Influence of Formulation Variables on the Performance of a Beclomethasone Metered Dose Inhaler

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INTRODUCTION

As part of ongoing studies[1] to evaluate the influence of formulation changes on metered dose inhaler (MDI) performance, a commercial beclomethasone dipropionate (BDP) MDI was reverse engineered, and the resulting formulation was used as a model system to investigate the effects of changes in excipient concentrations.

The reference listed drug (RLD) contains BDP, HFA-134a, and ethanol as a solution formulation. While the RLD does not contain a lubricant / surfactant, oleic acid (OA) was included to study its impact on the performance of the solution formulation, as a follow-on to our previous study of an oleic acid containing albuterol sulfate suspension formulation.[1] Statistical design of experiments (DOE) was used to vary the ethanol concentration in the range of 7 to 9% w/w and oleic acid in the range of 0 to 2% w/w.

METHODS AND EQUIPMENT

Ethanol and OA concentrations in the MDI formulations were determined using gas chromatography with flame ionization detection. BDP concentrations were determined by liquid chromatography with mass spectroscopic detection (LC-MSD) using a BDP-d5 internal standard, which provided a limit of quantitation (LOQ) of 20 ng/mL, 3% accuracy, 1.5% RSD, and a 2-minute run time.

Using a full 3^2 factorial design, nine BDP MDI batches were filled in random order (except that the extreme batches were filled first) using a two-step pressure filling process as outlined in Table 1. The following components were used: 17-mL uncoated aluminum cans (Presspart, Lancashire, UK), 50-µL metering valves (Aptar Pharma, Congers, NY), and actuators from the RLD.

MDIs were equilibrated at ambient conditions in the valve down orientation for 7 ± 2 days before testing was initiated.

EtOH	Oleic Acid (%)		
(%)	0.0	0.5	2.0
7	1	9	5
8	4	6	7
9	8	3	2

Table 1. Design of MDI batches with manufacturing order 1 – 9.

Aerodynamic particle size distributions (APSDs) were determined via Next Generation Impactor (NGI) aerosol sampling at a flow rate of 30 L/min. Two NGI aerosol samples were taken from each of two cans for each batch at beginning of can life, once using a USP induction port and once using an Alberta Idealized Throat (AIT, Copley Scientific, Colwick, UK), which is expected to be more physiologically relevant[2]. The AIT was coated with a thin layer of glycerol to simulate the mucosa[3], while the USP throat was not coated. Each NGI experiment consisted of two actuations, and collected BDP was assayed by LC-MSD. All NGI testing was performed by the same analyst.
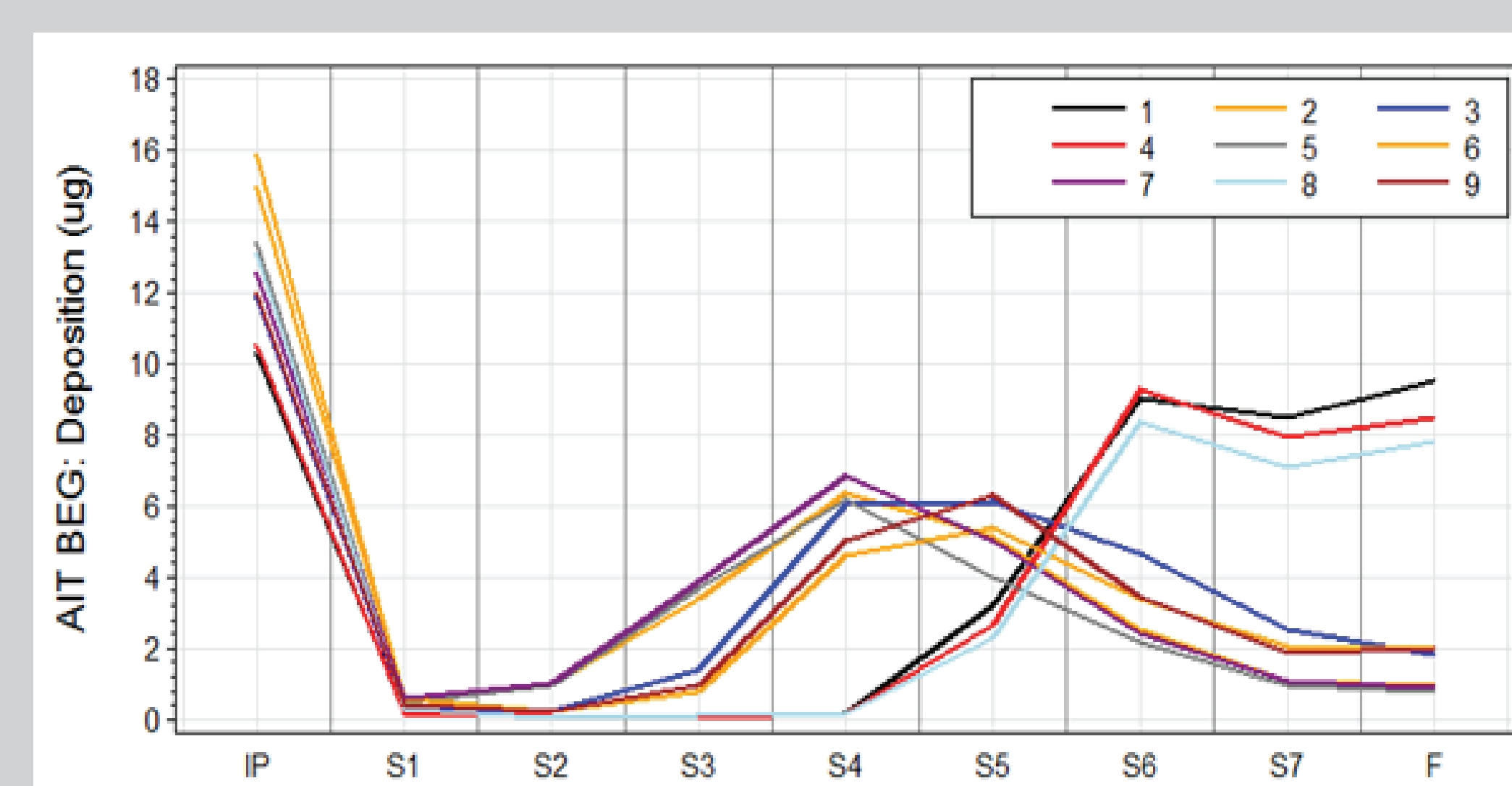
RESULTS & DISCUSSION

Ethanol and BDP concentrations in the RLD were determined to be 8.0% and 0.0820%, respectively.

Figure 1 shows the average APSD profiles for each batch using the AIT. The batches are clearly grouped into three sets (1, 4, 8), (3, 6, 9), and (2, 7, 5), which align with the different levels of oleic acid (0%, 0.5%, and 2% w/w, respectively). Figure 2 shows the relation between the AIT and USP throat profiles. There is no difference between throat or S3 deposition, but for S1 and S2 much less is deposited for the AIT. The region of S4 to MOC shows a gradual change in the ratio.
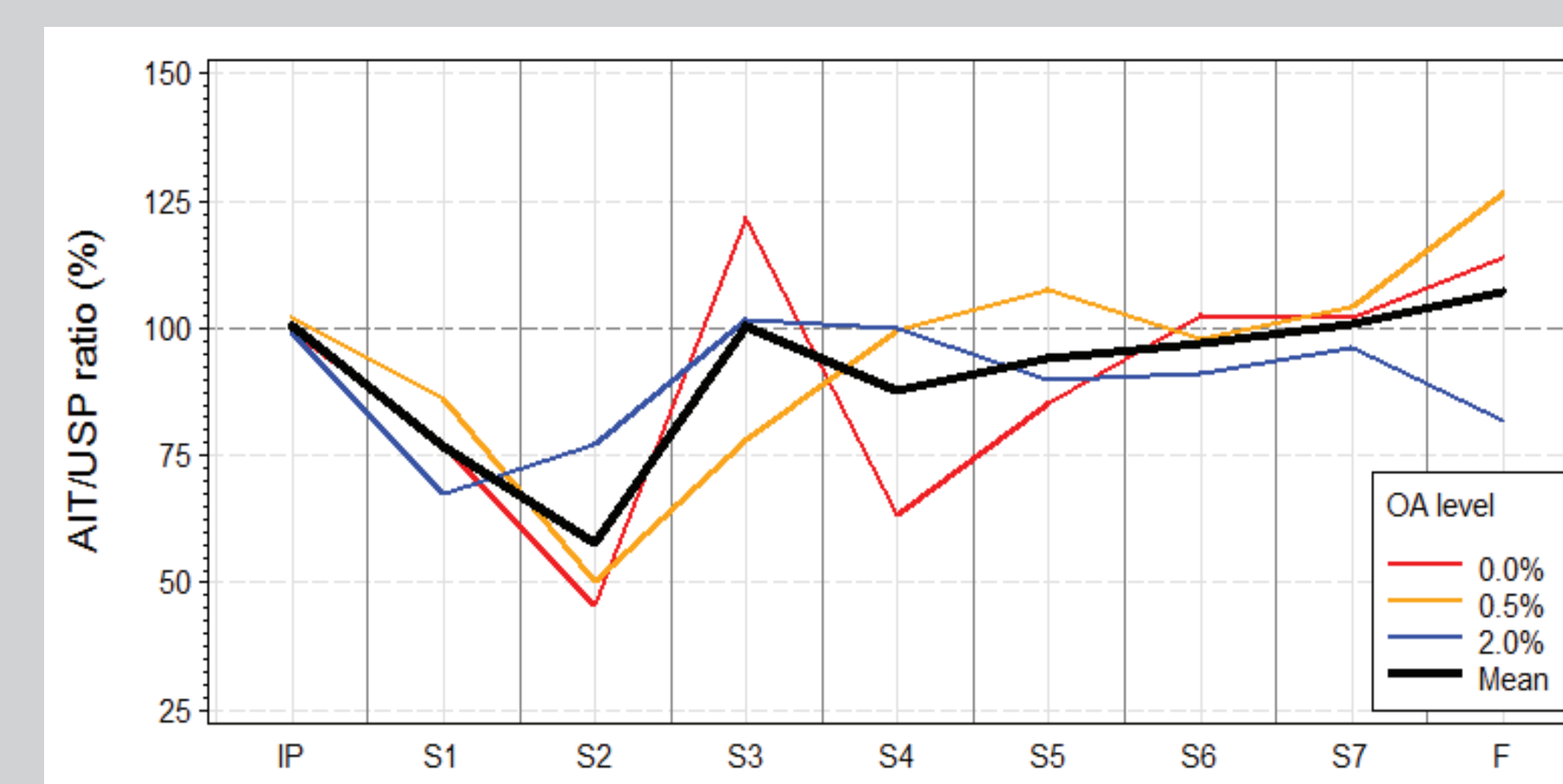
An ANOVA analysis (Table 2) evaluated the effects on two endpoints of interest, fine particle dose < 5 µm (FPD) and total dose (sum of IP, S1-S7, and MOC). The analysis shows a statistically significant effect at the 5% level by OA on FPD for both throat types. Over the range studied, ethanol did not have a statistically significant effect on the total dose or FPD.

FIGURE 2

AIT / USP deposition ratio (%).

	Total dose (µg)		FPD (µg)	
	AIT	USP	AIT	USP
EtOH	0.0917	0.5786	0.9919	0.5973
OA	0.2169	0.4521	0.0017	0.0121

Table 2. APSD total dose and FPD: ANOVA analysis (p-values < 0.05 highlighted yellow).

Mathematical modeling was undertaken to explore how the FPD depends on OA. Because no differences were observed between the throat types, results for the two throats were pooled for modeling. A variety of linear and non-linear models were tested, with none explaining more than 65% of the variation. The model FPD = 18.31 – 1.39*ln(OA) was selected to study the design space for OA. A specification for FPD of (20-a) to (20+a) µg was assumed, where a is determined so (20+a)/(20-a) = K , for K = 1 to 2.6. For example, if the ratio K between the upper and lower specification limits for FPD equals 2, we have a = 6.7, and thus the acceptance criteria is 13.3 to 26.7 µg.

By this construction, the range of OA changes allowable as the width of the specification increases is apparent (Figure 3). Note the extrapolation outside the studied domain should be performed with care.

FIGURE 1

AIT: average NGI deposition by NGI stage and batch.

FIGURE 3
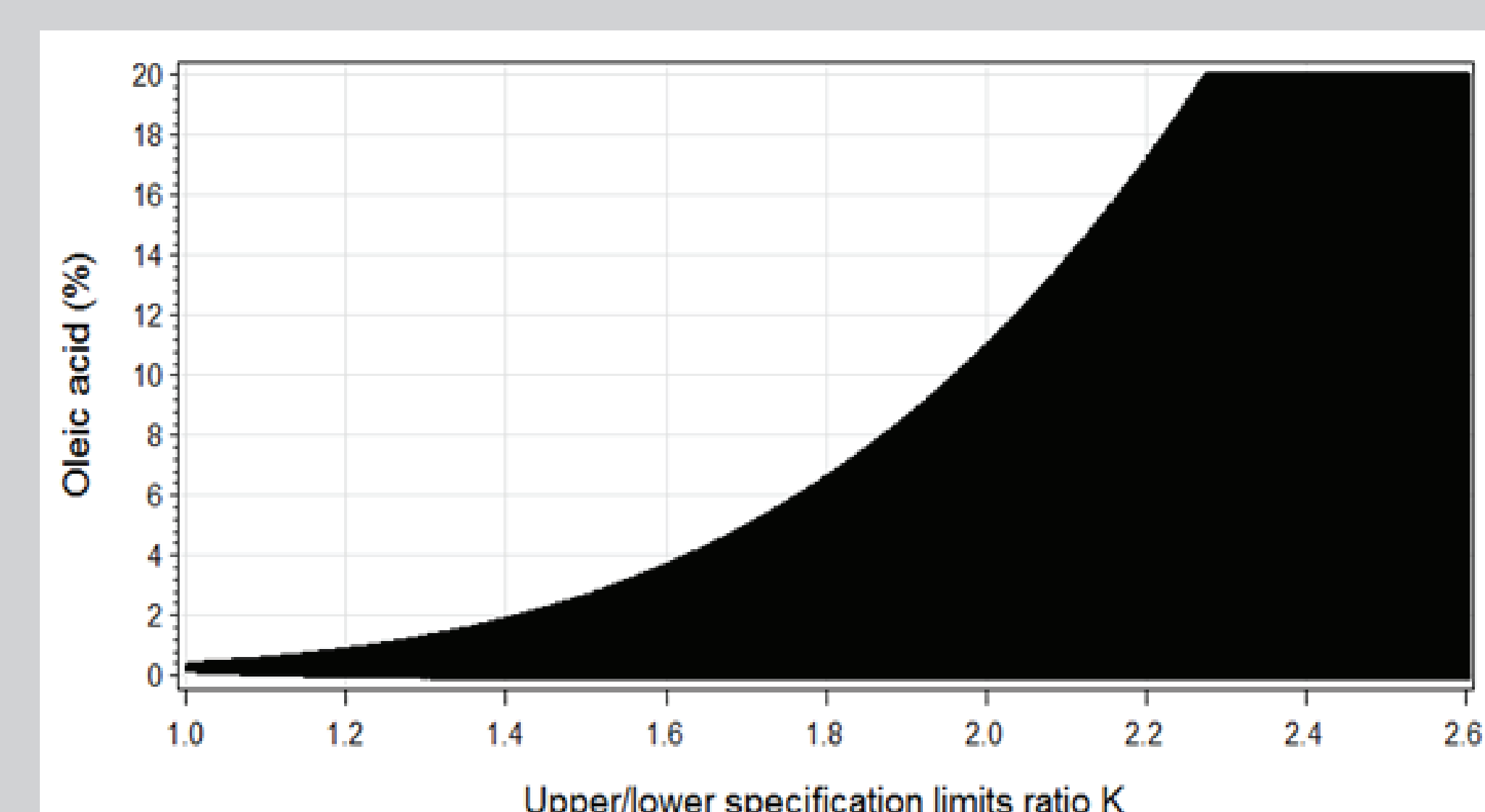
FPD: Design space for OA corresponding to specifications of increasing width.

CONCLUSIONS

A formulation based on a commercial BDP MDI was used as a model system for studying the influence of excipients on APSD and FPD. A design space was constructed showing the allowable range for OA as a function of specification limits.

ACKNOWLEDGMENTS

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