Preparation and evaluation of inhalable nintedanib microparticles using mechanofusion technique

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PURPOSE

This study aims to enhance inhalation efficiency and ensure homogeneity and high dispersion by using mechanofusion technology to optimize interactions among magnesium stearate (FCA), the carrier, and Nintedanib in inhalable formulations..

METHOD(S)

Nintedanib microparticles were prepared using a jet milling technique, and mechanofusion was used at 3,000 rpm for 10 minutes with the addition of magnesium stearate at concentrations of 0%, 1%, and 5% together with nintedanib and lactose. To confirm homogeneity and dispersion both directly and indirectly, Scanning Electron Microscopy (SEM), Particle Size Distribution (PSD), Raman Microscopy, and Next Generation Impactor (NGI) were used to evaluate aerodynamic performance.

Table 1. Formulation of DPI mixtures.

Formulation code	Formulation composition	Mgst : Nintedanib	process
PM-M0	Lactose (95%) - Nintedanib (5%)	-	
PM-M1	Lactose (95%) - Nintedanib (5%) - Mg st (1%)	1:5	Physical mi xture
PM-M5	Lactose (95%) - Nintedanib (5%) - Mg st (5%)	1:1	
MF-M0	Lactose (95%) - Nintedanib (5%)	-	
MF-M1	Lactose (95%) - Nintedanib (5%) - Mg st (1%)	1:5	Mechanofu sion
MF-M5	Lactose (95%) - Nintedanib (5%) - Mg st (5%)	1:1	

RESULT(S)

The interparticle interactions among lactose particles, nintedanib, and magnesium stearate were confirmed using PSD and SEM (Table 2, Figure 1). The NGI results showed that with the use of mechanofusion, the inhalation efficiency increased from 14.54% to 66.03% as the magnesium stearate ratio increased, whereas the physical mixed formulations did not exhibit a clear trend in inhalation efficiency with increasing magnesium stearate ratios (Figure 2). Raman microscopy analysis confirmed that the dispersion of nintedanib with the addition of magnesium stearate was significantly higher in mechanofusion compared to physical mixing (Figure 3).

Table 2. Particle size distribution of the physical mixture and Mechanofusion

Process	Materials	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)	Span
-	Lactose	17.87±1.16	49.53±0.86	87.67±5.03	1.41±0.1
	Raw Nintedanib	9.22±0.61	48.2±1.7	135±17.68	2.61±0.26
	JM Nintedanib	1.27±0.04	3.96±0.2	382.67±43.6	103.26±10.7
	Mg.st	1.88±0.04	5.03±0.07	14.47±0.87	2.5±0.13
Physical mixteure	PM-M0	8.52±1.16	46.63±0.25	85.77±0.6	1.65±0.04
	PM-M1	8.39±0.32	46.73±0.23	86.97±0.83	1.68±0
	PM-M5	5.79±0.28	43.13±0.06	83.9±0.87	1.81±0.03
Mechanofusion	MF-M0	12.47±0.25	47.2±0.35	83.3±2.03	1.5±0.04
	MF-M1	11.13±0.86	47±0.62	85.57±0.15	1.58±0.04
	MF-M5	6±0.49	46.57±1.76	91.3±11	1.83±0.16

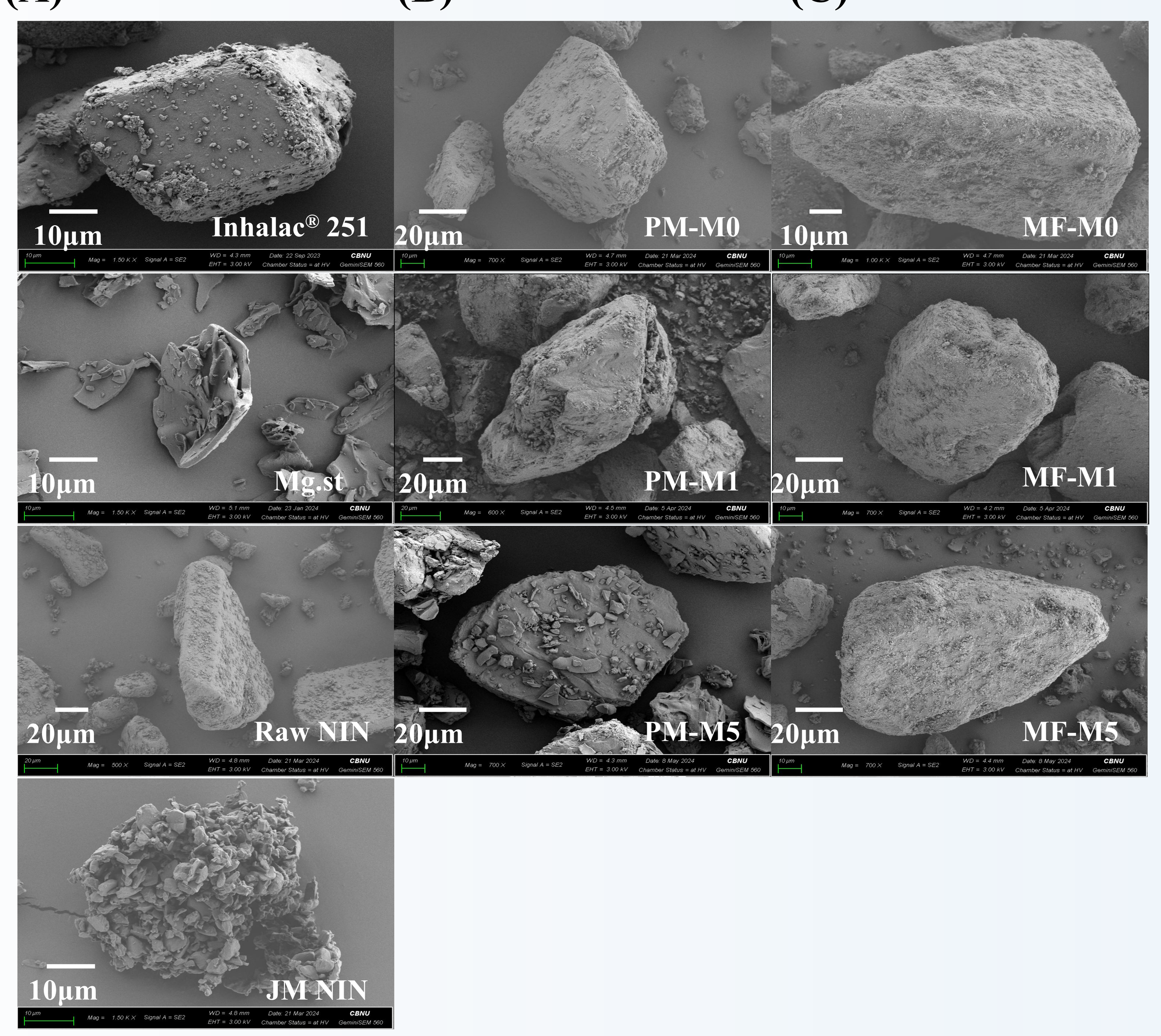

Figure 1. SEM micrographs of (A) raw materials, (B) Mechanofusion formulation (C) Physical mixture formulation.

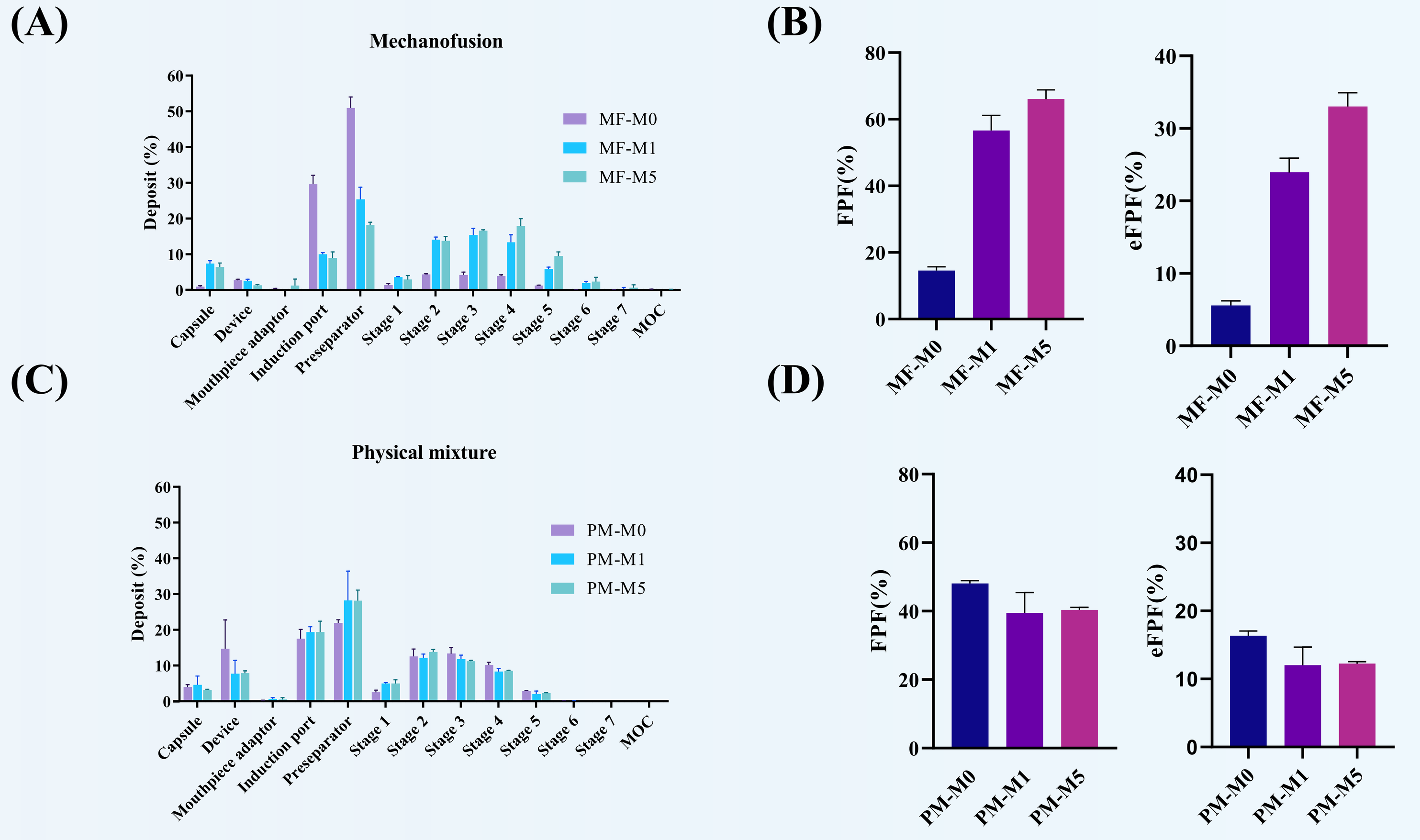

Figure 2. Percentage deposition in each stage of NGI : (A) Mechanofusion formulations, (C) Physical mixture formulations. FPF(%), eFPF according to Mgst ratio in NGI : (B) Mechanofusion formulations, (D) Physical mixture formulations.

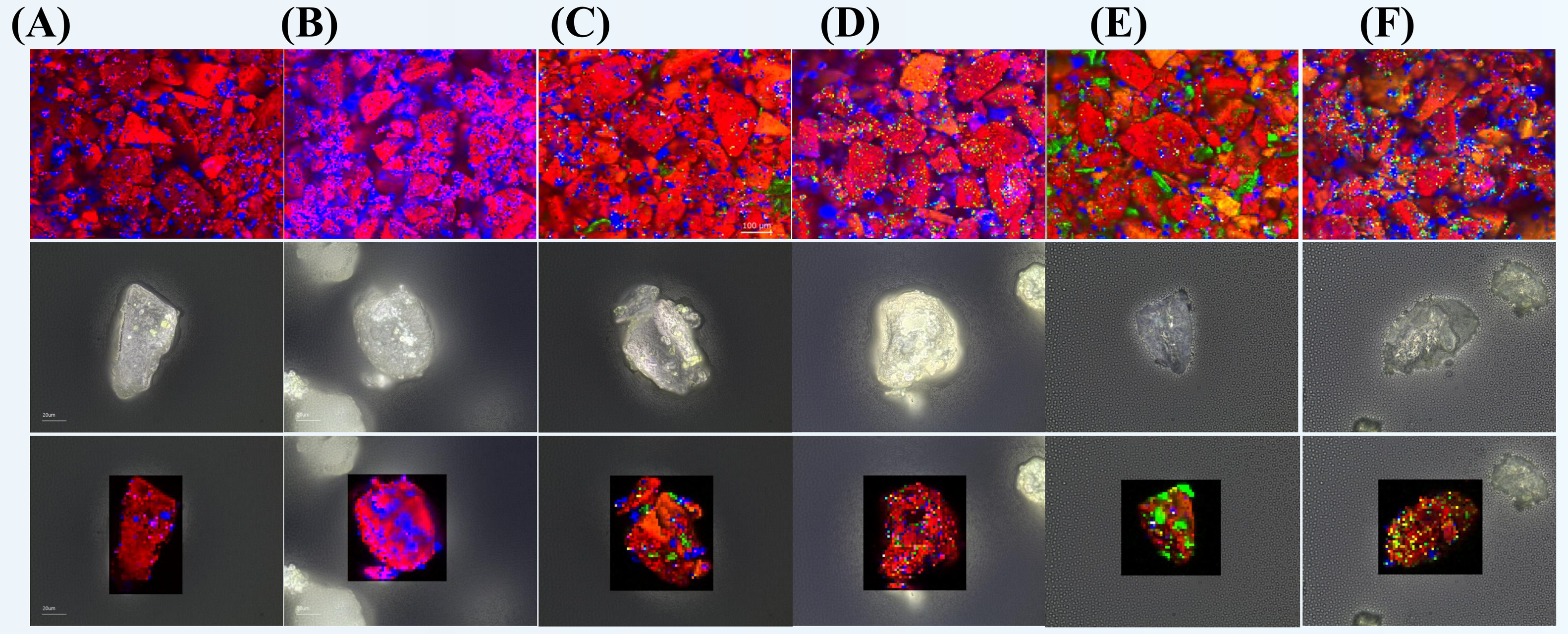

Figure 3. Dry powder bed(x20) and one particle CLS images of Raman microscopy : (A) PM-M0, (B) MF-M0, (C) PM-M1, (D) MF-M1, (E) PM-M5, (F)MF-M5. Red indicates lactose, blue indicates nintedanib, and green indicates magnesium stearate.

CONCLUSION(S)

Mechanofusion significantly improves inhalation efficiency, dispersion, and homogeneity in nintedanib formulations compared to physical mixing, highlighting its potential for optimizing pulmonary drug delivery.

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