

## SOUHRNY PŘEDNÁŠEK

PRACOVNÍ DEN SEKCE TECHNOLOGIE LÉKŮ  
S NÁZVEM

## „Pokroky ve farmaceutické technologii“

Dne 12. 9. 2018 se v Brně na půdě Veterinární a farmaceutické univerzity Brno konal čtvrtým rokem pracovní den Sekce technologie léků s názvem **Pokroky ve farmaceutické technologii** pořádaný Sekcí technologie léků České farmaceutické společnosti ČLS JEP a Ústavem technologie léků Farmaceutické fakulty VFU Brno. Akci finančně podpořila společnost Česká lékárna Holding, a.s. – provozovatel sítě lékáren Dr. Max. Akce byla jako každoročně zaměřena na představení současných trendů v oblasti farmaceutické technologie a byla ohodnocena v rámci systému kontinuálního vzdělávání ČLnK 15 body pro farmaceuty.

Konferenci navštívilo rekordních 110 účastníků z různých oblastí. Z akademické oblasti jsme přivítali účastníky z Farmaceutické fakulty VFU Brno, Farmaceutické fakulty UK Hradec Králové, Farma-

ceutické fakulty UK V Bratislavě, Vysoké školy chemicko-technologické v Praze, Vysoké školy báňské Technické univerzity v Ostravě a z Fakulty chemicko-technologické Univerzity Pardubice. Konference se účastnili také zástupci výzkumných organizací, a to Ústavu makromolekulární chemie AV ČR a Výzkumného ústavu veterinárního lékařství Brno. Z farmaceutických firem přijali naše pozvání zástupci firem PRO.MED.CS Praha, a.s., SOTAX Pharmaceutical Testing, s.r.o., BIOVETA, a.s., TEKRO, s.r.o., RosenPharma, a.s., FYTOPHARMA, a.s. Velmi nás potěšil také zájem lékárníků z nemocničních (IKEM Praha, MOTOL Praha, MOU Brno, FN u svaté Anny v Brně, Fakultní nemocnice Olomouc, Nemocnice Třebíč) a veřejných lékáren.

V úvodu pracovního dne účastníky přivítala předsedkyně Sekce technologie léků ČFS ČLS JEP doc. PharmDr. Kateřina Kubová, Ph.D., následně potom děkanka FaF VFU Brno doc. PharmDr. Ing. Radka Opatřilová, Ph.D., MBA, a předseda ČFS ČLS JEP prof. PharmDr. Martin Doležal, Ph.D.

V první sekci vystoupili:

- doc. Ing. Petr Zámstný, Ph.D. (VŠCHT, Praha) s přednáškou *Řešení problémů při plnění želatinových tobolek automatickými kapslovacími stroji*
- doc. PharmDr. Jan Gajdziok, Ph.D. (Ústav technologie léků FaF VFU, Brno) s přednáškou *Maskování chuti léčiv*



Předsedkyně Sekce technologie léků ČFS ČLS JEP doc. PharmDr. Kateřina Kubová, Ph.D. při zahájení akce



V první řadě – děkanka FaF VFU Brno doc. PharmDr. Ing. Radka Opatřilová, Ph.D., MBA a předseda ČFS ČLS JEP prof. PharmDr. Martin Doležal, Ph.D.



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- PharmDr. Lukáš Lázníčka (Nemocniční lékárna Královské Vinohrady, Katedra Farmaceutické technologie FaF UK, Hradec Králové) s přednáškou *Deriváty celulosy v magistraliter přípravě*

- PharmDr. Michal Budínský (Masarykův onkologický ústav, Brno) s přednáškou *Instrumentální radiofarmacie, krok ke zvýšení kvality a bezpečnosti*

Po krátké přestávce pokračoval pracovní den druhou sekcí, ve které vystoupili:

- PharmDr. Andrej Kováčik, Ph.D. (Katedra farmaceutické technologie FaF UK, Hradec Králové) s přednáškou *Kožní bariéra: od pokožky k modelovým membránám (a zpět)*

- PharmDr. Aleš Franc, Ph.D. (Ústav technologie léků FaF VFU, Brno) s přednáškou *Vývoj disoluční metody pro léčiva s okamžitým uvolňováním*

- Ing. Martina Urbanová, Ph.D. (Ústav makromolekulární chemie AV ČR, Praha) s přednáškou *NMR ve službách farmaceutického výzkumu*

- Mgr. Jan Elbl (Ústav technologie léků FaF VFU, Brno) s přednáškou *3D tisk ve farmaceutické technologii*

Za organizační výbor (doc. PharmDr. Kateřina Kubová, Ph.D., doc. PharmDr. et Mgr. David Vetchý, Ph.D., doc. PharmDr. Jan Gajdziok, Ph.D., PharmDr. Jakub Vysloužil, Ph.D., Vladimíra Kaiserová) mi dovoluje touto cestou poděkovat jak účastníkům, tak přednášejícím, kteří prezentovali velmi zajímavé a kvalitně připravené přednášky. Všichni společně vytvořili přátelskou atmosféru, která je nezbytná pro navázání tolik potřebné spolupráce odborníků z různých oblastí. Současně děkujeme všem za pozitivní ohlasy. Pevně doufáme, že se příští rok na „Technologickém dni“ zase sejdem.

*Za organizační výbor  
doc. PharmDr. Kateřina Kubová, Ph.D.*

## **TROUBLESHOOTING THE PROCESS OF CAPSULE FILLING USING DOSATOR-TYPE MACHINES**

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Sticking to dosator pins during capsule filling is not as common of a problem compared to sticking to punches during tablet compression due to the lower pressures involved, yet it may present serious difficulty in formulations comprising highly adhesive



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APIs. This work is aimed at developing and testing a laboratory approach to evaluate capsule filling formulation processability. The nature of the sticking problem lies in the process of ejecting the compacted slug from the dosator tube into the capsule body by the dosator pin. After the ejection is completed, the pin is being retracted, preferably leaving the slug intact within the capsule body. However, if substantial sticking occurs, the slug may be broken during the pin retraction and the part of the slug adhered to the pin face may be removed from the capsule.

An approach was suggested to evaluate the capsule filling formulation processability by measuring adhesion and strength parameters. The slug adhesion to the pin face was measured using GTP-1 (Gamlen Tableting Ltd., UK) in a 5mm tablet compression die having a movable base. The force required to move the base to detach it from the formed slug after compression was measured, providing detachment stress  $\tau_s$ , which was used as a measure of adhesion strength. The radial strength of the slug  $\sigma_t$  was measured using a tablet hardness tester Multitest 50 (Sotax, Switzerland), providing a measure of cohesion within the formulation.

Adhesion and cohesion parameters were tested for correlation with a capsule filling process waste, which represented the formulation processability. The best correlation was found for  $\tau_s/\sigma_t$  ratio, the high value of which indicated processability problems. The acceptable target value ensuring good processability was found around 2.5. The processability was further tested for sensitivity on the excipients used, API particle size, lubrication rate, filling pressure, and humidity. It was found that excipients play a significant role in sticking propensity. Pure excipient evaluation can provide some indication of its contribution to formulation performance, but combination effects were substantial for surface active excipients like lubricants. The sticking was sensitive to the particle size of the adhesive components of the formulation, the coarse particle providing much better performance. The lubrication rate was surprisingly found having a mixed effect on processability, the improper ratio of lubrication being even able to increase the sticking problems. Formulations exhibited different sensitivity to storage humidity, but increased humidity always promoted the processability problems. In conclusion, the suggested approach was found suitable for laboratory evaluation of capsule filling formulations processability.

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#### TASTE MASKING IN PHARMACEUTICAL TECHNOLOGY

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The oral route represents the most common administration way for majority of drugs. An unpleasant taste (usually bitter) of the drug can lead to neglect of the medication, thereby worsening the treatment efficacy. For this reason, taste masking is the key to increase the patient compliance, which is closely related to the success of therapy as well as to the commercial success of the medicinal product. Thus taste masking is an important part of the development of the dosage form.

The taste of the drug is perceived only when the active ingredient (API) is dissolved in the saliva and comes into contact with the receptors of the taste buds. Therefore, taste masking methods focus on avoiding dissolution of the drug in the saliva or influencing the ability of the drug to interact with the taste buds<sup>1)</sup>.

A versatile method of taste masking of all drugs does not exist<sup>2)</sup>. Optimal taste masking technology should use as few as possible excipients, equipment and process steps, should not adversely affect the bioavailability of the API or even the safety or stability of the product<sup>3)</sup>.

Taste masking methods can be divided into physical, chemical and physiological. Physical methods are coating, microencapsulation, viscosity enhancement, adsorption, pH change, granulation, and the formation of multiple emulsions and liposomes. Chemical methods include the addition of effervescent additives, complexation, and the formation of prodrugs or salts. Physiological methods include addition of sweeteners, flavourings, and taste receptor inhibition.

The most commonly used taste masking methods include coating, microencapsulation and granulation. The general principle of these methods is a delay of drug release in the oral cavity. Additionally, the release of the drug from the dosage form can be achieved by forming an insoluble complex with ion exchange resins, cyclodextrins or adsorbents. Changing the pH can result in insoluble drug precipitate formation. However, the use of these methods should not adversely affect the intended release of the drug in the lower parts of the gastrointestinal tract. The restriction of the drug-taste receptor interaction provide: modifying of the active molecule by formulating a prodrug or a salt; inhibiting the receptors for bitter taste; or suppressing the unpleasant taste of the drug by some intense flavours. Viscosity enhancers, effervescent additives or pH modifiers are mostly used in combination.



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Choosing the appropriate taste masking method depends on the properties of the drug – the intensity of the unpleasant taste or its solubility. The dosage form is essential for the selection of the taste masking method. Tablets are mostly swallowed as a whole, and their unpleasant taste is masked by coating. At present, specific types of tablets – orally dispersible and chewable tablets – are increasingly popular. In fast-disintegrating forms, taste masking is more complicated due to the longer period of API staying in the mouth. In the production of orodispersible dosage forms, it is often necessary to use flavours and sweeteners. To improve the taste of solutions most often flavours or complexation process are used. In addition, for suspensions the use of microencapsulation and addition of viscosity enhancers could be promising methods.

The taste masking of pharmaceuticals is now an integral part of pharmaceutical industry. Pharmaceutical companies are still developing innovative, taste masking technologies. Future research on taste masking will most likely focus on high-performance sweeteners of natural origin and searching for bitter taste blockers at the receptor level.

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#### DERIVATIVES OF CELLULOSE IN EXTEMPO-RANEOUS PREPARATION

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Extemporaneous preparation still plays an important role in the individual prescription of medicinal products. Many extemporaneously prepared products are based on the viscous, aqueous solutions of water-soluble cellulose derivatives or hydrogels as these are relatively easy to prepare<sup>1)</sup>. However, each batch has the individual viscosity properties due to the swelling and subsequent hydration upon different dissolving conditions.

Commercially available cellulose derivatives are generally designated with viscosity grade measured at 2% w/v concentration in water at 20 °C using an Ubbelohde viscometer. Unfortunately, the unexpected lack of a required polymer type make the compounding in a pharmacy very complicated. In this work, therefore, the relationship between the polymer concentration and viscosity of aqueous solutions of methylcellulose (MC), hypromellose (HPMC), and carmellose sodium (CMC) of various viscosity grades was studied.

The 2.0% w/v stock solution of MC and/or HPMC, respectively, was obtained by hot/cold method<sup>2)</sup> following with hydration in the refrigerator at 4 ± 1 °C for one week. For HPMC 78000, the stock concentration of 1% was prepared. By dilution with an appropriate volume of water, 0.50%, 1.00%, and 1.50% solutions of MC 400, MC 1500 and HPMC 4000, or 0.25%, 0.50%, 0.75% solutions of HPMC 78000, respectively, were prepared. Solutions of CMC were prepared by simple dissolution in cold water, one week hydration in cold and, similarly, diluted.

Kinematic viscosity in  $\text{mm}^2\text{s}^{-1}$  of the samples was measured using Ubbelohde capillary viscometer at 25 °C in agreement with European Pharmacopoeia. The dynamic viscosity in  $\text{mPa}\cdot\text{s}$  was calculated as the product of the kinematic viscosity and density of the solution ( $\text{mm}^3$  per gram), measured by the density meter (DMA 4100M Anton Paar, Austria). The relationship was modelled using an empirically proposed linear regression in which the transformation of viscosity by logarithm and the concentration by square root was recommended<sup>3)</sup>.

To obtain required value of viscosity, usually a high-concentration polymer solution batch is diluted. However, dilution is complicated with the fact that the viscosity/concentration relationship is not simply proportional. The actual parameters  $a$  and  $b$  of the generated  $\ln \eta/\sqrt{c}$  linear regressions allow to estimate the concentration of the cellulose derivative to achieve the desired viscosity as follows:

$$c = [(\ln \eta - b)/a]^2, \quad [1]$$

where  $c$  is the solution concentration (%) and  $\eta$  is dynamic viscosity ( $\text{mPa}\cdot\text{s}$ ).

This way, the concentration of individual cellulose derivatives having different viscosity grades can be predicted to obtain the optimum degree of viscosity properties desired in a given formulation. However, the complete polymer dissolution as well as number of concentration data influence the resulting precision of viscosity prediction.

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#### INSTRUMENTAL RADIOPHARMACY, A STEP IN QUALITY AND SAFETY IMPROVEMENT

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**Introduction:** The purpose of our study is to evaluate the effect of instrumental preparation of radiopharmaceuticals for positron emission tomography (PET) on radiation exposition of staff.

**Methods:** Instrumental preparation of radiopharmaceuticals has been used since 2004 as a tool of radiation protection optimization for the pharmacists and the pharmaceutical laboratory technicians after PET introduction to the Department of Nuclear Medicine of Masaryk Memorial Cancer Institute (MMCI) in 2003. During more than fifteen

years of providing PET radiopharmaceuticals, different equipment for preparation of radiopharmaceuticals including DDS-A,  $\mu$ DDS-A, and KAR1100 (all Tema Sinergie, Faenza, Italy) were used. An increase in the number of radiopharmaceutical for PET (either  $[^{18}\text{F}]$ fluorodeoxyglucose – FDG,  $[^{18}\text{F}]$ fluorothymidine – FLT,  $[^{18}\text{F}]$ sodium fluoride,  $[^{18}\text{F}]$ choline,  $[^{18}\text{F}]$ flutemetamol,  $[^{11}\text{C}]$ methionine) in one day resulted in the need to increase the number of instrumental equipment – two  $\mu$ DDS-As and one KAR1100. The radiation exposure of the hands of the staff was evaluated from ring dosimeters.

**Results:** The introduction of PET in 2003 resulted in a rise of the radiation dose above the legislation limits to radiopharmacists with a personal maximum of 814.4 mSv/year for hands and a collective dose of 2075.22 mSv/year for hands. As a tool of optimization, instrumental preparation of radiopharmaceuticals for PET using a DDS-A was introduced, which resulted in a rapid reduction of the radiation dose to a personal maximum of 106.97 mSv/year for hands and a collective dose of 429.6 mSv/year for hands in 2004. The increase in the number and types of PET radiopharmaceuticals used during one day required to upgrade the equipment used and to increase its number. In 2009, the former DDS-A was replaced by two  $\mu$ DDS-As. Another tool, a KAR1100 was installed in the middle of the year 2016. The use of a KAR1100 for the preparation of FDG resulted in a further significant reduction of radiation dose to the personal maximum of 16.67 mSv/year for hands and the collective dose of 120.95 mSv/year in the year 2017.

**Conclusion:** Introduction of PET and the need to prepare several different types of radiopharmaceutical for PET in one day can increase radiation exposure of radiopharmacists and pharmaceutical laboratory technicians. Introduction of instrumental methods in radiopharmacy is considered as an effective tool of radiation protection optimization.

#### SKIN BARRIER: FROM EPIDERMIS TO MODEL MEMBRANES (AND BACK)

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Ceramides (Cer) are the key building sphingolipids of the skin lipid barrier. Along with other lipids, they form multiple lipid membranes in the intercellular space of the *stratum corneum* (SC), the outermost layer of the mammalian epidermis. These major skin lipids (Cer, free fatty acids, and cholesterol in equimolar ratio) prevent excessive water loss from the body and hamper the penetration of undesired substances, allergens and microbes from the environment into the body. In fact, the development of such lipid-based barrier was an essential step in the evolution of life on dry land<sup>1)</sup>.

In general, when the skin barrier is injured, the levels of skin Cer are decreased. This fact correlates with a lower formation of long periodicity phase, the crucial lamellar



lipid organization in mammalian skin<sup>2</sup>). One possible way of how to reduce manifestation of skin diseases could be a topical application of skin Cer or their derivatives, *i.e.*, *pseudoceramides*, which could repair skin barrier function. Therefore, a better understanding of the role of the individual structural features of skin Cer can lead to a better design of (cheaper) barrier repair agents. For this investigation, the model skin barrier membranes are used. Indeed, these systems are quite simple; however, they mimic the SC permeability (*e.g.*, water loss) and microstructure (*e.g.*, lamellar packing) very well. For this, several techniques, such as infrared spectroscopy (deuterated lipids), X-ray powder diffraction or NMR spectroscopy have been used<sup>3</sup>).

Using a model membrane systems study, we found out that while shortening of Cer chains, an absence of *trans*-double bond, or methylation in the amide group result in an increase in membrane permeability; the removal of C-3 hydroxyl group in the sphingoid base backbone does not affect the membrane permeability to water<sup>4</sup>). Additionally, the role of Cer hydroxylation (in position C-4, C-6, C-2', and C-3 stereochemistry) and its impact on membrane permeability was investigated. The diversity of Cer in the skin and the reason why the epidermis synthesizes hydroxylated Cer are still unknown. 6-HydroxyCer<sup>5</sup>) probably facilitates the formation of the lamellar phase with long periodicity in model membranes, which is essential for the proper barrier function. This fact could explain the unique role of 6hydroxyCer in the skin, *i.e.*, to answer the question: “*Why does Nature synthesize 6hydroxyceramides only in the skin?*”

Model systems contributed to a better understanding of the role of structure-activity relationships of Cer in skin barrier function. The pieces of knowledge from this study could be used in atopic dermatitis treatment with topically applied Cer.

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#### DISSOLUTION METHOD DEVELOPMENT FOR IMMEDIATE RELEASE DRUGS

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The selection or development of a suitable dissolution method is crucial for evaluation of oral solid dosage forms with immediate drug release. The suitable method should reflect the physico-chemical characteristics of the incorporated drug substance/s, which are classified according to the Biopharmaceutical Classification System (BCS) into four classes upon their solubility and permeability<sup>1</sup>). Dissolution method can reveal changes in composition and behavior of testing dosage form; it therefore plays a key role in the development and manufacturing of the medicinal product, stability testing and clinical evaluation. A priority goal is to ensure both the efficiency and safety of the medicinal product<sup>2</sup>).

During the selection/development of suitable methods, an emphasis is placed especially on its discriminatory power, bio-relevancy of dissolution results, and a possibility to indicate stability of dosage form. Selection of medium composition and conditions of dissolution test close to those in the organism is essential<sup>3</sup>). It is possible to choose pharmacopoeial or so-called biorelevant media and a wide range of dissolution conditions for dissolution test performance, such as apparatus type, medium volume, rotation speed<sup>4</sup>), amount for sampling, number of tested units, and total dissolution time. In practice, sometimes it is not possible to cover all these nuances by one method, and therefore a combination of more methods is chosen depending on the nature of the drug<sup>5</sup>). In the list below, there are 15 recommendations for development of a new dissolution method for immediate release of oral dosage forms:

1. paddle speed 50–75 rpm or basket speed 75–150 rpm
2. medium volume 500–1000 ml (min. 250 ml for orodispersible tablets)
3. pH from 1.2 to 7.5 where drug is dissolved if it is possible in non-ionized form
4. pepsin addition in the case of hard gelatine capsules
5. surfactant (especially sodium lauryl sulphate 0.1–2%) in the case of poorly soluble BSC III or lipid formulations
6. biorelevant or biphasic media especially in the case of BCS III and IV and Lipinski molecules
7. gas-free medium (especially decarbonized by boiling or evacuation)
8. stability of dissolved drug in medium should be for 24 hours
9. sampling points: where 85% or more is released at pH 1.2 in 15 min (50 rpm paddle and 100 rpm baskets), one sapling point is sufficient. Otherwise, 5–9 sampling points should be distributed – the first one is before 15 minutes, the second one in 15 minutes, the last sampling point should be considered after 85% or in plot of released drug.
10. dissolution time is not recommended for more than 60–90 min

11. limit of the drug release should not be less than 75%
12. volume of dissolution medium during sampling should be taken into account in calculation
13. 6 sampling units may be inadequate; 12 is more predicative
14. visual checking during all time of dissolution is absolutely necessary (a camera is useful)
15. detection method should be a selective and indicative method (HPLC, etc.)

Several computational methods, such as factory similarity factor  $f_2$  or *AUC* (*Area under Curve*) or *DE* (*Dissolution Efficiency*) methods, are available for evaluation of dissolution profiles.

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#### SOLID-STATE NMR IN PHARMACEUTICAL RESEARCH SERVICES

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Presently, solid pharmaceutical products (tablets, capsules, granules, etc.) represent about 80–90% of the drug market. A sustained effort to maximize the therapeutic effect of newly discovered active pharmaceutical ingredients (APIs) leads to the search for and development of advanced drug formulations. This effort results in the formulation of multicomponent API-excipient systems, the physicochemical properties and performance of which are determined by a network of API-excipient, AP-API and excipient-excipient interactions. In this regard, a range of multicomponent and nanostructured systems that often combine the properties of solid and liquid materials have been developed. Besides the sophisticated supramolecular synthesis the development of these systems also requires an in-depth view into their local architecture at the atomic-resolution level. As these materials naturally exist at the borderline between the solid and liquid phases, the high-quality

diffraction data are inherently unavailable. Therefore the structural description of these materials requires development of novel and highly efficient strategies. The aim of all this process is formulation of computation-experimental procedures allowing for a precise characterization of the complex pharmaceutical systems including composite solids, nanocrystalline systems as well as partially ordered materials. In this regard, NMR crystallography belongs among the most successful approaches. In particular for pharmaceutical research a range of experimental strategies including analysis of solid forms (polymorphs, solvates), hydrogen bonding and crystal packing and/or solid-solid interactions (phase transformations, activation energies of molecular motions) have been developed and successfully applied. Solid-state NMR spectroscopy is also a technique which in many respects complements X-ray diffraction crystallography. This is given by the fact that ssNMR has the unique ability to probe electron environments of specific nuclei in the solid state over a large timescale, without the requirement of single crystal substrates or even homogeneous samples. Thus, ssNMR spectroscopy is not only suited for identifying different solid forms of drugs, but this technique can also provide detailed structural information useful for rationalizing physical properties of drug forms in terms of molecular and crystal structures as well. In this contribution we report our recent achievements in characterizing the atomic-resolution structure of complex pharmaceutical solids, such as hybrid organic-inorganic liquid-solid drug delivery systems, polymer-drug solid dispersions, and mucoadhesive buccal films.

#### 3D PRINTING IN PHARMACEUTICAL TECHNOLOGY

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3D printing is a rapidly growing technology. Amongst general industrial application it is also applicable in manufacturing of dosage forms. It is seemingly predetermined to be advantageously used as a manufacturing tool in the clinical phases of drug development and in individualised pharmacotherapy, due to its inherent flexibility. Properties of drug dosage forms, such as the dose, type of release mechanism, shape and colour, can be easily modified and the final form can be produced quickly in small batches. It is also possible to prepare dosage forms with properties unattainable by classic manufacturing. Flexibility being its greatest strength is, at least for now, its weakness as regulatory agencies do not offer a legal framework for such uses.

5 subtypes of 3D print have been researched and evaluated as a production tool in pharmaceutical technology till this day – binder jetting, SLS, FDM/FFM, SSE, and SLA. Binder jetting deposits a liquid binding agent onto a thin layer of powder material. The print head moves over the built platform

depositing binder droplets. When the layer is complete, the powder bed moves downwards and a new layer of powder is spread onto the built area. SLS (selective laser sintering) is in many ways similar to binder jetting (input material form, build platform behaviour). The main difference is that the laser beam is used to fuse powder material by sintering or partial melting, instead of a liquid binder.

FDM/FFM (fused deposition modelling) is the most widely used 3D printing technology. The product is built using strings of solid thermoplastic material in a filament form. The filament is pushed through a heated nozzle where it is melted. The nozzle moves around, laying down melted material at precise locations and amount following a pre-determined path. Material solidifies upon cooling allowing deposition of successive layers.

SSE (semi-solid extrusion) resembles FDM. It uses pressure-assisted extrusion and deposition of semi-solid material through a nozzle/syringe. The main difference is that there is no need for higher temperatures to melt input material.

Finally, SLA (stereolithography) uses a platform submerged into a tank of liquid photopolymer resin. Solidification of resin is done by a single-point laser of a specific wavelength. After the target areas of the layer have been exposed, the platform lifts up and lets a new layer of resin flow beneath. This process is repeated layer-by-layer to produce a solid part<sup>1)</sup>.

#### References

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