University of Szeged
Faculty of Pharmacy
Department of Pharmaceutical Technology

INNOVATIVE PHARMACEUTICAL FORMULATIONS AND EXCIPIENTS FOR NASAL DELIVERY OF DRUGS TO TARGET THE SYSTEMIC CIRCULATION

Summary of the Ph.D. thesis

Levente Kürti

Supervisors:
Prof. Dr. habil. Piroska Révész, Pharm.D., D.Sc.
Department of Pharmaceutical Technology
University of Szeged

Dr. habil. Mária Deli, M.D., Ph.D.
Biological Research Centre
of the Hungarian Academy of Sciences

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University of Szeged
Graduate School of Pharmaceutical Sciences

Educational Program: Pharmaceutical Technology
Head: Prof. Dr. Piroska Szabó-Révész

Department of Pharmaceutical Technology

Supervisors
Prof. Dr. habil. Piroska Szabó-Révész, Pharm.D., D.Sc.
Dr. habil. Mária A. Deli, M.D., Ph.D.

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1. INTRODUCTION

Intranasal administration is an effective way to deliver drugs into the systemic circulation as an alternative to the oral and parenteral routes for some therapeutic agents (Fig. 1). Undoubtedly, the nasal administration of medicines has been widely used for the treatment of topical nasal conditions such as nasopharyngitis or allergic rhinitis for many years. The nasal pathway may circumvent the blood–brain barrier and allow centrally acting pharmacons a direct transport route to the central nervous system. Concerning systemic delivery, drugs can be rapidly absorbed through the nasal mucosa, resulting in a quick onset of action, and avoiding degradation in the gastrointestinal tract and first-pass metabolism in the liver.

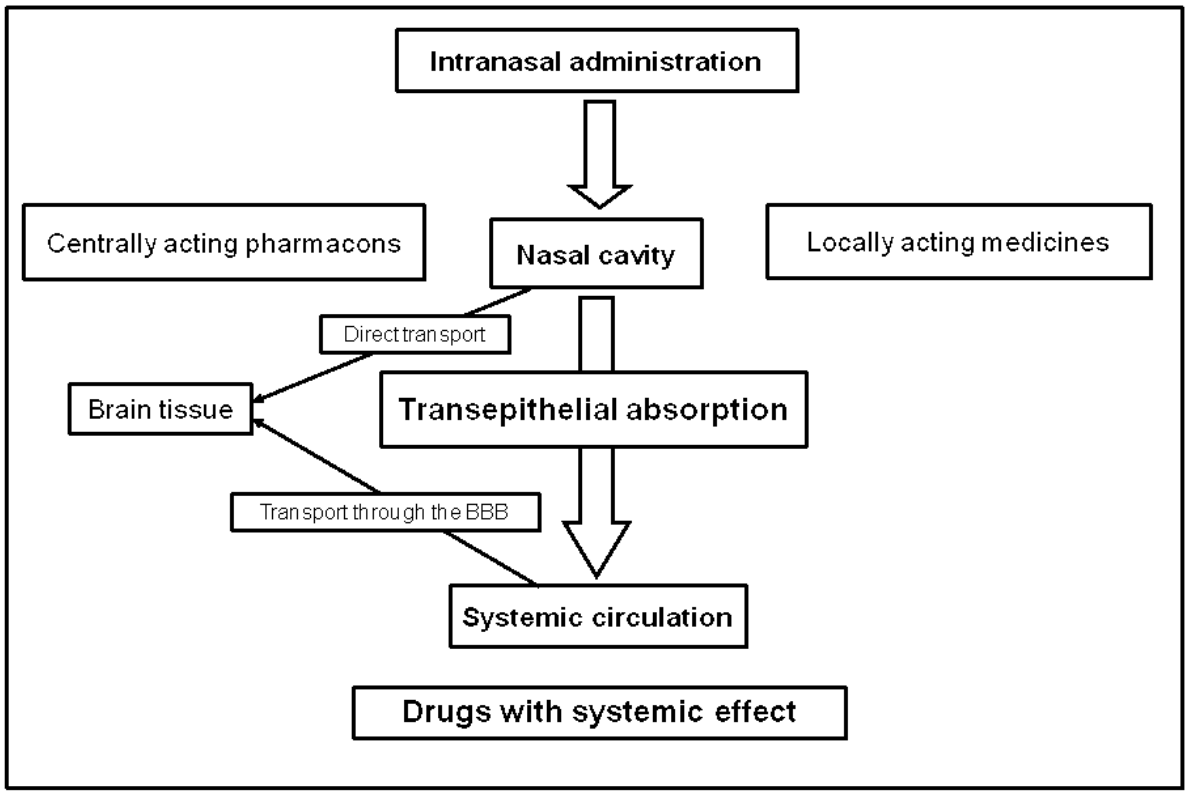

Fig. 1: *Intranasal administration of drugs. The target for drug delivery can be the nasal mucosa, the central nervous system or the systemic blood circulation.*

During the formulation of a pharmaceutical dosage form intended for intranasal application, several factors should be taken into consideration. The poor solubility of a drug and its low rate of dissolution can lead to insufficient absorption or delayed therapeutical effect. Indeed the nasally administered pharmaceutical preparations will be cleared rapidly from the nasal cavity into the gastrointestinal tract by the mucociliary clearance system.

2. AIMS

For the development of relevant strategies to overcome biological barriers (eg. nasal mucosa) and in order to screen the feasibility of drug nanoparticles, innovative excipients and novel pharmaceutical compositions for nasal delivery targeting the systemic blood circulation, *in vitro* permeability models are useful and relevant tools.

The aim of my scientific work was to establish an *in vitro* investigational protocol for drugs intended to use in nasal delivery (Fig. 2). The application of cell-based assays as well as conventional investigational methods of pharmaceutical technology is crucial for understanding the toxicity and efficacy of an innovative pharmaceutical composition.

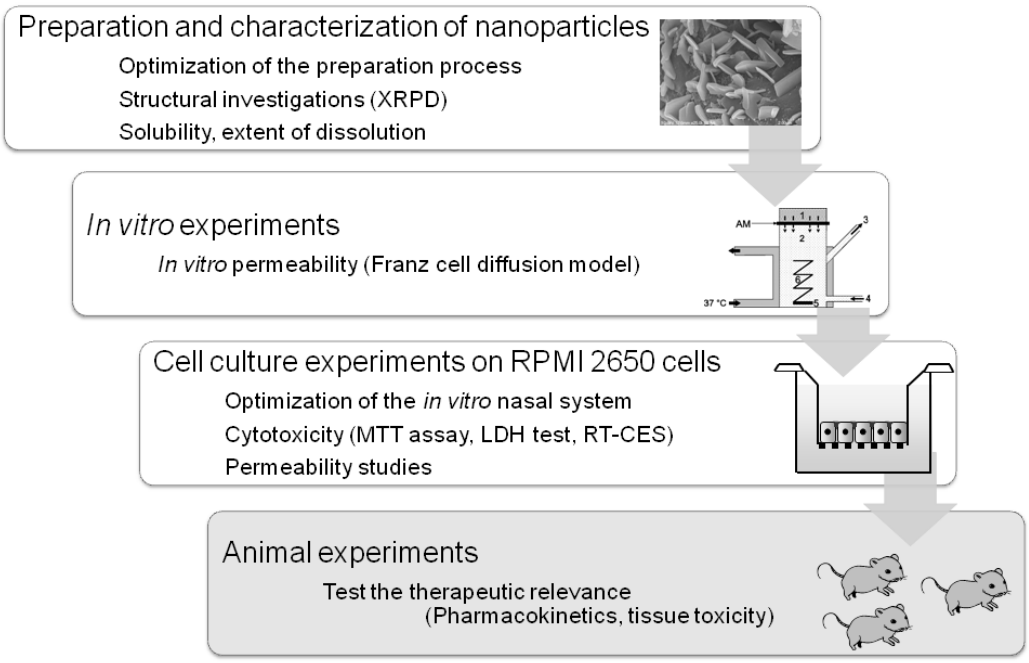

Fig. 2: *The steps of a nasal investigational protocol to screen innovative formulations (nanoparticles) and novel pharmaceutical excipients (permeation enhancers).*

The main steps of our experiments were the following:

(i) preparation and characterisation of meloxicam nanoparticles by co-grinding

(ii) optimization of the preparation process by factorial experiment design

(iii) establishment of *in vitro* methods for studying permeability of drugs in nasal formulations

(iv) optimization of a culture model of the nasal system using RPMI 2650 cells

(v) screen of the toxicity and efficacy of drug nanoparticles and pharmaceutical excipients by *in vitro* methods

3. MATERIALS AND METHODS

3.1. Preparation and characterization of meloxicam nanoparticles

Meloxicam (MEL) was obtained from EGIS Ltd. (Hungary). The grinding additives, polyvinylpyrrolidone (PVP) K25 and C30 were purchased from BASF (Germany). Polyethylene glycol (PEG) 6000 and 20 000 were from Sigma–Aldrich Chemie GmbH (Germany). MEL and carriers were mixed and charged into the chamber of the planetary monomill (Fritsch Pulverisette 6, Fritsch GmbH, Germany).

Determination of particle size was performed by scanning electron microscopic image analysis. Products were washed and centrifuged to separate the excipient from the MEL, so that individual MEL particles could be studied. The particle size and the surface morphology of the MEL particles were visualised by scanning electron microscopy (SEM). Samples were fixed onto a metallic stub with double-sided conductive tape (diameter 12 mm, Oxford Instruments, UK). Images were taken in secondary electron image mode on a Hitachi S-4700 Type II instrument (Japan) at an acceleration voltage of 10 kV.

MEL particle diameter distributions were obtained by analysing SEM images with the ImageJ software environment. Over 150 individual particle measurements were made in at least five different images in order to determine the particle size.

The following variables were the parameters featuring in the optimization (Table 1). A full factorial design plan was created and carried out with the MEL particle size distribution defined as response factor. All calculations were performed by using Minitab 14 (Minitab Statistical Software, USA).

Table 1 *Compositions of different samples, parameters of optimization*

Meloxicam/ excipient ratio	1:0.5, 1:1, 1:2
Excipients	PVP–C30, PVP–K25, PEG 6000, PEG 20 000
Revolutions per minute (rpm)	200, 300, 400

3.2. Investigations of the optimized products

The physical state of MEL in the different samples was evaluated by X-ray powder diffraction (XRPD) analysis. Diffraction patterns were analysed with a Miniflex II X-ray Diffractometer (Rigaku Co., Japan).

The solubility of MEL was determined at physiological conditions (pH 7.4, 37 °C) by addition of an excess of the drug to the solvent, after which the mixture was stirred on a

magnetic stirrer for 8 h, and the content of dissolved drug was analysed (Unicam UV/vis spectrophotometer, Germany). The extent of dissolution of MEL was studied in 50 mL phosphate buffer (PBS) at physiological conditions with Pharmatest equipment (Germany) at a paddle speed of 100 rpm.

3.3. Franz cell diffusion – *In vitro* permeability

In vitro permeability studies were performed with a vertical Franz–diffusion cell system (Hanson Research, USA) containing six cells. The donor phase contained MEL in 1 mg/mL and sodium hyaluronate in 5 mg/mL concentration, which were placed on the synthetic membrane impregnated with isopropyl myristate. Experiments were performed at 37 °C water bath. At predefined time points, samples of 0.8 mL were taken from the acceptor phase by the autosampler (Hanson Research, USA) and were replaced with fresh receiving medium.

3.4. Cell culture experiments

RPMI 2650 (ATCC cat.no. CCL 30) cells were grown in Eagle's minimal essential medium supplemented with 10% foetal bovine serum and gentamicin in a humidified 37 °C incubator with 5% CO_2. The cells were seeded on culture dishes at a density of 5×10^5 cells/cm^2 and the medium was changed every 2 days. For the cell viability assays cells were passaged to 96-well plates, for immunohistochemistry and nucleus staining cells were cultured on glass coverslips. For permeability studies cells were cultured on Transwell filter inserts (polycarbonate membrane, Corning Costar Co., USA). All surfaces were coated with rat tail collagen before cell seeding. Cell growth and morphology were monitored using a Nikon Eclipse TE2000 microscope (Nikon, Japan).

The culture model was optimised by testing the 24-h effect of retinoic acid (RA) in three different concentrations: 0.01, 100, 300 μg/mL. Hydrocortisone (HC) was examined at 500 nM; 8-(4-chlorophenylthio) adenosine 3',5'-cyclic monophosphate sodium salt (CPT-cAMP) at 250 μM in the presence of 17.5 μM 4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone (RO20-1724, Calbiochem, Germany), a phosphodiesterase inhibitor.

Electron microscopy

RPMI 2650 cells grown on Transwell filter membrane were fixed. After washing with cacodylate buffer several times, the membranes of the culture inserts with the cells were removed from their support and placed into 24-well chamber slide and were postfixed in OsO_4. Finally the membranes of the culture inserts with the cells were removed from their

support and embedded in Taab 812 (Taab, UK). Following polymerisation, ultrathin sections were cut perpendicularly for the membrane using a Leica UCT ultramicrotome (Leica Microsystems, UK) and examined using a Hitachi 7100 transmission electron microscope (Hitachi Ltd., Japan). Electron micrographs were made by Megaview II (lower resolution, Soft Imaging System, Germany). Brightness and contrast were adjusted if necessary using Adobe Photoshop CS3 (USA).

Immunohistochemistry

To stain for junctional proteins RPMI 2650 cells cultured on rat tail collagen coated glass coverslips were washed and fixed. After washing cells were blocked with bovine serum albumin and incubated with primary antibody anti–β–catenin (Invitrogen, USA). Incubation with secondary antibody Cy3–labeled anti-rabbit IgG and Hoechst dye 33342 to stain cell nuclei lasted for 1 h. Between and after incubations cells were washed. Coverslips were mounted in Gel Mount (Biomeda, USA) and staining was examined by Olympus Fluoview FV1000 confocal laser scanning microscope.

Cytotoxicity assays

Real-time cell electronic sensing (RT-CES) is a label-free technique for dynamic monitoring of living cells. The xCELLigence system (Roche, Switzerland) utilises an electronic readout called impedance to non-invasively quantify adherens cell proliferation and viability. A special 96-well E–plate (Roche, Hungary) contains microelectronic sensor arrays. Culture media was added to each well for background readings than cell suspension was dispensed at the density of 6×10^3 cells/well. The cells were kept in an incubator for 24 h and monitored every 5 min. The cell index at each time point was defined as $(R_n–R_b)/15$, where R_n is the cell–electrode impedance of the well when it contains cells and R_b is the background impedance of the well with the media alone.

Lactate dehydrogenase (LDH) release, the indicator of cell membrane damage, was determined from culture supernatants by a commercially available kit (Cytotoxicity detection kit LDH, Roche, Switzerland).

Living cells convert the yellow dye 3-(4,5-dimethyltiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) to purple, insoluble formazan crystals. After treatments the cells were incubated with MTT solution in an incubator. The amount of formazan crystals was dissolved in dimethyl sulfoxide and determined with a microplate reader (Fluostar Optima, BMG Labtechnologies, Germany).

Viability and nuclear morphology of RPMI 2650 cells were confirmed by fluorescent staining. *Bis*-benzimide (Hoechst dye 33342) labels the nuclei of both viable and dead cells. Ethidium-homodimer-1 (Molecular Probes, USA) cannot pass through the plasma membrane of viable cells, therefore only stains dead cells. Cell layers grown on coverslips were treated with surfactants, then *bis*-benzimide and ethidium-homodimer-1 was added. At the end of incubation cells were fixed, washed, mounted, and analysed using a fluorescent microscope (Nikon Eclipse TE2000, Japan) and photographed by a Spot RT digital camera (Diagnostic Instruments, USA).

Nasal epithelial permeability studies

The flux of MEL and fluorescein isothiocyanate labeled dextran (FITC-dextran, mw: 4.4 kDa) across epithelial cell layers were determined in permeability assays. RPMI 2650 cells were seeded onto Transwell filter inserts and grown for 2 days than the RPMI 2650 cells were treated with RA and HC for 24 h. The inserts were transferred to 12-well plates containing 1.5 mL Ringer–Hepes solution in the basolateral compartments. In apical chambers the culture medium was replaced by 500 μL formulations containing 1 mg/mL MEL prepared in Ringer–Hepes. In case of studying permeability enhancers the culture medium from the apical chambers was replaced by 500 μL Ringer–Hepes containing 100 μg/mL FITC-dextran and the selected concentrations of permeability enhancers. The plates were kept in an incubator for 1 h on a rocking platform. After incubation the concentrations of the drug and the marker in samples from the basolateral compartments were determined and the apparent permeability coefficients (P_{app}) were calculated as described by Youdim et al. (Drug Discov Today 8, 997, 2003).

4. RESULTS AND DISCUSSION

4.1. Preparation and characterization of meloxicam nanoparticles

With PVP–C30, it was possible to decrease the average MEL particle size (d_{SEM}) below 250 nm and the average SD below 50%. This was a significant improvement relative to the additive-free grinding result. The optimum co-grinding parameter set for PVP–C30 was a MEL to excipient ratio 1:1, and a rotation frequency of 400 rpm.

Table 2 *Optimized products*

Grinding excipient	Drug to excipient ratio	Rotation speed (rpm)	d_{SEM}±SD (nm)
PVP–C30	1:1	400	140.4±69.2
PEG 6000	1:2	400	173.8 ± 60.3

The crystallinity of MEL was decreased in the co-grinding process with PVP–C30; in the other optimized product, which contains PEG 6000 the crystallinity of MEL did not change significantly as compared to the physical mixture. The crystalline MEL was altered in the co-grinding process with the amorphous excipient, PVP–C30, leading to amorphous nanoparticles. With PEG 6000 as excipient, MEL nanocrystals were prepared and the crystallinity of MEL was proved by XRPD (Fig. 3).

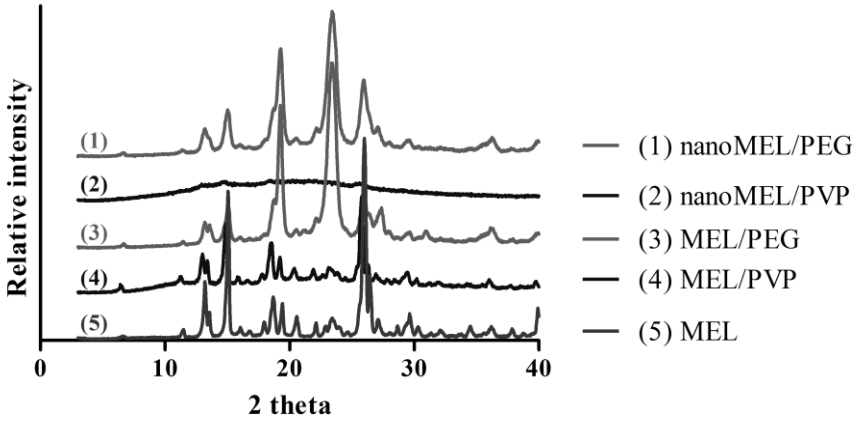

Fig. 3: *X-ray powder diffraction spectra of the optimized products (1, 2), the physical mixtures of the components (4, 3) and meloxicam (5).*

4.2. Dissolution of meloxicam nanoparticles

Amorphous MEL nanoparticles showed favourable dissolution properties at physiological conditions. In one hand the solubility of MEL elevated up to about 1 mg/mL (Fig. 4A), on the other hand the extent of dissolution also increased, complete dissolution of MEL was observed in 15 min (Fig. 4B).

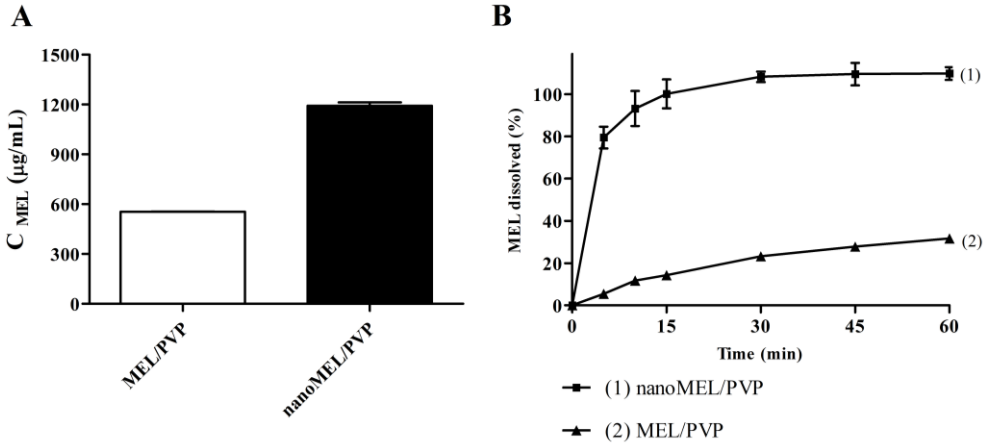

Fig. 4: *(A) Solubility of meloxicam (MEL) in case of the physical mixture (MEL/PVP) and the co-ground product (nanoMEL/PVP) in phosphate buffer (pH 7.4, 37 °C). (B) The extent of dissolution of MEL in case of the physical mixture (MEL/PVP) and the co-ground product (nanoMEL/PVP) in phosphate buffer (pH 7.4, 37 °C). MEL/PVP, meloxicam and polyvinylpyrrolidone C30 mass ratio 1:1.*

The cumulative amount of MEL that diffused through a synthetic membrane from the different pharmaceutical compositions was measured against time (Fig. 5). The diffusion from the composition containing MEL nanoparticles and sodium hyaluronate was quicker, 25% of MEL was released from the formulation containing MEL in nanonized form *vs.* 10% in case of the physical mixture in the first 2 h.

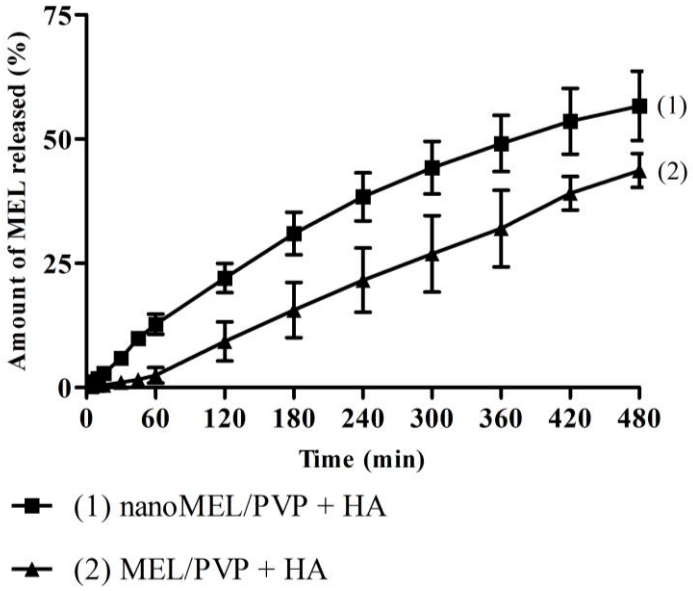

Fig. 5: *In vitro permeability of meloxicam through an artificial membrane in case of the physical mixture (MEL/PVP) and the coground product (nanoMEL/PVP) in phosphate buffer (pH 7.4, 37 °C). MEL/PVP, meloxicam and polyvinylpyrrolidone C30 mass ratio 1:1; HA, sodium hyaluronate (5 mg/mL).*

4.3. *In vitro* cell culture model of the nasal barrier

Due to the importance of systemic nasal drug delivery there is a need for cell culture models of the nasal barrier for testing various compounds and pharmaceutical compositions. The properties of such *in vitro* systems need to be compared with *in vivo* circumstances.

In our experiments RPMI 2650 cells grew as mono- or multilayers and reached confluence in liquid–liquid interface culture condition. The presence of intercellular junctions was confirmed by electron and immunofluorescent microscopy. Besides morphological investigations the functional properties of the nasal epithelial barrier such as resistance and paracellular permeability were also proved.

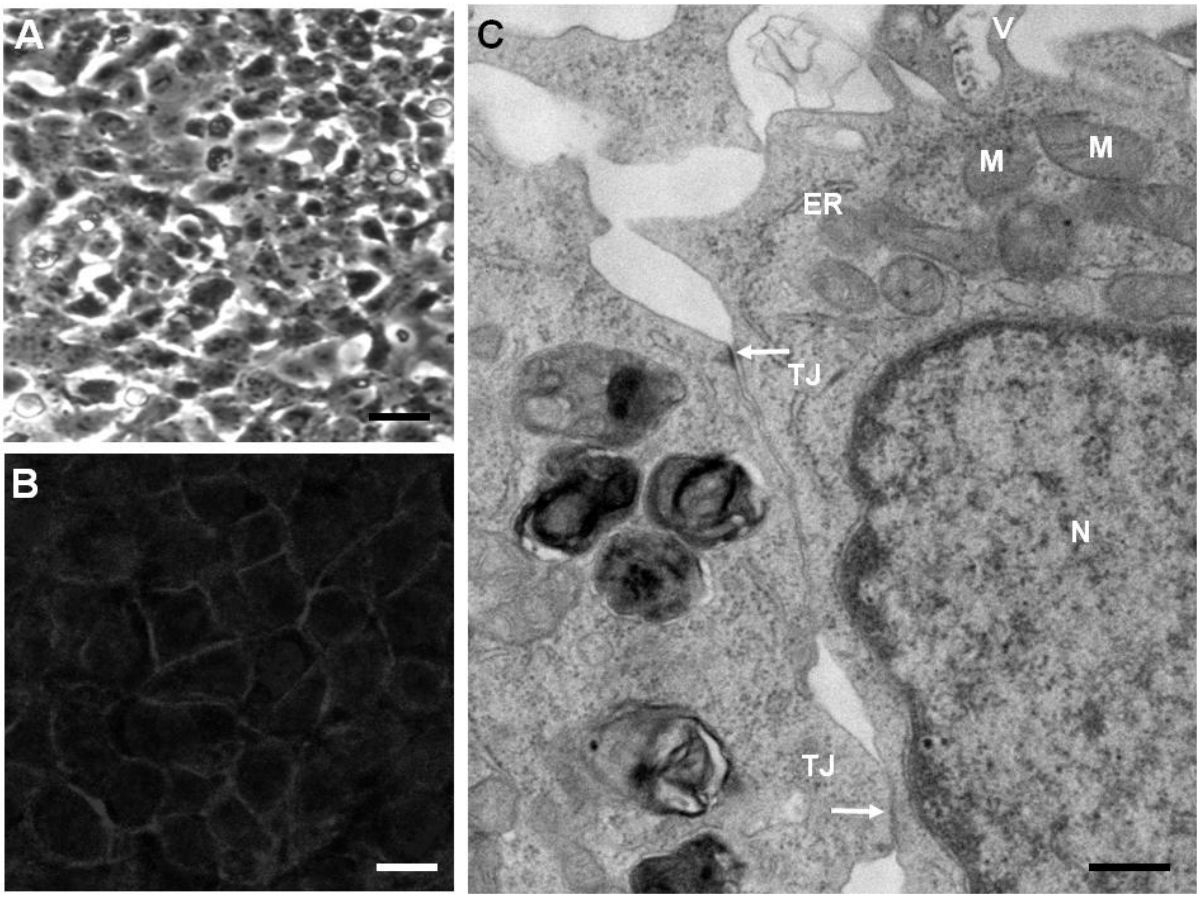

Fig. 6: *Morphological characterisation of RPMI 2650 human nasal epithelial cell line. (A) Phase contrast microscopic image of the cells (bar: 25 µm) and (B) confocal microscopic image of β–catenin immunostaining (bar: 10 µm) show cobble-stone, epithelial morphology. (C) Electron microscopic image of RPMI 2650 cells where arrows indicate tight intercellular junctions (N, nucleus; M, mitochondrion; ER, endoplasmatic reticulum; TJ, tight junction; V, microvilli; bar: 250 nm).*

Advantages of the presented *in vitro* nasal system include simplicity of culture, reproducibility, suitability for permeability studies and RT-CES. RPMI 2650 cells model the respiratory zone of the human nasal epithelium which is the most important absorption surface for nasally administered drugs to the systemic circulation. The absence of cilia and air–liquid interface can be considered as limitations of this nasal model. The presented data support that RPMI 2650 cells can be successfully used to establish an *in vitro* model of the nasal barrier and to test toxicity and epithelial permeability.

4.4. Permeability of meloxicam nanoparticles across the *in vitro* nasal barrier

To test the biological effects of the MEL nanoparticles an *in vitro* cell culture model of the nasal barrier, human RPMI 2650 cells were used. Impedance measured by RT-CES non-invasively quantifies adherens cell proliferation, viability and cell layer integrity. The RT-

CES results indicated no sign of disruption in the integrity of the RPMI 2650 cell layers, which could be observed in the toxicity control group (Fig. 7A).

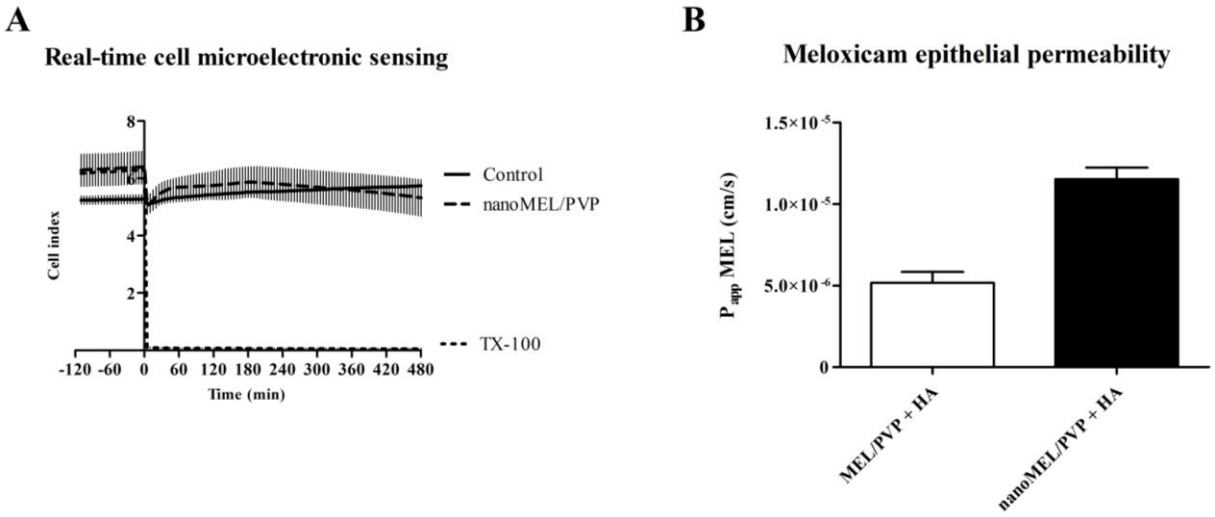

Fig. 7: *(A) Real-time cell microelecronic sensing measurement of cell viability and integrity of human RPMI 2650 nasal epithelial cells treated by vehicle and the co-ground product (nanoMEL/PVP). (B) Apparent permeability coefficients (P_{app}) of MEL in case of the physical mixture (MEL/PVP) and the co-ground product (nanoMEL/PVP) measured across human RPMI 2650 nasal epithelial cell layers. MEL/PVP, meloxicam and polyvinylpyrrolidone C30 mass ratio 1:1; HA, sodium hyaluronate (5 mg/mL); TX-100, TritonX-100 (10 mg/mL).*

The flux of MEL through the human RPMI 2650 cell layers was significantly slower than in the case of the Franz cell diffusion model, reflecting the more complex nasal barrier model of the *in vitro* cell culture system. The permeability coefficient of MEL for the composition containing MEL nanoparticles and sodium hyaluronate was 1.2×10^{-5} cm/s *vs.* 0.5×10^{-5} cm/s in case of the physical mixture (Fig. 7B).

4.5. Effects of sucrose esters and reference surfactants on epithelial barrier integrity

Sucrose esters elicited dose-dependent TEER changes (Fig. 8A–B). At 0.1 mg/mL concentrations both laurate and myristate sucrose esters led to a significant and transient TEER decrease, while 0.3 mg/mL and higher concentrations caused an irreversible drop of TEER. Tween 80 at 10 mg/mL dose also resulted in a significant TEER decrease, while the lower concentration, similarly to 1 and 10 mg/mL concentration of Cremophor RH40 did not cause changes as compared to control group.

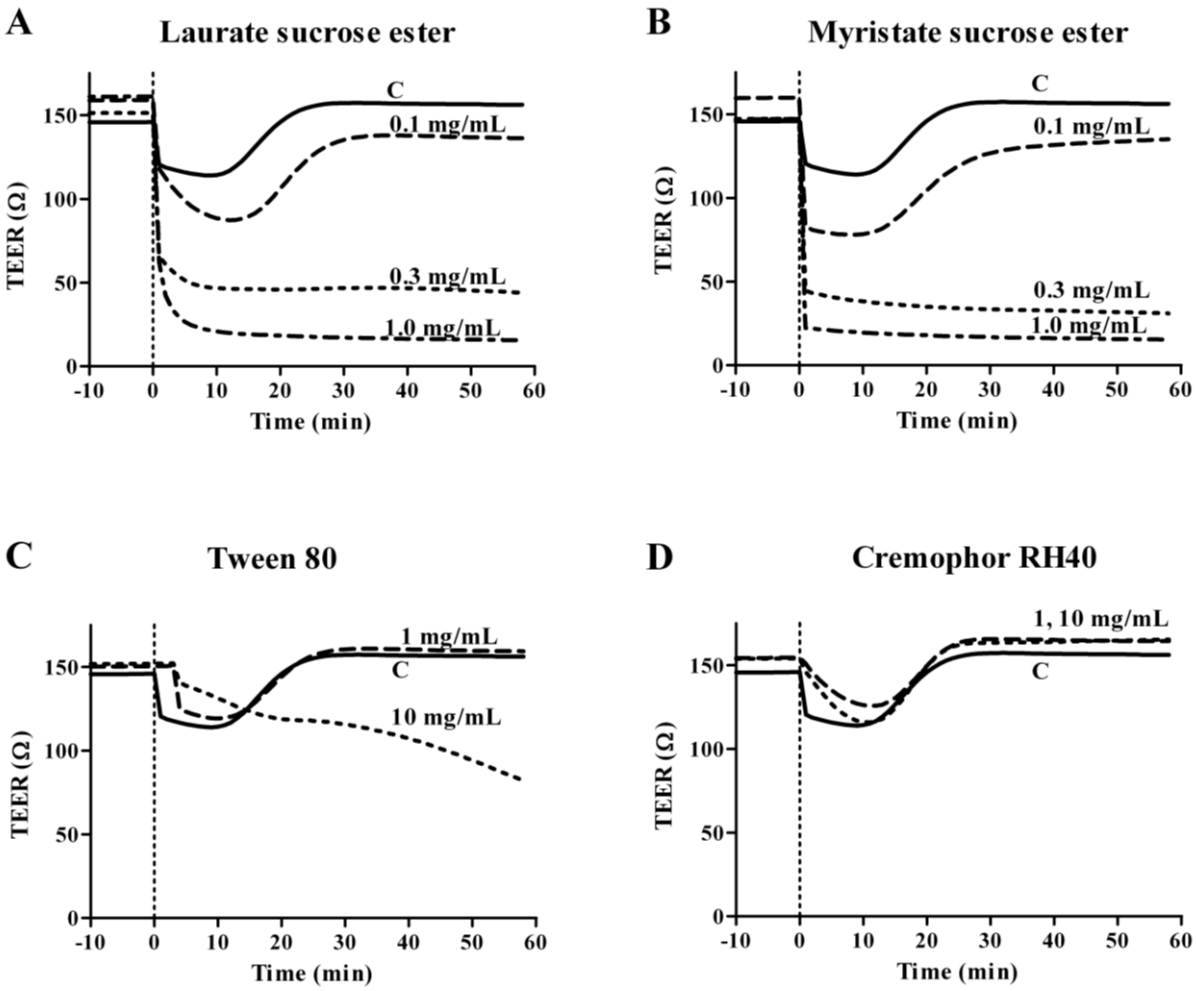

Fig. 8: *Kinetics of the changes in transepithelial resistance of RPMI 2650 cells after treatment with surfactants. Broken line at 0 minutes indicates the onset of treatment. Data are presented as mean, n=4. C, control; TEER, transepithelial electric resistance.*

By treating the confluent layers of RPMI 2650 epithelial cells with previously determined safe, non-toxic concentrations of various surfactants, permeability experiments with FITC-dextran, a hydrophilic paracellular marker with an average molecular weight of 4.4 kDa, the size of a peptide were performed. Laurate sucrose ester increased significantly the permeability of RPMI 2650 cell layers in a concentration-dependent manner (Fig. 9A). After 1-h treatment with 0.1 mg/mL laurate sucrose ester the apparent permeability coefficient of FITC-dextran was increased by 50%.

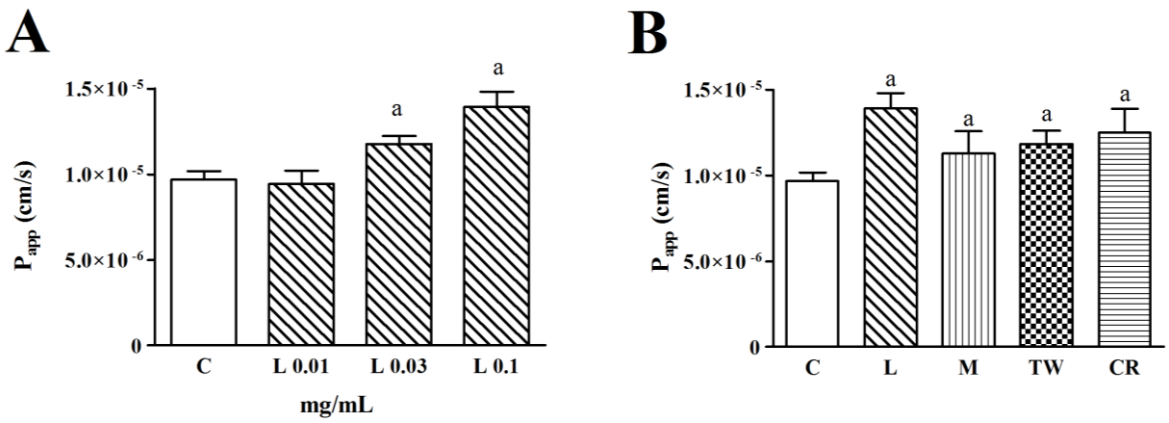

Fig. 9: *The effect of non-toxic doses (0.01, 0.03, 0.1 mg/mL) of laurate sucrose ester (A) and of excipients applied in the same concentration of 0.1 mg/mL (B) on the apparent permeability coefficients of FITC-dextran on confluent RPMI 2650 cell layers. a: significantly different as compared to control group, p<0.05. Data are presented as mean±SD, n=3. C, control; CR, Cremophor RH40; L; laurate surose ester; M, myristate sucrose ester; TW, Tween 80; P_{app}, apparent permeability coefficient.*

Comparing the effects of sucrose esters and the reference surfactants on the permeability for the marker molecule across epithelial cell layers, the same, non-toxic concentration of 0.1 mg/mL was chosen for all compounds. All excipients increased significantly the epithelial paracellular permeability; the largest increase was seen in case of laurate sucrose ester, the P_{app} values were elevated from 9.7×10^{-6} cm/s to 1.4×10^{-5} cm/s after 1-h treatment (Fig. 9B).

5. SUMMARY

Novel sites of drug administration for systemic delivery and novel formulations offer numerous opportunities to develop innovative pharmaceutical compositions. The nasal pathway represents an alternative route for non-invasive systemic administration of drugs, although the nasal epithelium forms a restricting barrier. Nanonization of drugs is a great possibility to increase solubility and to augment permeability through mucosal barriers. Pharmaceutical excipients may help to increase the solubility of active agents and enhance the permeability of molecules with larger molecular mass like peptides via the modulation of the paracellular pathway.

An *in vitro* investigational protocol have been established to produce, characterize and screen innovative pharmaceutical solutions, namely meloxicam drug nanoparticles and

sucrose esters, novel biodegradable non-ionic surface active excipients to enhance nasal drug delivery. Both conventional investigational methods of pharmaceutical technology and cell-based assays have been used.

Using meloxicam as a model drug and polyvinylpyrrolidone as an excipient nanoparticles have been successfully produced by a co-grinding process optimized in a factorial experimental design. The physicochemical properties of these amorphous drug nanoparticles were favourable as compared to physical mixture. Increased solubility, enhanced extent of dissolution and *in vitro* permeability were found which are crucial parameters for nasal delivery. A human nasal epithelial cell culture model was established, characterized and optimized by morphological and functional methods. This model based on RPMI 2650 cells was applied for toxicity and permeability measurements. Nanonization resulted in enhanced permeability for meloxicam across epithelial cell layers without cellular toxicity and damage to barrier integrity. Sucrose esters at low doses altered paracellular permeability for a peptide-sized marker molecule of nasal epithelial cells without toxic effects.

The presented nasal investigational protocol may contribute to the development of new pharmaceutical compositions and better screening systems for nasal delivery of pharmacons.

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