Virtual special issue of Nordic POP

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Published in:
European Journal of Pharmaceutical Sciences

DOI:
10.1016/j.ejps.2024.106737

Published: 01/06/2024

Document Version
Final published version

European Journal of Pharmaceutical Sciences 197 (2024) 106737

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Editorial

Virtual special issue of Nordic POP: Patient-oriented products

Prescribing medicine today is based on a one-size-fits-all principle. There is, however, a clear need for more personalized solutions in several critical therapy areas. Recent development within the genomics and diagnostic fields has enabled development of new innovative medicinal products relying on a combination of diagnostic tools and personalized doses. This approach is paving the way towards future health care systems based on personalized medicines. Limited attention has been given to the personalized end-product requirements for optimal therapeutic performance. Complex dosing regimens will require advances in product design to enable precise administration of the most appropriate dose. Innovations in pharmaceutical product design are required to alleviate potential problems. With this guiding principle as a common goal, the university hub Nordic POP (*Nordic Patient-Oriented Products*) was formed and funded by NordForsk for the years 2018-2025. The beauty of the Nordic POP spirit is to bring out the synergies in pharmaceutical sciences in the Nordic region. The willingness of academia and industry to share knowledge, infrastructure and resources has been the perfect ground for collaborative initiative to blossom and bear fruit. To showcase a few of the activities generated via these joint efforts, this Virtual Special Issue (VSI) presents innovative patient-oriented products, including new product design principles, novel methods for better understanding of the product performance, and bring us forward towards a paradigm shift in the manufacturing of these products. With these approaches, new personalized treatment strategies can be designed and the individual variation between patients can be considered.

1. Printing technologies for personalized dosage forms

A series of papers in this VSI focus on manufacturing of personalized dosage forms using additive manufacturing, also known as 3D printing. Amongst the various 3D printing methods available, especially semi-solid extrusion (SSE) 3D printing, popularly referred to as “3D bio-printing” when involving cells, stands out for pharmaceutical manufacturing due to its operation at room temperature and a wide range of suitable excipients to prepare printable gels and flexible tablet designs.

Koshovyi et al. (Koshovyi et al., 2023) used SSE-based 3D printing of eucalyptus extracts to produce rapidly dissolving preparations suitable for oral immediate-release dosage forms to treat staphylococcal infections. This showcases an innovative approach to formulate oral dosage forms of plant extracts with otherwise poor compression properties for conventional tableting. Mathiyalagan et al. (Mathiyalagan et al., 2023) developed nanoparticle-based printing inks for SSE to manufacture tablets containing the poorly water-soluble drug piroxicam. The drug was first nanoformed using the Controlled Expansion of Supercritical Solution (CESS®) technology in order to improve its dissolution rate. This study highlights the versatility of SSE for the production of personalized dosage forms with precise dose control encompassing enabling drug formulations to address challenges associated with poor water solubility.

A key challenge in SSE is the development of inks with suitable rheological properties for 3D printing. Korelc et al. (Korelc et al., 2024) investigated poly(vinyl alcohol-co-vinyl acetate) copolymers with variable monomer ratio on the resulting properties of hydrochlorothiazide films manufactured by SSE. The drug release rate and mechanical properties of the films were fine-tuned by the monomer ratios in the copolymer. In the above-mentioned studies, Mathiyalagan et al. (Mathiyalagan et al., 2023) used hydroxypropyl methyl cellulose or hydroxypropyl cellulose to formulate inks containing the nanoformed piroxicam, while Koshovyi et al. (Koshovyi et al., 2023) used polyethylene oxide to form a gel applicable for SSE after mixing it with the nanoemulsified eucalypt extract. Bansal and co-workers (Maru et al., 2023) also used nanoemulsions as a delivery strategy to improve the oral bioavailability and attenuate the cardiac toxicity of celecoxib. Here, poly(δ-decalactone) (PDL) was used both as an oil as well as in copolymerized form together with poly(ethylene glycol) as the surfactant of the nanoemulsion. This way, PDL-based nanoemulsions are suitable for development of oral formulations for poorly soluble drugs. No printing was involved in this study, but as the above-mentioned studies also have shown, the combination of nanotechnology and printing technologies can be an especially powerful one in the manufacturing of tailor-made medicines (Preis and Rosenholm, 2017).

Tho and co-workers (Larsen et al., 2024) explored another versatile 3D printing technology, fused deposition modeling (FDM), for the fabrication of honeycomb-shaped tablets loaded with an amorphous formulation of prednisolone. Crucial for FDM printing is the preparation of drug-loaded filaments by hot-melt extrusion, which are stable during storage and exhibit suitable printability for FDM. The study revealed the dependence of drug load and polymer molecular weight on the microstructure of 3D printed tablets. 3D printing is not only versatile to manufacture oral dosage forms, but also opens up new avenues for other administration routes. Scherließ’ group (Wostry and Scherließ, 2023) showed that carrier particles for inhalation can be engineered based on a combination of *in silico* studies using the discrete element method and 3D printing. The impact of particle geometry on drug loading capacity was elucidated, highlighting the unique capacity of 3D printing to tailor-design carrier particles for inhalation.

https://doi.org/10.1016/j.ejps.2024.106737

Available online 1 March 2024

2. Biorelevant *in vitro* models for early drug development of personalized products

With increasing product complexity and personalization, novel preclinical methods are also required for better foreseeing and understanding the product performance *in vivo* and ensuring high product quality. In this VSI, Brandl and co-workers (Eriksen et al., 2023) designed a novel cell-free *in vitro* setup based on an artificial biomimetic permeation barrier and microdialysis-sampling, and tested it for quasi-continuous monitoring of the dynamic dissolution/bioconversion/permeation of fosamprenavir. The proposed novel tool proved to be very promising in gaining an in-depth mechanistic understanding of the bioconversion/permeation interplay of phosphate-ester prodrugs like fosamprenavir, including transient supersaturation events. In another study by the team, they carried out *in vitro* combined dissolution/permeation studies to better understand the mechanism behind oral bioavailability enhancement of nanocrystal formulations (Lynnerup et al., 2023). Bergström and co-workers (Barmpatsalou et al., 2024) developed a canine artificial colonic mucus model that can be used to study drug permeation across colonic mucus. The developed canine mucus can be implemented in various assays and setups enabling its flexible use during early stages of drug development. di Cagno and colleagues (Tzanova et al., 2023) addressed drug dissolution/permeation with the aid of UV-localized spectroscopy and advanced data fitting to extract parameters for diffusivity and bound/free drug fractions of cyclodextrin and liposome formulations carrying three chemically diverse drug compounds. The proposed method proved to be adequate for calculating free drug fractions in these formulations, and supported the drug diffusion/permeation theory that the unbounded drug fraction is the main driving force for drug permeation across a membrane. The behavior of liposomes in presence of bile salts were also studied by Bohsen et al. (Bohsen et al., 2023) who determined the liposomes/bilayer integrity in the presence of intestinal bile salts by symmetric flow field-flow fractionation (AF4) coupled to multi-angle laser light scattering (MALLS) and a differential refractive index (dRI) detector. The AF4/MALLS/dRI technique can explain the underlying mechanisms during bile salt-induced liposomal breakdown. Furthermore, Kabedev and co-workers (Zhuo et al., 2024) used a combination of experimental and computational approaches to study the stabilization mechanisms of β-lactoglobulin-stabilized amorphous solid dispersions (ASDs). The experimental methods, such as differential scanning calorimetry and X-ray power diffraction, were supplemented with molecular dynamics simulations to identify the maximum drug loadings for ASDs with five different drug compounds, revealing the underlying stabilization factors. This highlights the capacity of computer simulations to predict ASD stability.

On a more molecular level, Ýr Þorgeirsdóttir et al. (Þorgeirsdóttir et al., 2023) made use of an alternative fluorescent label (selenomethionine, M^{Se}) to tag cell-penetrating peptides (CPPs) that are frequently used to increase drug delivery across the blood-brain barrier. The small size and amino acid nature of M^{Se} coupled to CPPs led to minimal alterations of the physicochemical properties of the CPPs as studied on brain capillary endothelial cell models compared to traditionally used fluorophores. Suominen et al. (Suominen et al., 2023) identified decreased function variants of efflux transporter ABCG2, which may increase systemic drug exposure by increasing drug absorption and plasma levels and therefore cause interindividual pharmacokinetic variability. Such *in vitro* phenotype classification may help to design more personalized drug treatments in the future.

Overall, these studies contribute to the toolbox of formulation scientists during early drug development to facilitate and accelerate development of personalized treatment strategies. These *in vitro* methods also contribute to the implementation of the 3Rs (refinement, reduction, and replacement) of animal usage in the drug development process. In this context, computational tools have quickly gained importance to support these efforts and can now be recognized as an integral part of research carried out in both the academic and industrial sectors of the Nordic POP community.

It is evident from this collection of publications in the VSI, that Nordic POP covers several disciplines. Bringing different disciplines together with the common goal of future patient-oriented products has shown to be a very efficient way to boost pharmaceutical development in the Nordic countries, and we are looking forward to continuing to do so for many years to come. Ensuring the fulfillment of this task is the newly NordForsk funded network Nordic Pharma Train (*Nordic Pharmaceutical Translation and Innovation*) that will be kicked off in autumn 2024. Through Nordic Pharma Train we will continue the research activities highlighted in this VSI, with a strengthened collaboration and commitment of Nordic industrial and clinical partners. This renewed commitment to continue our efforts to develop personalized treatment strategies will extend from 2024 to 2029, with the aspiration that its impact will reach far into the future.

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