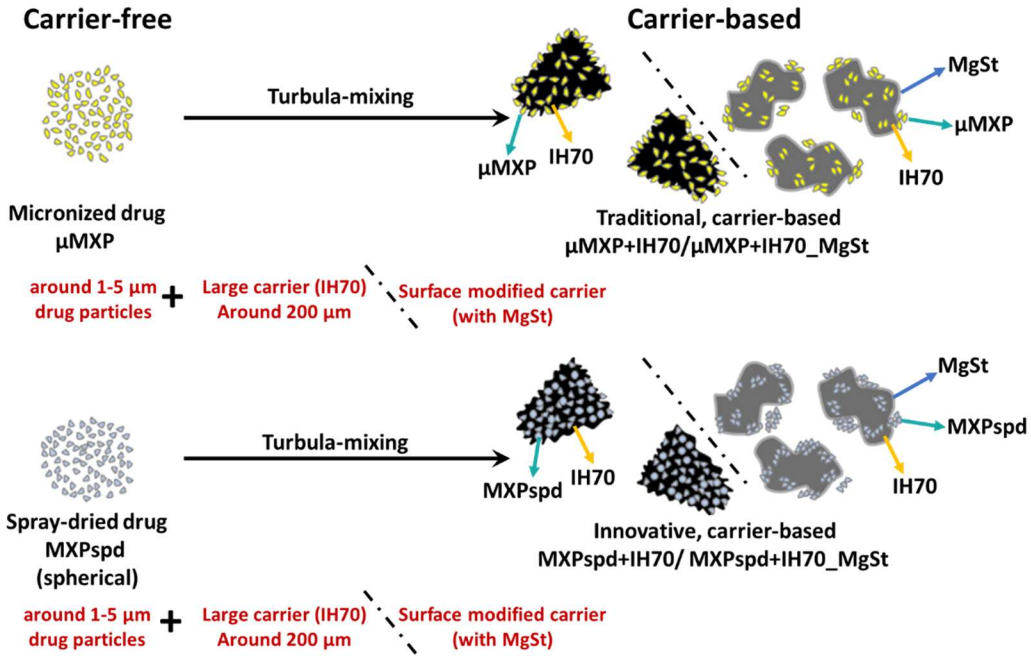
How contact angle measurements can help to develop pulmonary NSAID delivery systems.

Compared to drug administration through swallowing, a delivery via the lung is much more effective due to the lung´s large surface area, the thin membrane and outstanding blood supply that guarantees for a fast drug absorption. The traditional carrier-based dry powder inhaler formulations—consisting of carrier particles and drugs—are most widely used for the therapies via the lung. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) that are applied through inhalation can efficiently decrease the progression of cystic fibrosis and chronic obstructive pulmonary disease. However, there is so far still no marketed NSAIDs for pulmonary administration available. This motivated Ambrus and colleagues to develop an innovative dry powder inhalation (DPI) product with improved lung deposition.

As a test system for inhalation-based drug delivery they used Meloxicam potassium (MXP) as the active pharmaceutical ingredient, lactose monohydrate Inhalac® 70 (IH70) as the carrier particle and magnesium stearate (MgSt) as the surface-modifying agent. The authors prepared a row of samples with and without carrier utilizing either micronized (µMXP) or spray dried (MXPspd) MXP to have different drug particle morphologies (**Picture 1**). The different forms of MXP were analyzed regarding their particle size distribution by scanning electron microscopy and different sizes as well as morphologies of raw MXP, µMXP and MXPspd were detected. Normally, drug particles with 1-5 µm diameters are optimal to deposit in the tracheobronchial region while larger particles are deposited mainly in the upper respiratory tract and even smaller particles are largely exhaled. The data show the raw MXP displayed column-shaped crystals with a rough surface (D(0.5):52.27 µm), µMXP exhibited uneven surface and a rather large size distribution (D(0.5):3.60 µm), and MXPspd showed monodisperse spherical morphology with dimples on the surface (D(0.5):2.11 µm). When

applied the carrier particles, the µMXP and MXPspd formulations demonstrated completely different behaviors depending on whether IH70 was modified with magnesium stearate or not. On unmodified IH70 particles the distribution uniform while on magnesium stearate treated IH70 a patchy distribution was observed. These different morphologies play an important role in the interparticle interactions and the aerodynamic behaviors.



Picture 1: *The preparation process for carrier-free samples and carrier-based samples.*

To further investigate the interparticle interactions, they investigated their wettability, surface polarity and cohesion work which can be calculated from the wettability results. As shown in **Table 1**, the polarity of IH70 is significantly higher than for IH70_MgSt; moreover, the cohesion work for µMXP is bigger than for MXPspd.

Table 1: *Contact angles (water and diiodomethane), polarity, and cohesion work of the applied material in the formulations.*

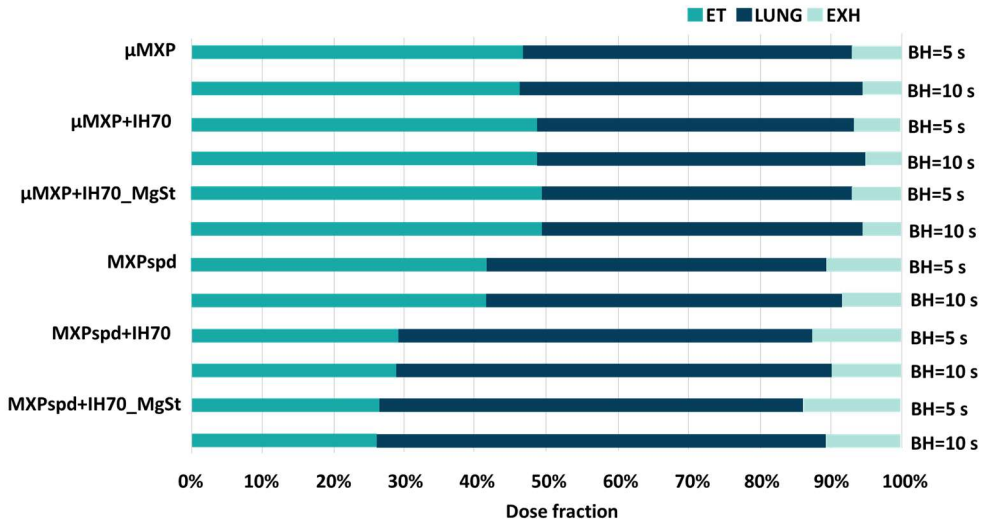
materials	θ_{water}(°)	$\theta_{diiodomethane}$(°)	Polarity (%)	Wc (mN/m)
µMXP	25.13	23.53	44.09	150.50
MXPspd	26.40	29.90	45.58	146.74
IH70	3.30	6.00	44.72	164.92
IH70_MgSt	64.60	62.00	42.44	–
MgSt	102.63	68.64	9.79	53.92

Calculations of the adhesion work (W_{adh}), the adhesion force (F_{adh}), the spreading coefficient (S_{21}) of the carrier-based formulations were also determined based on the above wettability data. **Table 2** shows that MXPspd-based formulations possessed much lower F_{adh} values than µMXP-based formulations, resulting in their more favorable aerodynamic values. Because the spherical MXPspd contacts to IH70/IH70_MgSt over smaller surface areas than µMXP particles. In addition, the presence of MgSt further declined W_{adh} and F_{adh} leading to further improvement of the aerodynamic values. Negative numerical values of S_{21} (which shows the probability of material 2 on the surface of material 1) indicated less favorable spreading of MXP particles on the carrier surface.

Table 2: *The adhesion work (W_{adh}), the adhesion force (F_{adh}), the spreading coefficient (S_{21}) in the case of the carrier-based samples*

Products	W_{adh} (mN/m)	$F_{adh} * 10^{-3}$ (mN)	S_{21}
µMXP + IH70	104.98	1.168	6.87
µMXP + IH70_MgSt	76.55	0.849	−37.44
MXPspd + IH70	102.67	0.674	8.55
MXPspd + IH70_MgSt	76.80	0.493	−34.83

The aerodynamic results and airway deposition of the inhaled drug were quantified by an *in vitro* lung model and stochastic lung models, respectively. The results indicate that the spray-dried drug MXPspd and the surface-modifying agent MgSt improved the lung deposition results. Hence, as **Picture 2** shown, MXPspd-based formulations showed great improvement with a higher LUNG value and a lower ET value. In addition, *in vitro* dissolution test illustrated that MXPspd-based samples also exhibited the best dissolution results.



Picture 2: *In silico simulation results of the studied dry powder inhalation formulations (ET: extrathoracic airways; LUNG: bronchial and acinar parts; EXH: exhalation fraction)*

In conclusion, an innovative, carrier-based NSAID formulation that can be applied via inhalation with excellent *in vitro* lung deposition results was developed by optimizing the interparticle interactions and drug particle properties. Finetuning the surface wettability of the formulation particles greatly improved aerodynamic properties. This innovative formulation holds great promise for improving the effectiveness of cystic fibrosis and chronic obstructive pulmonary disease therapy in the future.

An optical contour analysis system OCA (DataPhysics Instruments GmbH, Germany) was used in this research.

For more information, please refer to the following article:

Development of an Innovative, Carrier-Based Dry Powder Inhalation Formulation Containing Spray-Dried Meloxicam Potassium to Improve the In Vitro and In Silico Aerodynamic Properties; Edit Benke, Árpád Farkas, Piroska Szabó-Révész, Rita Ambrus; *Pharmaceutics* **2020***,* 12, 535; DOI: 10.3390/pharmaceutics12060535