Preparation of Rivaroxaban Dry Powder for Inhalation Using a Two-Step Milling Process

Song-Ye Chan[1], Seong-Hoon Jeong[1], Dong-Wook Kim[2], Ji-Hyun Kang[3] and Chun-Woong Park[1*]

[1]Chungbuk National University, Cheongju, 361-763, Republic of Korea

[2] College of pharmacy, Wonkwang University, Republic of Korea

[3]Jeonbuk National University, Republic of Korea

INTRODUCTION

Rivaroxaban (RVX) is a direct oral anticoagulant (DOAC) recommended as a first-line treatment for pulmonary embolism (PE). While RVX offers superior clinical benefits over low-molecular-weight heparin (LMWH), it carries a higher risk of major bleeding, highlighting the need for research into low-dose administration strategies.

METHODS

RVX DPI formulations were prepared using a two-step milling process, bead milling (BM) followed by air-jet milling (JM), with L-leucine(1%,5%,10% w/w) as a force control agent (FCA). (Table. 1). Physicochemical properties were analyzed using SEM (Fig. 1), laser diffraction, XRD (Fig. 2A), and DSC (Fig. 2B), while aerodynamic performance was evaluated using a next-generation impactor (NGI). In-vivo pharmacokinetics (PK) and tissue distribution studies were conducted in Sprague-Dawley rats, comparing intratracheal instillation (ITI) with oral administration.

Table 1. Formulations of milled RVX dry powder.

(mg)	BM-only	JM-only	BM-JM	BM-JM-1L	BM-JM-5L	BM-JM-10L
RVX	20	20	20	20	20	20
LEU	-	-	-	0.2	1	2
D.W	130	-	130	130	130	130
Process.	BM	JM	BM-JM	BM-JM	BM-JM	BM-JM

CONCLUSION

This study optimized RVX DPI formulations using a two-step milling process (BM followed by JM) with L-leucine and demonstrated the potential of pulmonary delivery as an effective alternative for PE treatment, enabling reduced drug doses and minimized systemic side effects.

RESULTS

The BM-JM formulation demonstrated a Dv50 of 2.84 μm, indicating a particle size suitable for inhalation (Fig. 3). Formulation with L-leucine further improved particle dispersion, with BM-JM-5L achieving the highest fine particle fraction (FPF) of 72.10% and enhanced particle uniformity (Fig. 4). PIV analysis showed that BM-JM formulation exhibited superior particle dispersion compared to Raw-RVX and single-step formulations, with reduced aggregation and improved aerosol characteristics (Fig. 5, Table. 2). In in-vivo pharmacokinetic studies, BM-JM-5L demonstrated a 1.6-2.55-fold higher relative bioavailability compared to oral administration and maintained significantly higher lung drug concentrations (Fig. 6, Table. 3).

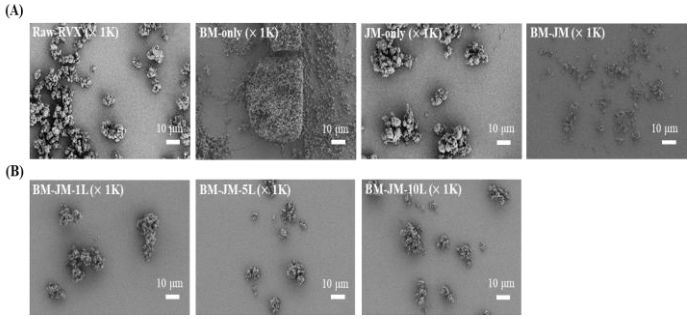

Figure 1. Scanning electron microscope images. (A) Raw-RVX, BM-only, JM-only, and BM-JM, (B) BM-JM-1L, BM-JM-5L, and BM-JM-10L.

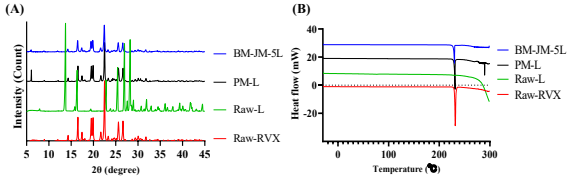

Figure 2. Physicochemical properties of milled RVX formulation with LEU. (A) X-ray diffraction (XRD) pattern, (B) Differential scanning calorimetry (DSC) thermogram.

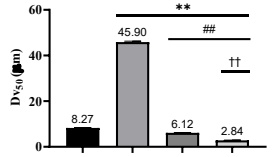

Figure 3.Dv50 (μm) values in particle size distribution.

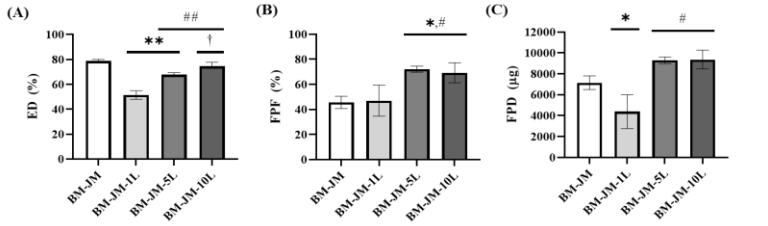

Figure 4. *In-vitro* aerodynamic performance characteristics of BM-JM, BM-JM-1L, BM-JM-5L, and BM-JM-10L. (A) ED (%), (B) FPF (%), (C) FPD (μg).

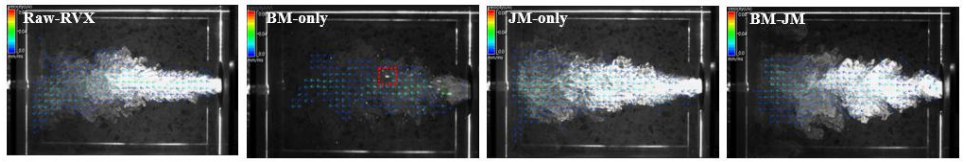

Figure 5. Vector images of particle flow filed emitted from DPIs of Raw-RVX and milled RVX dry powders.

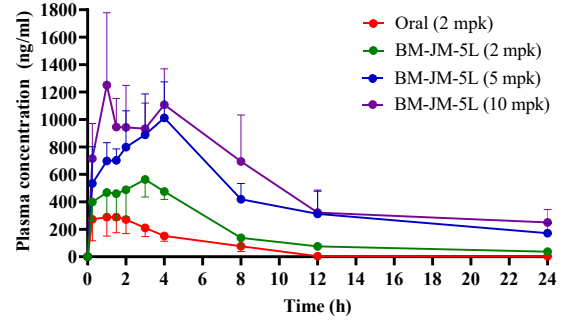

Figure 6. In-vivo pharmacokinetics study (n=5)

Table 3. Pharmacokinetic parameters of RVX for oral groups and inhalation groups in SD-rats.

Parameters	Oral (2 mpk)	BM-JM-5L (2 mpk)	BM-JM-5L (5 mpk)	BM-JM-5L (10 mpk)
$t_{1/2}$ (h)	3.38±0.89	6.27±1.82	8.76±1.54	10.46±3.29
T_{max} (h)	1.43±1.10	2.80±0.45	3.80±0.45	3.80±2.68
C_{max} (ng/ml)	314.76±110.71	566.61±134.22	1029.48±256.54	1334.64±465.97
AUC_{0-t} (ng·hr/ml)	1614.59±452.15	3945.45±666.26$^{\#}$	10272.88±2516.56**,†	12880.85±565.1**,††
CL/F (L/h/kg)	1.31±0.38	0.45±0.07	0.42±0.11	0.30±0.04
Relative BA	-	2.44	2.55	1.60