University of Pannonia
Doctoral School of Chemical Engineering and Materials Sciences

Pharmaceutical formulation by nano spray drying

Summary of PhD dissertation

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2023

1. Introduction and objective

Traditional pharmaceutical products (tablets, capsules, syrups, ointments, etc.) often have poor biological efficacy and typically provide unregulated drug delivery. The requirement for new types of drug delivery systems is to achieve a broad and targeted effect with minimal damage to the tissues concerned. Spray drying is a major manufacturing option for powder-based drug delivery formulates. The nano spray drying device (Büchi B-90) enables the production of submicron to micron-sized granular products by means of a special piezoelectrically excited vibratory droplet formation technology and electrostatic particle collection. Delivery of the drug, either captured in nanostructured microparticles or bound to nanocarriers, can significantly improve bioavailability in the body to achieve maximum therapeutic effect.

In my work, I investigated the different effects of nano spray drying and the usability of products made by this process for different applications.

For samples containing metronidazole (MTZ), spray drying from solution and from suspension solution was investigated. In case of samples dried from solution, my aim was to investigate the effect of operational parameters and compositional variables on the structure of submicron and micron-sized MTZ polymer solid dispersions produced by nano spray drying. In addition to the amorphous or crystalline state of the active ingredient, particle size and morphology were also investigated to obtain information on the structure of the resulting micronized solid dispersions.

A nanosuspension solution containing MTZ in complexed form was prepared at the Supramolecular Chemistry Research Group of the Research Centre for Natural Science, where protonated MTZ was complexed by supramolecular cross-linking of 4-sulfonatocalix[4]arene (SCX4) polysaccharide chains and protonated chitosan. Since spray drying is a promising technology in modern pharmaceutical industry and one of the processes used to stabilize nanosuspensions, I investigated how this process affects the properties of self-assembled chitosan-$MTZH^+$ -SCX4 nanoparticles by converting them into powder form.

I prepared products from levocetririzine dihydrochloride (LC) for nasal and dermal application. My aim was to produce dry powdered microcapsules of LC by nano spray drying. For nasal drug delivery, three different mucoadhesive polymers, β-cyclodextrin (β-CD), and its three derivatives were selected as encapsulating material. I investigated the effect of the carriers on the powder characteristics, *in vitro* release and permeability of the drug on the nasal mucosa. For dermal application, the aim was to prepare a new gel formulation of the drug for topical

application against allergic oedema. The oleogel formulation was chosen as the basis for the formulation, since it is a promising carrier for transdermal delivery. Microencapsulation of LC by polymer resulted in solid form that was suspended into gel. The *ex vivo* penetration was investigated in human abdominal skin and *in vivo* efficacy of the drug was studied in mouse model.

2. Experimental and testing methods

The powder-based products were produced with the Büchi-B-90 nano spray dryer. For the determination of the drug content, UV-VIS spectrophotometric method was used, and the particle size and distribution data were determined by laser diffraction method. The morphology of microcapsules was investigated by scanning and transmission electron microscopy. In addition to thermoanalytical measurements, powder X-ray diffraction measurements were used to characterise the solid phase state of the products. The newly formed molecular bonding was studied by Fourier transform infrared spectroscopy. I also investigated the *in vitro* release and permeability of the nasal powders, which were measured using standard device. LC powder was suspended into oleogels for dermal application. The *ex vivo* skin penetration behaviour of the gels was studied by confocal Raman spectroscopy. *In vivo* anti-inflammatory experiments were performed in a mouse model of ear edema induced with croton oil.

3. New scientific results

1. I prepared nanostructured metronidazole-polymer microparticles using crystalline metronidazole and amorphous hydroxypropyl methylcellulose and polyvinylpyrrolidone polymers by nano spray drying method. Melting point decrease phenomenon was observed by differential scanning calorimetry between the bulk metronidazole and the drug-loaded spray-dried products. Peak broadening was indicated by powder X-ray diffraction measurements, which could be the result of formation of small drug crystallites. The differential scanning calorimetry, X-ray diffraction and transmission electron microscopic analysis supported my assumption that the metronidazole-polymer microparticles were nanostructured solid dispersions in which the nanometer size crystals and the molecularly dispersed fraction of the active ingredient distributed in the amorphous polymer matrix (S1).

2. Nanosuspension of protonated metronidazole-macrocyclic 4-sulfonatocalix[4]arene complex crosslinked with protonated chitosan was nano spray dried using hydroxypropyl methylcellulose additive, therefore I managed to develop a storable and concentrated form of the chitosan-metronidazole-4-sulfonatocalix[4]arene drug-carrier complex. In the obtained solid dispersion, metronidazole was integrated in the polymer matrix partly in a stable crystalline and partly in a molecularly dispersed form according to differential scanning calorimetry and X-ray diffraction analysis. The molecularly dispersed metronidazole content was significantly higher in the product dried from chitosan-metronidazole-4-sulfonatocalix[4]arene nanoparticle suspension in the presence of hydroxypropyl methylcellulose than in that one spray dried from the metronidazole+hydroxypropyl methylcellulose solution attributable to the interaction between the protonated metronidazole and the 4-sulfonatocalix[4]arene in acidic medium, as well as to the lack of chloride ions available for neutralization of the free $MTZH^+$ in the presence of also positively charged chitosan-metronidazole-4-sulfonatocalix[4]arene complex (S2).

3. Dry powder microparticles were produced from levocetirizine dihydrochloride for nasal administration by nano spray drying process. I found that beta-cyclodextrin, randomly methylated-beta-cyclodextrin, sulfobutyl-ether-beta-cyclodextrin sodium salt, (hydroxypropyl)-beta-cyclodextrin, hydroxypropyl methylcellulose, polyvinyl alcohol and polyvinylpirrolidone were suitable additives to produce easy-to-handle powder product with high yield. X-ray mapping showed that, while the raw material was crystalline, the drug-additive composites were amorphous in all products (S4).

4. Nano spray drying of levocetirizine dihydrochloride active ingredient was achieved with hydroxypropyl methylcellulose polymer carrier. The originally crystalline active ingredient was embedded in its amorphous state into the amorphous polymer according to X-ray diffraction investigations. The nano spray-dried powder could be easily and homogeneously dispersed in dermal oil gel in order to obtain an effective formulation for the treatment of allergic edema. Qualitative *ex vivo* penetration studies using a Raman microscopic correlation mapping proved the epidermal and also the upper dermal enrichment of the preparation. Furthermore, the addition of menthol penetration enhancer enriched the drug in the upper dermis of human abdominal skin, which is beneficial considering the expected effect. *In vivo* tests on mouse model of ear edema induced by croton oil showed similar anti-inflammatory efficiency of my levocetirizin-loaded oil gel to commercial Fenistil gel; moreover, the gel volume, and consequently the applied drug amount, could be decreased considerably with the addition of menthol (S3).

4. Publication list

Publications on which the dissertation is based:

S1. **Mirankó, M.**, Trif, L., Tóth, J., Feczkó, T. (2021). Nanostructured micronized solid dispersion of crystalline-amorphous metronidazole embedded in amorphous polymer matrix prepared by nano spray drying Advanced Powder Technology, 32(7), 2621-2633.

IF: 4.969

S2. **Mirankó, M.**, Megyesi, M., Miskolczy, Z., Tóth, J., Feczkó, T., Biczók, L. (2021). Encapsulation of metronidazole in biocompatible macrocycles and structural characterization of its nano spray-dried nanostructured composite. Molecules, 26(23), 7335-7349.

IF: 4.927

S3. **Mirankó, M.**, Tóth, J., Fodor-Kardos, A., Móricz, K., Szenes-Nagy, A. B., Gácsi, A., Spaits, T., Gyenis, J., Feczkó, T. (2022). Topical Formulation of Nano Spray-Dried Levocetirizine Dihydrochloride against Allergic Edema. Pharmaceutics, 14(12), 2577-2587.

IF: 6.525

S4. **Mirankó, M.**, Tóth, J., Bartos, C., Ambrus, R., Feczkó, T. (2023). Nano-Spray-Dried Levocetirizine Dihydrochloride with Mucoadhesive Carriers and Cyclodextrins for Nasal Administration. Pharmaceutics, 15(2), 317-329.

IF: 6.525

Other publication:

Hajba-Horváth, E., Biró, E., **Mirankó, M.**, Fodor-Kardos, A., Trif, L., & Feczkó, T. (2020). preparation and in vitro characterization of valsartan-loaded ethyl cellulose and poly (methyl methacrylate) nanoparticles. RSC advances, 10(72), 43915-43926.

Conference presentations:

Mirankó, M.; Tóth, J.; Feczkó, T. (2018) Preparation of microencapsulated composite drug carriers by nano spray drying (in Hungarian), XVIII. PhD Students Materials Science Day, November 26, 2018, Veszprém, Hungary

Mirankó, M.; Tóth, J.; Feczkó, T. (2019) Preparation of nanostructured drug-polymer composites by nanopowder drying (in Hungarian), 12th Roundtable Conference of the Crystallization and Drug Formulation Section, April 29, 2019, Balatonszemes, Hungary

Mirankó, M.; Tóth, J.; Rippelné, Pethő D. (2019) Preparation of microencapsulated composite drug carriers by nano spray drying (in Hungarian), XXXIVth OTDK Section of Chemistry and Chemical Engineering, March 21-23, 2019, Budapest, Hungary

Mirankó, M.; Trif, L.; Tóth, J.; Feczkó, T. (2020) Structure of drug-polymer composites prepared by nano spray dryer, 6th International Conference on New Trends in Chemistry October 17-18, 2020, E-Conference

Mirankó, M.; Trif, L.; Tóth, J.; Feczkó, T. (2022) Microencapsulation of metronidazole by nano spray drying, 50th Technical Chemical Days Anniversary Conference, April 26-28, 2022, Veszprém, Hungary