

Fundamental Evaluation and Characterization of Etoricoxib Solid Dispersions Prepared by Spray Drying

M. Pimparade, J. Tran-Dinh, M. Rane and A. Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA
www.colorcon.com

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Introduction

Hypromellose acetate succinate (HPMCAS) is a widely used polymer for improving the solubility of BCS Class II drugs through the formation of amorphous solid dispersions. HPMCAS is amenable to processing via hot melt extrusion (HME) or solvent based spray drying applications¹. Spray drying is a method that creates dry particles from a solvent based solution that is atomized through a nozzle and dried instantly, forming an amorphous solid dispersion of the drug in the polymer matrix. The selection of polymer grade is a very critical decision for development of successful amorphous solid dispersions. The purpose of this study was to evaluate different grades of HPMCAS for development of etoricoxib spray dried dispersions (SDD).

Methods

Amorphous solid dispersions of etoricoxib (ETO) and different grades of hypromellose acetyl succinate (HPMCAS 716G, 912G and 126G; International Flavors and Fragrances Inc.) in 1:3 w/w ratios of drug: polymer, were prepared using a lab spray dryer (ProCept 4M8-Trix) as described in Table 1. Clear solutions of ETO and HPMCAS (10% w/w solid content) were prepared and spray dried using the following process conditions: 0.8 mm nozzle size, 10 L/min nozzle gas flow, 5 g/min spray rate, 0.4 m³ / min air flow and 80°C inlet air temperature. The ASD powders were characterized by X-ray powder diffraction (XRPD; Equinox 100, Thermo Scientific, USA), differential scanning calorimetry (DSC; Q200, TA Instruments), particle size distribution (Mastersizer 2000, Malvern Instruments Ltd.) and scanning electron microscopy (SEM; Phenom XL, Phenom World). Dissolution behavior of all the samples in 1000 mL of phosphate buffer pH 6.8 at 37°C, with USP apparatus II (Agilent) at 75 rpm, were evaluated. Aliquots were analyzed spectrophotometrically at 236 nm.

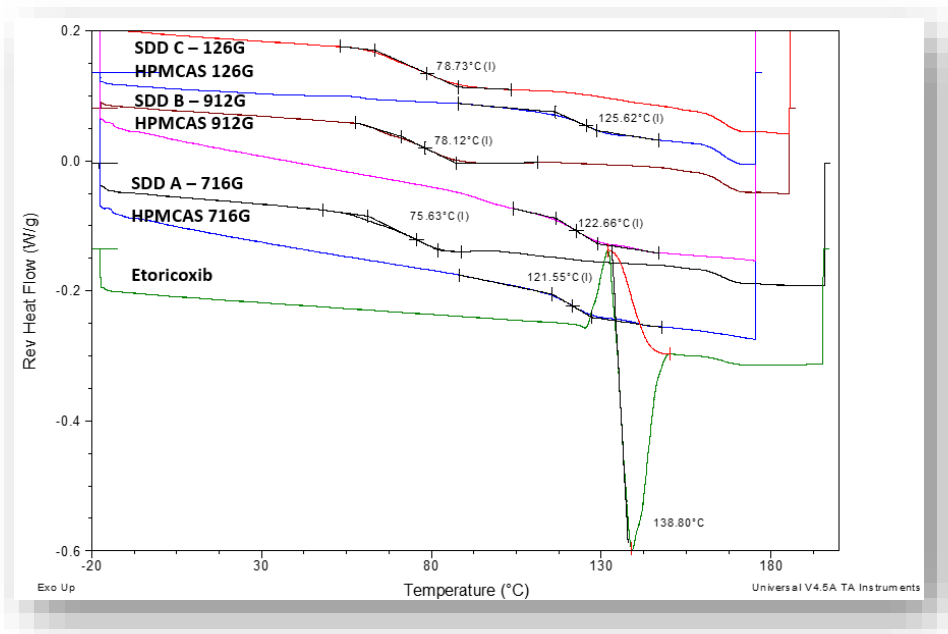
Table 1. Preparation of Spray Dried Dispersions of Etoricoxib

Formulations	Etoricoxib (%)	HPMCAS 716G (%)	HPMCAS 912G (%)	HPMCAS 126G (%)	Solid Content (%w/w)	Nozzle Gas Flow (L/min)
SDD A – 716G	25	75	--	--	10	10
SDD B – 912G	25	--	75	--	10	10
SDD C – 126G	25	--	--	75	10	10

Results

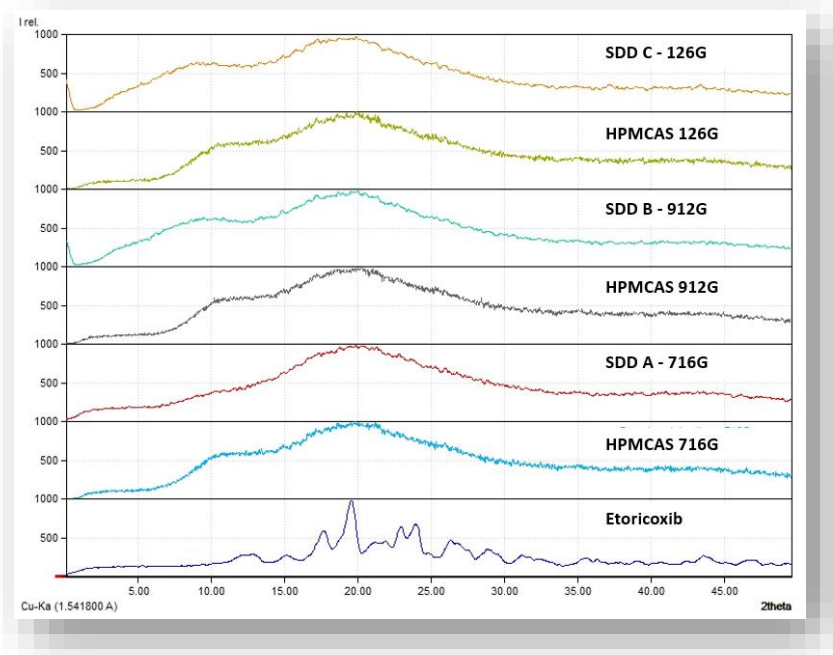
Figure 1 shows the thermograms of pure ETO, pure polymers (HPMCAS) and three SDD. Pure ETO showed sharp melting peak at 138°C, which did not appear in the SDD, indicating the amorphous form of ETO in dispersions. Furthermore, the SDD showed single glass transition temperature confirming homogenous distribution of amorphous ETO throughout the polymeric matrix.

Figure 1. DSC Thermograms of Drug (ETO), Polymer (HPMCAS) and their Spray Dried Dispersions (SDD)



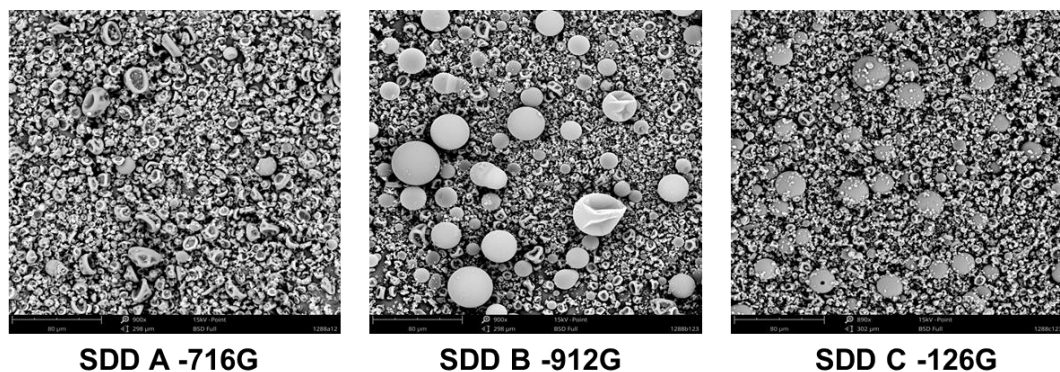
In XRPD evaluation, pure ETO exhibited characteristic diffraction peaks and ASDs showed a typical “amorphous halo”, with no ETO peaks (Figure 2). These results affirmed the presence of drug in an amorphous form for all SDD.

Figure 2. XRPD Diffractogram of Drug (ETO), Polymer (HPMCAS) and their Spray Dried Dispersions (SDD)



SEM images did not show ETO crystals in spray dried dispersions. All three formulations had very comparable shape and particle size distribution (Figure 3 and Table 2). These images suggested that the grade of HPMCAS did not affect the particle size and shape of SDD.

Figure 3 : SEM images of Spray Dried Dispersions (SDD) (900X magnification)



Loss on drying data of ASDs are shown in Table 2, indicating any residual moisture or organic solvent content. All spray dried dispersions had similar percentage weight change, and there was no notable difference in LOD for ASDs with different grades of HPMCAS.

Table 2. LOD and Particle Size Distribution of Spray Dried Dispersions (SDD)

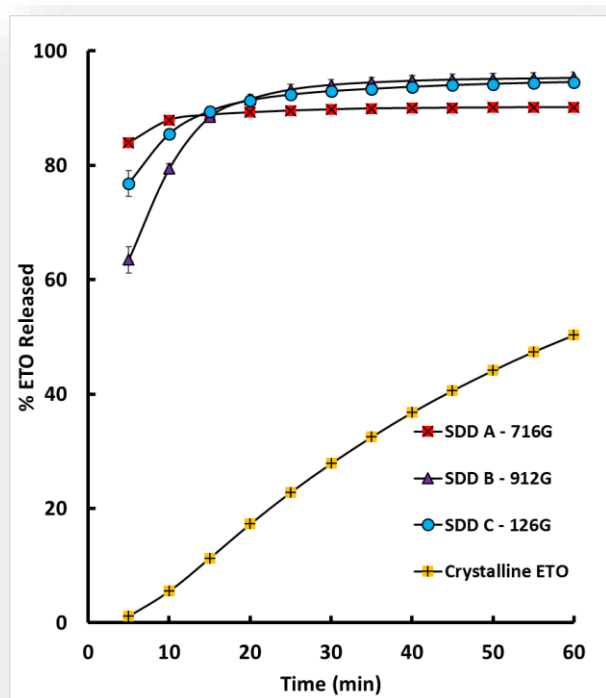
Formulations	% LOD	d(0.1) μm	d(0.5) μm	d(0.9) μm
SDD A – 716G	2.9	1.7	7.2	18.6
SDD B – 912G	3.3	1.8	7.6	28.9
SDD C – 126G	2.6	2.1	8.1	22.2

The spray dried dispersions had very rapid drug dissolution, which could be attributed to presence of HPMCAS and small SDD particle size (Figure 4 and Table 3). For all formulations, more than 80% of drug was dissolved at 20 minutes, and different grades of HPMCAS did not alter the rate and extent of drug dissolution rate. Overall, there was significant increase in the apparent solubility of ASD compared to crystalline ETO (Figure 4).

Table 3. Apparent Solubility of Crystalline Etoricoxib and SDDs in Phosphate Buffer pH 6.8

Formulations	Solubility @ 1h ($\mu\text{g/mL}$)	Solubility @ 3h ($\mu\text{g/mL}$)
SDD A – 716G	90.14	90.35
SDD B – 912G	95.32	95.64
SDD C – 126G	95.54	95.41
ETO Crystalline	50.32	84.64

Figure 4 : Dissolution Profiles of Crystalline Etoricoxib (ETO) Powder and Spray Dried Dispersions (SDD)



Conclusions

ETO amorphous solid dispersions comprising of three grades of HPMCAS were successfully produced by a spray drying process. Solid state characterization techniques confirmed the presence of drug in an amorphous form. All SDD had significant increase in the apparent solubility and dissolution compared to crystalline ETO in pH 6.8 phosphate buffer. All three grades of HPMCAS showed similar physicochemical properties and dissolution profiles for ETO ASDs.

References

1. HPMCAS for Spray-Dried Dispersion (SDD), Dupont Nutrition and Biosciences. <https://www.pharma.dupont.com/pharmaceutical-brands/HPMCAS.html>. Accessed August 20, 2019.

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