Development of meloxicam potassium-containing co-spray-dried inhalation powder with sodium stearate

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Abstract: Pulmonary drug delivery (PDD) has potential for both local and systemic therapy. Our research group is focusing on the development of dry powder inhalation (DPI) systems for PDD due to their beneficial properties. Although there is not yet a marketed inhalation product for non-steroidal anti-inflammatory drugs (NSAIDs), their therapeutic use in several lung diseases is well established and successful DPI developments have been performed with them. Sodium stearate (NaSt) is a promising excipient for DPI development, but its role in NSAIDs has not yet been investigated. Thus, the aim was to study DPI samples produced by co-spray-drying, applying meloxicam potassium (MXP) as an NSAID drug, and different concentrations (0-2 w/w%) of NaSt. Physicochemical investigations, *in vitro* lung deposition, and *in vitro* drug release measurements were performed. It can be stated that co-spray-drying of MXP with NaSt resulted in remarkable morphological differences by increasing the concentration of NaSt, which had a positive effect on cohesive work. Furthermore, applying of NaSt accelerates the dissolution in simulated lung fluid (SLF). NaSt as excipient has a future for the formulation of the DPI systems because there are in the development focus the attaintment of the higher FPF values and improvement of dissolution in SLF.

Keywords: *pulmonary drug delivery, dry powder inhaler, meloxicam potassium, sodium stearate, aerodynamic properties*

1. Introduction

Pulmonary drug delivery (PDD) offers the possibility to treat both local and systemic diseases (1). Several advantages of administering drugs via the lungs in comparison to oral drug delivery are supported (2). This is a non-invasive approach, and the drug can achieve C_{max} within minutes (3,4), moreover, a dose of one-tenth of the oral dose is adequate to reach the same therapeutic effect (5,6). These are attributed to the fact that the gastrointestinal (GI) tract is avoided so that hepatic first-pass metabolism and/or enzymatic inactivation does not occur along the GI tract (7,8). Moreover, the side effect profile of the used active pharmaceutical ingredient (API) could be more beneficial compared to oral drug delivery (9). In view of the above-mentioned advantageous features of PDD, a number of drugs have been tested on pulmonary administration recently (10,11).

In connection with PDD, four major classes of inhalation products can be identified (nebulizers, pressurized metered-dose inhalers, Soft Mist Inhalers, DPIs) (12). Of these four possible solutions for PDD, dry powder inhalation (DPI) systems are still considered the most promising development line in terms of advantages and disadvantages and their potential for widespread use (13). For DPIs, a basic distinction can be made between traditional carrier-based formulations and carrier-free formulations (14). For the former, micronized particles are on the big carriers and these small particles drift down from the surface of carriers during inhalation (15). For the latter, special formulation techniques (spray drying, spray-freeze drying, supercritical-fluid technology) and excipients are used to achieve inhalation favourable particles (16).

The role of non-steroidal anti-inflammatory drugs (NSAIDs) in the pulmonary system is to directly suppress inflammation and indirectly reduce disease progression. In both cystic fibrosis and chronic bronchitis, a very similar pathophysiological process takes place throughout the disease progression (17), which evolves slowly into respiratory failure (18). It has been established in chronic bronchitis that cigarette smoke not only causes inflammation but also degrades cystic fibrosis transmembrane conductance regulator (CFTR) gene expression, thereby inducing an ''acquired'' CFTR dysfunction (19). In cystic fibrosis, CFTR gene mutation is an autosomal recessive genetic disorder (20,21). In addition, NSAIDs may be

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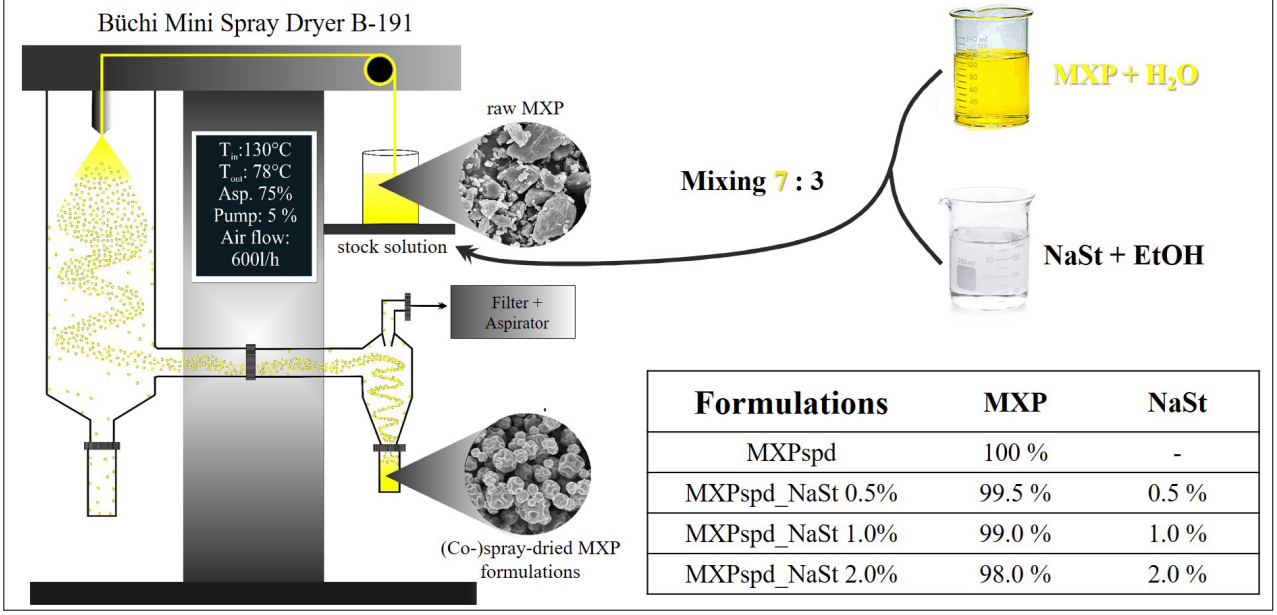

Formulations	MXP	NaSt
MXPspd	100 %	-
MXPspd_NaSt 0.5%	99.5 %	0.5 %
MXPspd_NaSt 1.0%	99.0 %	1.0 %
MXPspd_NaSt 2.0%	98.0 %	2.0 %

Figure 1 *Schematic diagram of the preparation of the samples and details of the composition of the powders.*

applied as adjunctive therapy in non-small cell lung cancer, as COX-2 is also overexpressed. So the use of COX-2 inhibitors may slow down the progression of malignancies (22,23).

However, no products containing NSAIDs for PDD are on the market. At the same time, there is a growing number of publications dealing with NSAID administration in the lungs (15). Physicochemical characteristics of the drugs are fundamental to the formulation of DPI powders, so it is preferable to apply a water-soluble salt form of the applicable API. For instance, meloxicam potassium (MXP), which is patented by Egis Pharmaceuticals Ltd., is an intermediate in the production of meloxicam (MX) with a water solubility (13.1 mg/mL at 25 °C) far higher than that of MX (4.4 **μg**/mL at 25 °C) and hundreds of times more soluble than MX at the pH of bronchi (pH 7.4) (24–26). Our research group has already published several successful developments of inhalation powders for both MX (6,27,28) and MXP (15,29).

A number of excipients have been shown to have a beneficial effect on particle habit (e.g. L-leucine, Ammonium carbonate, Polyvinyl Alcohol, etc.) during the production of carrier-free DPIs, and thus influence aerodynamic performance (30–32). The positive effect of sodium stearate (NaSt) in spray-dried DPI formulations has been confirmed for example in the case of theophylline, tobramycin, ciprofloxacin hydrochloride. The optimal NaSt concentration for a given drug requires individual investigation in each case. Typically, NaSt concentrations of 0-2 w/w% are studied (33–35). Furthermore, Parlati et al. found that the effect of this excipient (tested up to 2 w/w%) on A549 lines did not affect cell viability to a greater extent than pure tobramycin (35). To our knowledge, the role of the NaSt excipient has not yet been investigated in NSAID-containing DPIs.

The present work aimed to study DPI formulations prepared by co-spray-drying, using MXP, and different concentrations (0-2 w/w%) of NaSt. Furthermore, physicochemical, *in vitro* lung deposition, and *in vitro* drug release studies were performed with the prepared microcomposites.

2. Materials and methods

2.1. Materials

MXP (Egis Pharmaceuticals PLC, Budapest, Hungary) was used as a drug. NaSt (Alfa Aesar, Heysham, UK) was applied as a solid excipient during co-spray drying for the purpose of habit modification of the drug. 96% ethanol (EtOH, AppliChem GmbH, Darmstadt, Germany) was used as a liquid excipient in the stock solution of the samples.

2.2. Sample Preparation

The samples were prepared by co-spray drying of MXP and NaSt from the solution. At first, a 1.5 w/v% aqueous solution was made applying MXP

at 80 °C and an ethanolic solution containing 0/0.0175/0.035/0.07 w/v% of NaSt at 80 °C. Afterward, the two solutions were blended in a ratio of 7:3 at 80 °C. This was co-spray dried with the Büchi B-191 apparatus (Mini Spray Dryer, Büchi, Switzerland) using the following parameters: inlet heating temperature, 130 °C; outlet heating temperature, around 78 °C; aspirator capacity, 75%; pressured airflow, 600 L/h, feed pump rate, 5%. So, the solid samples contained 100/99.5/99.0/98.0 w/w % of MXP and 0/0.5/1.0/2.0 w/ w % of NaSt (Figure 1).

2.3. Measurement of the residual EtOH and water content

The residual EtOH content of the samples was determined using a Mettler Toledo TG 821e thermal analysis system (TG) combined with a quadrupole mass spectrometer (MS, Pfeiffer Vacuum, model ThermostarTM GSD 320), and the analysis was performed applying STARe thermal analysis program V9.1 (Mettler Inc., Schwerzenbach, Switzerland). The determination was carried out by measuring 3-5 mg per formulation in 40 µl aluminum pans. The initial temperature was 25 °C, the final temperature was 350 °C, and the applied heating rate was 10 °C/min. The test was run in a nitrogen atmosphere (constant nitrogen gas flow: 100 mL/min). The TG-MS contact was made with a silica capillary held at 120 °C.

The residual solvent content was measured by TG-DTA using a Mettler Toledo TG 821e thermal analysis system with STARe V9.1 thermal analysis software (Mettler Inc., Schwerzenbach, Switzerland) at a constant dry nitrogen gas flow of 100 mL/min. Aluminum pans were used for formulations and reference. Recordings were taken at a constant heating rate (10 °C/min) until 350 °C. The TG-DTA furnace was pre-equilibrated at room temperature and all samples (between 12 and 20 mg) were measured as quickly as possible to minimize moisture uptake or loss from the formulation. The loss in mass was noted and the solvent content (% on a wet basis) was estimated from the normalized measurements, the actual mass being divided by the initial mass. The residual water content is calculated as the difference between the residual solvent content and the residual EtOH content. Water loss basically happened between 5 and 110 °C, furthermore, a higher temperature was applied to determine the bound water.

2.4. X-ray Powder Diffraction (XRPD)

Structural characterization of the raw MXP and prepared formulations were carried out with the BRUKER D8 Advance X-ray powder diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). Cu K λI radiation (λ = 1.5406 Å) was used as the radiation source. The solid-state forms were measured by scanning at 40 kV and 40 mA, with an angular range of 3°- 40° 2-Theta, a step time of 0.1 s/step and a step size of 0.01°. X-ray calibration was accomplished with a silicon disc. DIFFRACT plus EVA software was used to analyze the results. Diffractograms were corrected with Kα2, smoothed and after background removal evaluated.

2.5. Particle Size Distribution

To determine the particle size distribution of the samples, laser diffraction was used (Malvern Mastersizer Scirocco 2000, Malvern Instruments Ltd., Worcestershire, UK). About 0.5 g of sample was filled into a dosing tray. The dry assay procedure was followed and the air was applied as the dispersion medium for the tested particles. The dispersion air pressure was adjusted to 2.0 bar to determine whether particle abrasion had occurred. Furthermore 75% vibration feed, 12 s measuring time settings were used. Three parallel measurements were performed. The particle size distribution was described by D [0.1], D [0.5], and D [0.9] values.

2.6. Scanning Electron Microscopy (SEM)

The shape, surface features and approximate size of the samples were examined by scanning electron microscopy (SEM) (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan) at an acceleration voltage of 10 kV. A sputter coating machine (Bio-Rad SC 502, VG Microtech, Uckfield, UK) was used to induce electrical conductivity on the surface of the samples. The used air pressure was 1.3-13.0 MPa. Samples were coated with gold-palladium (90 s) in an argon atmosphere with a gold sputtering module placed in a high vacuum evaporator.

2.7. Interparticle Interactions

Contact angle (Θ) was obtained with the Dataphysics OCA 20 (Dataphysics Inc. GmbH, Germany). Pastilles of the samples were compressed from 0.10 g of material using a 1-ton hydraulic press

(Perkin Elmer hydraulic press, Waltham, USA). Each sample was measured three times. This implies that three pastilles per formulation were dripped with polar liquid (distilled water) and the other three pastilles were dripped with dispersion liquid (diiodomethane). Simultaneously with the dripping, a recording was made by setting the instrument to a time interval of 1-25 s; this allowed the change in contact angle to be detected and determined. Thus, the contact angles of the used two different fluids – always at the same second – were found. The surface free energy (γ_s) of the formulations – which consists of two parts: a dispersive part (γ_s^d) and a polar part (γ_s^p) i.e. ($\gamma_s = \gamma_s^d + \gamma_s^p$) – was obtained using the Wu equation. The surface tension of the applied liquids is given in the literature ($\gamma_1 = \gamma_1^d + \gamma_1^p$) distilled water γ^p= 50.2 mN/m, γ^d = 22.6 mN/m; and diiodomethane γ^p = 1.8 mN/m, γ^d = 49 mN/m (36). In Wu's equation, there are only two unknowns (37), the disperse (γ_s^d) and polar components (γ_s^p) of the materials under consideration, which are already expressible:

$$(1 + \cos\Theta)\gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \quad (1)$$

where Θ = contact angle; γ = surface free energy; s = solid phase; l = liquid phase; d = dispersion component; and p = polar component

The cohesive work (W_c) is defined as twice the surface free energy (38):

$$W_c = 2 \times \gamma_s \quad (2)$$

2.8. In vitro Aerodynamic Investigation

Aerodynamic particle size distribution (APSD) of the formulations was measured with the Andersen Cascade Impactor (ACI) (Copley Scientific Ltd., Nottingham, UK). This equipment is approved for APSD testing by the European Pharmacopoeia 2.9.18 /Methods Chapter/, United States Pharmacopoeia /Test Chapter <601>/ and the Chinese Pharmacopoeia /Chapter <0951>/ (15). Flow rates of 28.3 ± 1 L/min were generated using a vacuum pump (High-capacity Pump Model HCP5, Critical Flow Controller Model TPK, Copley Scientific Ltd., Nottingham, UK) and measured applying a mass flow meter (Flow Meter Model DFM 2000, Copley Scientific Ltd., Nottingham, UK). Prior to the *in vitro* aerodynamic studies, eight collection plates of the impactor were coated with a mixture of Span® 80 and cyclohexane (1 + 99 w/w%) to allow replicate inhalation into ACI. The amounts of the microcomposites were loaded into the – transparent, size 3 – DPI hard gelatin capsules (Coni-Snap®, Capsugel, Bornem, Belgium) which mass has been calculated so that the MXP content is 1.3 mg for each formulation, which is equivalent to one-tenth of the oral dose of the drug (15). Breezhaler® (Novartis International AG, Basel, Switzerland) DPI device was used during the measurements. The study used two inhalation cycles of 4 s per capsule (3 capsules (39) were measured per *in vitro* test). The inhalator, capsules, mouthpiece, induction port, eight plates of the impactor, and filter were washed with methanol + pH 7.4 phosphate buffer (60 + 40 v/v%). The concentration of MXP was detected using an ultraviolet-visible spectrophotometer (ATI-UNICAM UV/VIS spectrophotometer, Cambridge, UK) at a wavelength of 364 nm. Based on the amount of MXP in the washed elements, the emitted fraction (EF), the fine particle fraction (FPF) and the mass median aerodynamic diameter (MMAD) were calculated. The EF was determined as the percentage of the MXP in the cascade impactor washed elements (excluding MXP in the DPI device and capsules). FPF is the percentage of drug particles with an aerodynamic diameter below 5 microns. MMAD is represented as the diameter of the particles deposited in the ACI at which 50 w/w% of the particles have a lower and 50 w/w% have a higher diameter. FPF and MMAD values were calculated with the help of KaleidaGraph 4.0 (Synergy Software, Reading, PA, USA) and a plot of the cumulative percentage undersize of the API on a log probability scale versus effective cut diameter (15).

2.9. Release Assay

Dissolution studies were carried out on the raw MXP and spray-dried samples. The studies were conducted in a simulated lung fluid – SLF (pH 7.4) – which contained the following ingredients in 900 mL: NaCl 0.68 g L^{-1}, $NaHCO_3$ 2.27 g L^{-1}, Gly 0.37 g L^{-1}, NaH_2PO_4 H_2O 0.16 g L^{-1}, $CaCl_2$ 0.02 g L^{-1} and H_2SO_4 5 mL 0.1 M (40). Dissolution tests were run under controlled conditions in beakers utilizing 30 mg of sample in 2.5 mL SLF with stirring at 50 rpm (41) for 7 measurement times using a 0.45 μm (40) pore size syringe filter (Nantong FilterBio Membrane Co., Ltd., Nantong, China). Each sample was tested in triplicate. The quantity of dis-

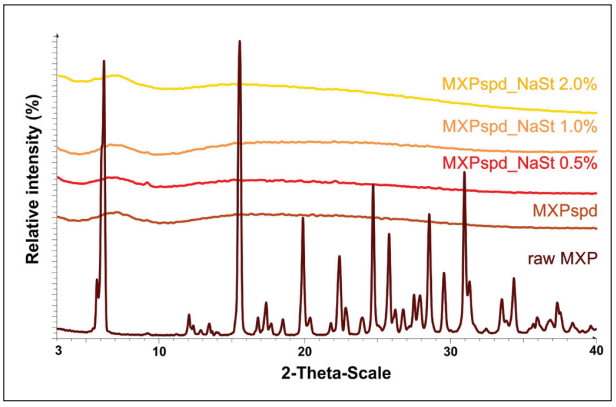

Figure 2 *Figure 2. XRPD pattern of the raw MXP and the (co-)spray-dried DPI samples.*

solved MXP was detected using a UV/VIS spectrophotometer (ATIUNICAM UV/VIS spectrophotometer, Cambridge, UK) at a wavelength of 362 nm. The linearity of the calibration curve for MXP in SLF was y = 0.0426x. The unit of slope is mL/μg. The LOD of MXP was 0.093 μg/mL and the LOQ of MXP was 0.281 μg/mL in the SLF medium.

2.10. Statistical Analyses

Statistical analyses were performed with t-test calculations at the 0.05 significance level and one-tailed hypothesis applying Social Science Statistics, available online (42). All published data represent the ± SD of three parallel experiments (n = 3).

3. Results and discussion

3.1. Residual EtOH and water content

According to ICH Q3C(R6) guidelines, the residual EtOH content should not exceed 0.5%, all prepared samples met this requirement. The residual water content of the formulations was in the range of 3.24% to 3.73%. For spray-dried DPIs, residual water content values between 0.24% and 9.02% have been reported in the literature. Therefore, the given values can be regarded as appropriate. Low water content is required for the DPI powders to aerosolize and disperse successfully and to reach the lungs efficiently (43).

3.2. Habit

XRPD studies were carried out to obtain useful information on the structure of the raw MXP and the (co-)spray-dried samples. The knowledge of the structure of the APIs used can be crucial for aerodynamic behaviour, dissolution, efficacy, compatibility with excipients, stability of the dosage form. The crystalline nature of the raw MXP was confirmed. MXP peaks were detected at the following 2Θ values: 6.04, 15.35, 24.52, and 30.94. For the (co-)spray-dried drug, no peaks were found in the XRPD patterns, indicating the amorphous nature of these formulations (Figure 2).

SEM records of the (co-)spray-dried samples are shown in Figure 3 For all formulations, it can be said that they are composed of particles with a dense structure, i.e. no pores or hollows are visible. It can be observed that the individual morphology (roughness, dimples) of the particles are nearly identical for MXPspd, MXPspd_NaSt 0.5%, and MXPspd_NaSt 1.0% when examined sample by sample. In contrast, for MXPspd_NaSt 2.0%, the individual morphology of the particles within the sample varies, i.e. some particles are almost smooth in surface while others contain varied dimples. Although it has been shown from literature descriptions that dimples are more aerodynamically advantageous than particles with a smooth surface (44). Nevertheless, our previous publication (43) has highlighted that particles with nearly identical morphologies, especially those containing dimples, can be highly agglomerated, thereby making their aerosolization and dispersion more difficult.

The particle size distribution results for the DPI samples are very favourable, with an average particle size of around 2 microns for all formulations and a remarkable percentage of particles in the

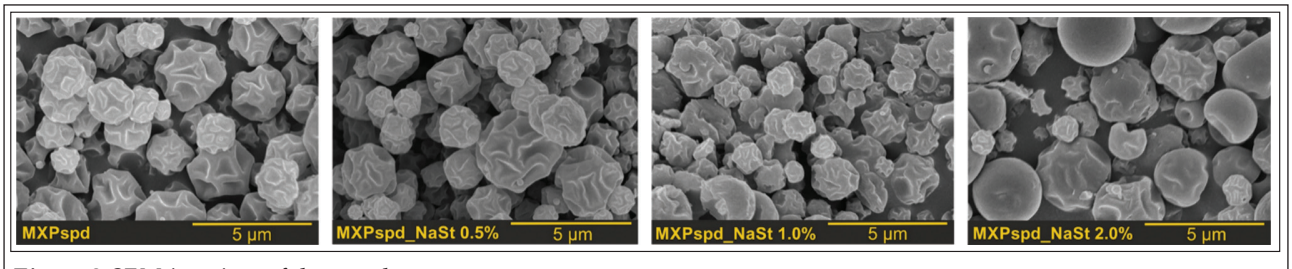

Figure 3 *SEM imagines of the samples.*

Table I *Particle size distribution and W_c results of the samples.*

Formulation	D [0.1] (μm)	D [0.5] (μm)	D [0.9] (μm)	W_c (mN/m)
MXPspd	1.329 ± 0.02	2.318 ± 0.12	3.947 ± 0.14	154.12
MXPspd_ NaSt 0.5%	1.107 ± 0.09	2.138 ± 0.05	2.893 ± 0.24	160.40
MXPspd_ NaSt 1.0%	1.057 ± 0.03	1.942 ± 0.13	3.578 ± 0.11	153.74
MXPspd_ NaSt 2.0%	1.099 ± 0.03	2.144 ± 0.11	4.168 ± 0.18	130.76

samples between 1 and 5 microns (Table I), which is also beneficial for lung therapy (45). This is important because it has been observed that a major part of particles below 1 micron is exhaled (46). Furthermore, particles with a dense structure above 5 microns and non-dense particles above 10 microns are deposited in the upper airways (28). With respect to the W_c, the results correlate with those described for morphological characteristics. That is, for the first three samples, the surface of the particles with nearly identical indentations can be highly connected, which resulted in higher W_c compared to the MXPspd_NaSt 2.0% sample. The higher W_c predicts more difficult dispersion and aerosolization. In the case of MXPspd_NaSt 2.0%, the different particle shapes in the sample are less agglomerated, and it should be noted that the lower W_c value compared to the other samples may be due to the fact that NaSt (as demonstrated by Parlati et al. (35)) can accumulate on the surface of the particles during co-spray drying, which is known to be a lubricant excipient (47).

3.3. *In Vitro* Aerodynamic Assessment

In vitro aerodynamic testing of the samples with the ACI was performed at a flow rate of 28.3 L/min. The FPF, MMAD and EF results for the tested formulations are shown in Table II It can be concluded that all samples obtained very good lung deposition results despite the fact that the testing corresponds to diseased lungs. The MXPspd_NaSt 2.0% sample yielded the best *in vitro* aerodynamic values, which is in agreement with the results described in section 3.2. That is, the morphology and W_c value of this sample are the most advantageous with the application of 2% NaSt, which was reflected in the most favourable aerodynamic diameter – MMAD – and lung deposition – FPF – values. In terms of EF, this sample also achieved the highest value, which can be explained by the fact that this formulation is less agglomerated than the other samples due to its favourable habit, and thus can disperse and aerosolize easier, which helps the sample to sweep out from the DPI capsule better. In addition, in terms of EF, only the MXPspd_NaSt 2.0% formulation meets the requirement that the value must be between 85 and 115% for APSD testing (46).

3.4. *Release Assay Test Results*

In vitro dissolution results of raw MXP and spray-dried formulations in SLF are illustrated in Figure 4 The results show that raw MXP was not fully dissolved even after 15 minutes. In the case of spray-dried samples, the *in vitro* dissolution results were much better due to the particle size distribution, increased specific surface area, and the amorphous nature of the formulations. The results also clearly show that the samples prepared by co-spray drying using NaSt (MXPspd_NaSt 0.5%; MXPspd_NaSt 1.0%; MXPspd_NaSt 2.0%) dissolved faster in about 1 minute than the MXPspd formulation without NaSt.

4. Conclusion

To summarise the study, in the case of MXP, for the first time, a development with the use of NaSt was carried out and successfully implemented. The MXPspd_NaSt 2.0% sample had the most favourable habit and thus *in vitro* aerodynamic results. Furthermore, *in vitro* dissolution was faster due to the presence of NaSt. It was confirmed that the optimum NaSt concentration may vary from drug to drug, since for ciprofloxacin hydrochloride, under the same manufacturing conditions, the use of 0.5% NaSt gave the most favourable results (34). Overall, the investigation of excipients

Table II *In vitro aerodynamic results of the samples measured at 28.3 L/min flow rate.*

Formulation	FPF (%)	MMAD (μm)	EF (%)
MXPspd	74.30 ± 1.16	2.97 ± 0.03	84.01 ± 0.73
MXPspd_NaSt 0.5%	76.76 ± 0.89	2.93 ± 0.11	85.52 ± 1.11
MXPspd_NaSt 1.0%	79.82 ± 1.34	2.74 ± 0.08	85.95 ± 0.58
MXPspd_NaSt 2.0%	84.03 ± 1.65	2.49 ± 0.17	88.13 ± 0.92

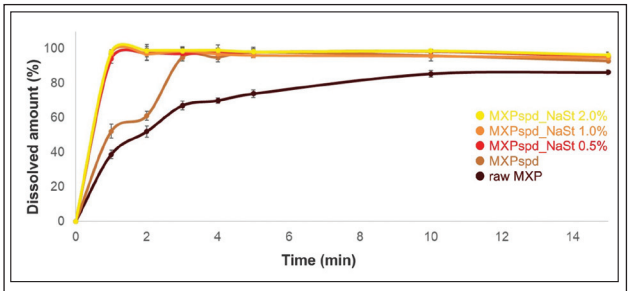

Figure 4 *In vitro dissolution results in SLF of raw MXP and prepared formulations.*

already proven in other pharmacological groups is justified for the formulation of NSAIDs for pulmonary use and there is still much scope for the development of NSAID-containing DPI formulations.

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