgr. David Vetchý, Ph.D., Ph.D., PharmDr. Jakub Vysloužil, Ph.D.) mi dovoluji za závěr poděkovat všem, kdo se na organizaci letošního ročníku podíleli. Děkujeme děkance FaF doc. PharmDr. Ing. Radce Opatřilové, Ph.D. MBA, za podporu akce a společnosti Česká lékárna Holding, a.s. – provozovatel sítě lékáren Dr. Max. za podporu odborného vzdělávání v oblasti farmaceutické technologie. Dále děkujeme kolegyním z ÚTL Vladěce Kaiserové, Anetě Škrhánkové, Zuzaně Radičové a Marcelle Kachlíkové za skvělou organizaci obcerstvení. V neposlední řadě děkujeme jak účastníkům, tak přednášejícím, kteří prezentovali zajímavé, aktuální a kvalitně připravené přednášky, za příjemně strávené odpoledne s farmaceutickou technologií a budeme se těšit na další ročník.

za organizační výbor  
doc. PharmDr. Kateřina Kubová, Ph.D.

#### EFFECT OF FORMULATION AND TECHNOLOGICAL PARAMETERS ON THE UNIFORMITY OF SCORED TABLET HALVES

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Scored tablets are used by pharmaceutical manufacturers to enable splitting of a tablet into two or more

parts. While some preparations use scoring only to enable breaking a single dose into several smaller portions to facilitate swallowing, other ones are intended to produce dosage units of a weaker strength than the original tablets. Since the tablet parts (most typically halves or quarters) represent dosage units, they should exhibit necessary uniformity. The legislation requires basically the produced halves not to differ from the half of the tablet strength by more than 15% for at least 50% of samples and by more than 25% in the rest of them<sup>1)</sup>. However, there are opinions to control the uni-

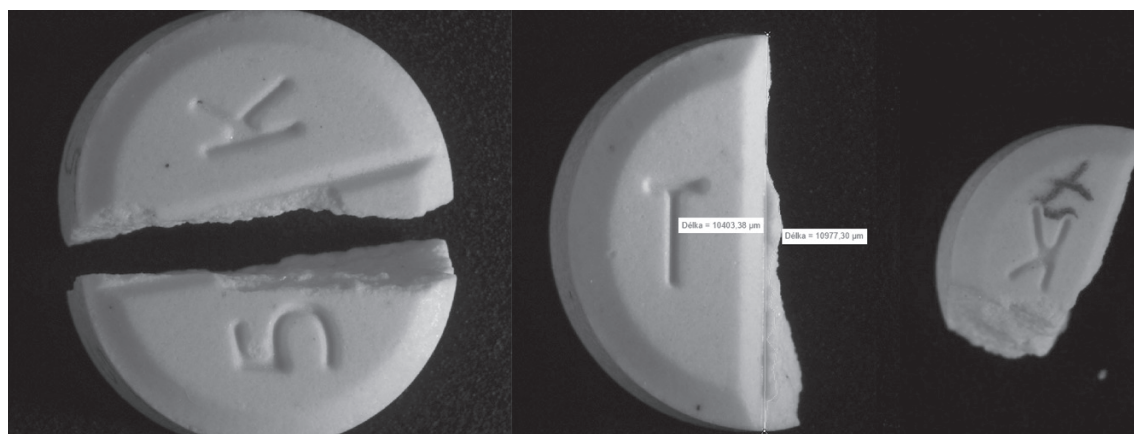


Fig. 1. Example of factors determining halved tablets non-uniformity: misplaced fracture (left), rough fracture plane (middle), chipping (right)

formity more strictly, such as those represented in the FDA guidance<sup>2)</sup>, which essentially require the tablet halves to comply with the same quality standards as the whole tablets of an equivalent size. The objective of this work was to analyze which factors can possibly affect the content uniformity of tablet halves and suggest suitable measurement techniques to analyze the effects of technological and formulation parameters on such factors.

The dose uniformity of the halved tablet is determined by the homogeneity of the formulation which was used to produce the tablet as well as by the mass uniformity of the split parts of the tablet. The homogeneity issue can be approached by similar methods as the homogeneity of any other powder or granular formulation, i.e. the homogeneity testing must be performed using a sample size which is comparable to that of the dosage unit. Scored tablets require this scale of scrutiny to be equal to the smallest split part of the tablet which is intended for administration.

The mass uniformity of split parts is determined by three factors: (a) the correct position of the fracture along the score-line, (b) the smoothness of the fracture plane, (c) the presence of chipping, causing formation of small chips in addition to intended major parts of the tablet. These factors are illustrated in Fig. 1 and they can be caused by quite different properties of the material, so that it is useful to separate them.

The correct position of the fracture is facilitated by materials which are sensitive to brittle fracture. An experimental study of round, flat-faced tablets having a score-line on both faces was performed, measuring their tensile strength by the standard diametrical test using a Multitest 50 hardness tester (Sotax, Switzerland) in the direction parallel along the score-line ( $\sigma_s$ ) and in the perpendicular direction ( $\sigma_0$ ). The values of  $\sigma_s/\sigma_0$  close to 1 indicated poor ability of the score-line to determine the fracture position, while the lower values of the ratio indicated better performance. For laboratory testing it was suggested to determine both stresses on each tablet to eliminate the effects of in-

creased tablet variability. Since both tests are destructive, it is suggested to calculate  $\sigma_0$  from the calibrated model  $\sigma_0 = A \cdot e^{B \cdot \varepsilon}$ , according to Osei-Yeboah<sup>3)</sup>, where A and B are regression parameters and  $\varepsilon$  is the tablet porosity. Also, the measurement procedure can be simplified using brittle fracture index (BFI) values according to Okoye<sup>4)</sup>, replacing the real score-line by a hole drilled through any ordinary tablet shape. Laboratory tests using this method revealed a strong positive correlation between the moisture content in the tablets (expressed as LOD, %) and the probability of misplaced fractures.

The roughness of the fracture plane was characterized by the use of optical microscopy using an SMZ18 (Nikon Instruments Europe B. V., Netherlands). The tablet was manually split using the standardized procedure and the length of the fracture edge ( $l$ ) and the length of the straight line ( $l_0$ ) connecting the border points of the fracture edge were measured using a microscope. The ratio  $l/l_0$  was used as a measure of roughness or unevenness of the fracture. The results indicate a strong effect of compression pressure and particle size of compressed material on this parameter. The chipping factor was not studied separately in this study, but it could be determined easily by expressing the tablet weight loss during splitting.

It can be therefore concluded that a 4-factor approach to evaluate scored tablet halves content uniformity was developed, which can not only evaluate the non-uniformity, but also suggest the probable causes thereof. It may then facilitate the formulation or processing changes to improve the product properties.

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#### CAN THE ANGLE OF INTERNAL FRICTION BE PREDICTED FROM SIMPLE DYNAMIC CONSOLIDATION?

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In pharmacy, flow and packing properties of powder material represent complex characteristics reflecting particularly its particle size and morphology. The inter-particle friction forces acting between particles in a powder bed can be measured traditionally as the angle of internal friction (AIF) by a shear cell method. Considering that an AIF at a normal stress should be comparable with that one at gravitational consolidation, the aim of this work was to study if the AIF can be predicted from the simple dynamic of gravitational consolidation.

Seven commercially available types of lactose powders having different particle characteristics were used as model substances; the consolidation behaviour under gravity due to a specific number of taps in a range of 0–30 (logarithmical order) was studied. Using the values of the bulk, tapped and true (helium pycnometry) density, the porosity factor was determined.<sup>1, 2)</sup> The AIF<sub>PN</sub> value was estimated from the slope of a linear relationship between the porosity factor and the number of taps.<sup>1, 2)</sup> The results were compared with AIF<sub>JC</sub> obtained from linearized yield locus at optimal consolidation state using Jenike shear cell measurement.

A significant linear correlation (ANOVA,  $r = 0.825$ ;  $p = 0.0223$ ) was observed between the AIF<sub>PN</sub> and the AIF<sub>JC</sub>. Moreover, a good agreement was observed even between AIF values and previously detected static and dynamic flow properties of investigated lactose samples.<sup>3)</sup> As the powder volume reduction is the result of friction/lubrication between particles in the powder bed, the AIF represents a good characteristic of flow and consolidation behaviour of particulate material.

In conclusion, the results of this study demonstrated the usefulness of the analysis of dynamic powder consolidation behaviour under controlled tapping in prediction of AIF. Although the Jenike shear cell represents a sophisticated method in powder industry, simple analyses of bulk and tapped densities are standard procedures in pharmaceutical technology. However, more research is necessary using additional materials.

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#### DISSOLUTION WITH THE FLOW CELL AND ITS USE IN TABLET ANALYSIS

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The flow cell can be used to analyse tablets, capsules, suspensions, powders and granules. Dissolution using this device is employed as a supportive method for developmental activities in the pharmaceutical laboratory.

The device operates in the open or closed modes; the assembly is changed by screwing the tubing system. Depending on the type of pharmaceutical substance, an analytical HPLC or a UV/VIS spectrophotometer are used.

When analysing tablets, the correct size of the tablet cell (12 mm or 22.6 mm) and the corresponding tablet holder located inside the flow cell must be used according to their size.

For good analytical results it is important to use a correct cell composition. The dissolution process is influenced by the medium used and its velocity during the whole flow, the type of flow (laminar) and the appropriate filter. GF/D and GF/F filters are standard and can be layered.

The dissolution must be optimized before routine measurement.

This method helps in the formulation of tablets – the flow cell sees even more “finer” differences between the tablets, which cannot be affected by classical dissolution with paddles or baskets. The different behaviours of tablets can be differentiated according to whether the micronized or non-micronized API has been used to make the tablets, differentiate different batches of the APIs in an otherwise equally formulated tablet and can differentiate the different sources of the API used. We can also let crushed tablets be released in the flow cell.

During the analysis of the tablets, the pH of the flowing medium can also be changed at any one time in all cells.

The flow cell for tablets, when properly set up and with a correct analytical ending, can help with developmental problems with tablet dissolution using conventional dissolution devices.

**BIOLOGICAL TREATMENT IN RHEUMATOLOGY**

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Biological treatment has fundamentally changed the therapeutic approach to the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis. Biological treatment has been made possible by two fundamental facts – firstly by a better knowledge of the pathogenesis of autoimmune rheumatic diseases and secondly by the possibility of biologically producing a molecule that is able to intervene into the pathogenetic process.

TNF (tumour necrosis factor) alpha cytokine plays a key role in the pathogenesis – the mechanism of biological drugs lies in the inhibition of TNF cytokine and its subsequent action. These are called bDMARD. TNF blockade reduces the inflammatory response by suppressing both local and systemic production of pro-inflammatory cytokines. TNF blockages can be achieved by two different mechanisms, either by the application of monoclonal antibodies against TNF (by infliximab, adalimumab, certolizumab, golimumab) or by a soluble receptor (etanercept). TNF is a pleomorphic cytokine that has multiple pro-inflammatory functions. The clinical effect of blockade with monoclonal antibodies or soluble receptors occurs within a few days or weeks.

The beneficial clinical effect assessed for example by the ACR 20 response (the ACR – American College of Rheumatology – criteria is a standard criterion to measure the effectiveness of various arthritis medications or treatments in clinical trials for rheumatoid arthritis) can be achieved in 50–70% by the first anti-TNF treatment, while the response to the second anti-TNF treatment may be slightly lower. Anti-TNF treatment suppresses disease activity, improves the functional status and quality of life of patients with rheumatic diseases. Furthermore, it slows down the structural progression of the disease and thus slows the progression of irreversible functional changes.

The efficacy of anti-TNF treatment is higher in early forms of diseases, but the treatment is also effective in longer-lasting rheumatic diseases. Anti-TNF treatment is relatively safe, but rare side effects may occur.

In addition to the original biological drugs, cheaper biosimilar copies are now available. Biosimilar drugs are bio-therapeutic products that are similar in quality, safety and efficacy to the original product.

Recently, the possibilities of treatment in rheumatology have been expanded by a whole new group of very effective drugs, so-called targeted synthetic disease-modifying antirheumatic drugs of the Janus kinase family – tsDMARDs. JAK inhibitors are synthetic small molecules that represent a new therapeutic option by a different mechanism of action. They interfere with intracellular signalling through inhibition of JAK enzymes. The treatment is being administered orally.

**DOSAGE FORMS FOR PEDIATRIC PATIENTS**

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Ensuring the availability of specific formulations in a suitable form for pediatric patients is currently an important requirement for manufacturers who are motivated to develop them (e.g. by extending patent protection). The reason why efforts have been made to develop and use dosage forms specifically intended for pediatric patients is that the pediatric patient is not a miniature of an adult. The stage of development of children is different, therefore their pharmacotherapy requires special preparations of optimized composition, which is not harmful or dangerous for the immature organism with regard to the active and auxiliary substances used.

The offer of specific child forms is still insufficient, pharmacotherapy often involves the use of adult products in the so-called off-label indication<sup>1)</sup>. In the EU, 45 to 60% of medicines are prescribed in this way<sup>1, 2)</sup>.

Pediatric patients may be given medications by a variety of routes, depending on age. While the youngest children (newborns and preterms) are usually administered rectally or parenterally, oral administration is dominant in older children. Oral administration, however, is hampered by the high demands placed on the dosage forms by pediatric patients, which determine compliance with treatment. Emphasis is placed on the acceptable sensory qualities of the formulations, the shape and dimensions of the solid dosage forms, which enable their easy swallowing, etc.

Liquid oral preparations still occupy an important place on the pediatric market. They are preferred primarily because of their flexibility in the administered dose. The problem remains that there may be errors in measuring dosages. Therefore, there is an effort to develop accurate metering devices or single dose formulations.

Solid dosage forms, which are nowadays preferred, provide good stability and wider possibilities in masking the inappropriate taste of drugs. Moreover, the solid form can be widespread worldwide due to its stability. Unlike liquid formulations, however, conventional solid dosage forms can cause swallowing problems that can be eliminated using particulate systems, such as minitabets and granulates, which also have improved dosage flexibility while retaining the advantages of conventional solid dosage forms.

The trend in the development of child-specific products is aimed at testing and investigating existing excipients for use in the pediatric population, as well as developing new gentle excipients. Furthermore, the development of medicines for children to be made available on the market with a wide range of strengths of the active substance, possibly in a form that can be individualized according to actual needs, should be encouraged in order to avoid inappropriate modifications to existing products.



With a view to individualizing therapy and increasing compliance of pediatric patients, the development of oral forms could be directed to minitables and orally dispersible formulations. Another promising pathway in development could be nasally administered drugs such as vaccines to minimize the fear and pain of patients from needle preparations, or buccally and sublingually administered products. For long-term pediatric patients of all ages except preterms, the trend could be towards the development of small, well-tolerated transdermal products, which are insufficient on the market.

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## MODELLING OF HUMAN AIRWAYS AS A TOOL FOR EFFICIENT INHALATION THERAPY

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The engineering approach is a problem-solving technique that can be applied not only in the aerospace or automotive industry but also to biological systems, phar-

macology and medicine. However, its successful application in this field depends on efficient communication between the engineering, pharmaceutical and medical communities.

This contribution focuses on the application of experimental and computational fluid and particle mechanics (CFPD) in the development of more efficient inhalation therapy. The discussion of the basic deposition mechanisms of inhaled particles (inertial impaction, interception, sedimentation, diffusion, and electrostatic precipitation) is followed by introduction of the Brno lung model. The model is a simplified representation of human airways containing the nasal and oral cavity and tracheo-bronchial tree down to the seventh generation of branching (see Fig. 1)

The model exists in several variants which all share the identical initial digital geometry of human airways. The same digital geometry is used for both computational simulations and experimental measurements. The importance of validation of computationally acquired results by experiments and restraints given by the *in vivo* measurements are emphasized.

The story of a failure of Exubera inhaled insulin is used to illustrate the limits of the current technology. Technical, medical and marketing problems, namely a rushed introduction to the market, unanswered questions of side-effects, unwieldy appearance and design, and missing insurance coverage are identified.

The future of the research of inhaled medication is envisioned mostly in simulations of lung diseases, morphological and physiological changes they cause and the effects the changes have on the deposition of inhaled particles. The required ability to predict local deposition hot-spots is mentioned as well as the need for faithful simulation of airway wall movement, mucociliary clearance mechanisms, hygroscopic growth and the electrostatic forces. Lastly, airway development since early childhood, surfactant delivery, and gender differences are identified as possible future challenges.

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Fig. 1. Visualization of the Brno lung model – the variant of the segmented replica of airways serving for measurement of inhaled particle deposition.

## FILM WOUND DRESSING CONTAINING DEXPANTHENOL

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In recent years, the amount of knowledge about the processes of wound healing has significantly increased, resulting in wound dressings of varying composition and effects<sup>1)</sup>. One of the options are film dressings, which are thin, flexible and transparent dressings, impermeable to microorganisms and moisture but oxygen- and moisture vapour-permeable. Film dressings are indicated for mi-

nor burns and lightly exuding wounds. They can be also used to cover and protect the skin after surgery. Modern film dressings are primarily manufactured from synthetic polyurethane, however the trend is to prepare films from natural materials or their derivatives. Films intended for wound application have been prepared for example from gelatine, chitosan or collagen<sup>2)</sup>. One of the promising materials for this purpose is also sodium carboxymethyl cellulose (NaCMC). It is a nontoxic, biocompatible cellulose derivative with excellent film-forming properties. Because of this, NaCMC is widely used in cosmetics, medicine and pharmacy. At present it is used as an absorbent dressing in wound therapy, nevertheless film dressings from this material have not been used in clinical practice yet<sup>3)</sup>.

The aim of this study was the formulation, preparation and evaluation of polymer films based on NaCMC containing dexpanthenol as the active ingredient. Dexpanthenol is a widely used substance especially in dermatology, stomatology and otorhinolaryngology. It is used in the treatment of skin diseases because it plays an important role in accelerating the epithelization of skin and wound healing. It is also a safe substance and it has a long history in dermatology<sup>4, 5)</sup>. Moreover, dexpanthenol has a good potential for incorporation into a film wound dressing because films are intended for wounds in the final phase of healing and dexpanthenol can contribute to better and faster epithelisation

and hence wound healing. The films were prepared by the solvent evaporation method from NaCMC in the form of nonwoven textile. Films without an active ingredient were used for comparison. Organoleptic and microscopic evaluation as well as testing of the properties important for wound application (pH, swelling and mechanical properties) were carried out. Mass content uniformity and drug content uniformity were determined as well. Both types of films (with/without dexpanthenol) had good organoleptic properties and also optimal parameters for wound application. The films showed satisfactory mass content uniformity and those with dexpanthenol also drug content uniformity.

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