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QbD - How Particle Size And Glyceride Composition Affect The Performance of Sustained Release Tablets With Compritol 888 ATO

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PURPOSE

Understanding the potential effect of excipient variation on the quality of the final dosage form is fundamental to provide a robust manufacturing process and safe drug products. Critical excipient attributes must be identified to assess the risk to the drug product and eventual severity of harm to the patient. Risk assessment however should be well deliberated. Not all excipient attributes must be systematically taken into account but those that are directly related to the manufacturing process, the formulation and the extent of variability of the excipient.

OBJECTIVES

1) Identify the critical material attributes (CMAs) of glyceryl dibehenate (Compritol® 888 ATO, sustained release agent).
2) Evaluate their effects on sustained release tablets prepared by direct compression.

METHOD

The variability of over 350 Compritol® 888 ATO batches was determined and the monograph specifications considered for an overall risk assessment for a direct compression process. Nine batches were used to evaluate the effect of the glyceride content and particle size on tablet properties. Different size fractions of Compritol® 888 ATO were obtained by sieving.

Tablets of 333.3 and 1000 mg were produced at 30 rpm using a 10 station rotary press (RIVA Piccola) with 100 mg theophylline anhydrous as sparingly soluble model drug and 500 mg metformin HCl with high aqueous solubility respectively (Table 1).

Table 1. Tablet compositions to evaluate the effect of gycerides and particle size on tablet attributes

Ingredients (%)	Theophylline		Metformin HCl
	Glyceride evaluation	Particle size evaluation	Used for both evaluations
Drug	30	20	50
Compritol® 888 ATO	19.5	15	30
Diluents	50	64.5	19
Mg stearate	0.5	0.5	1

RESULTS

Composition and variability of Compritol® 888 ATO

All evaluated Compritol® 888 ATO batches were within the specification limits and exhibited low variability as indicated in Figure 1.

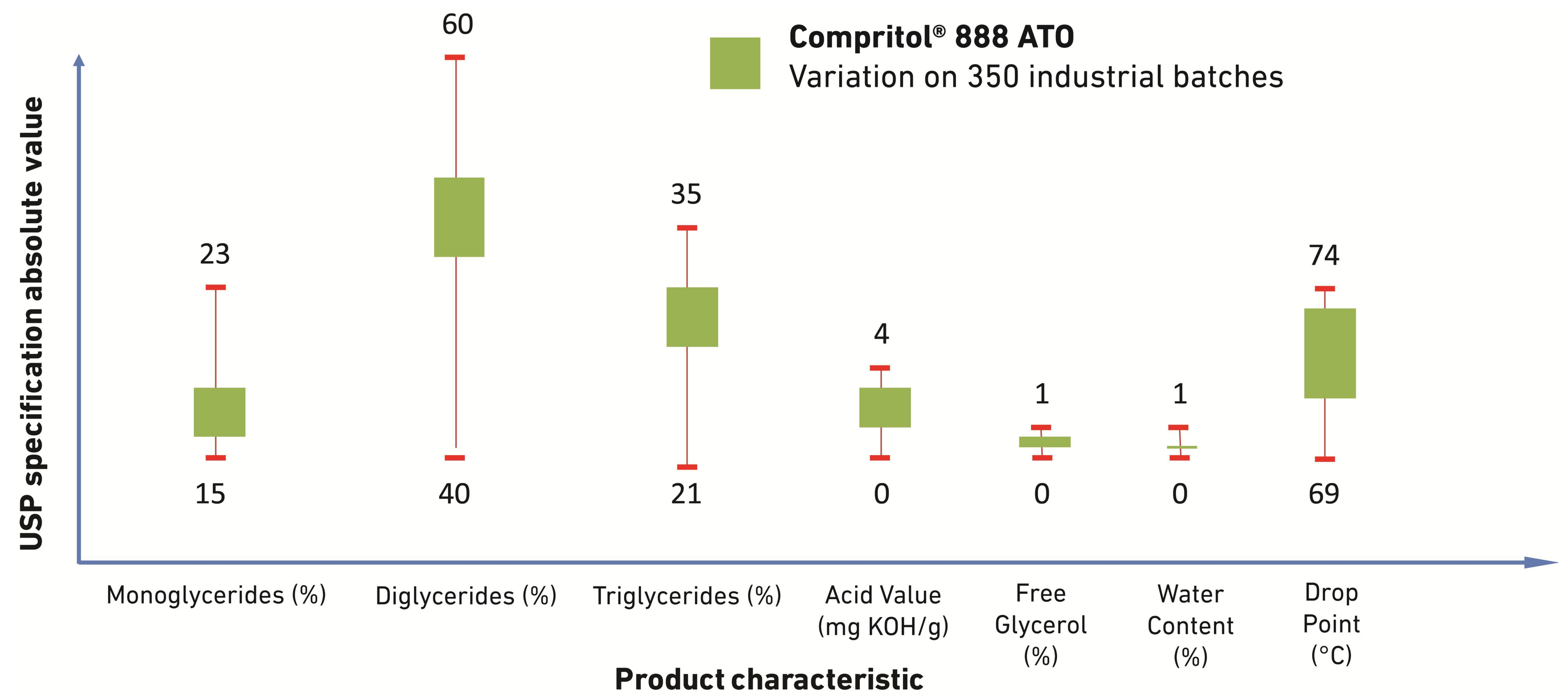

Figure 1. USP/NF monograph specifications of glyceryl dibehenate and mean values of about 350 batches of Compritol® 888 ATO.

Risk assessment for direct compression with Compritol® 888 ATO

Glyceride composition (as main component) and particle size were investigated for their potential effects on tablet attributes. As the importance of the glycerides on the final drug product is unknown yet in a direct compression process the 'risk' was considered high for each processing step (Table 2). Due to the low threshold values all other specifications were considered uncritical in this process.

Table 2. Overall risk assessment for a direct compression process with Compritol® 888 ATO

	Blending	Lubrication	Compres-sion	Tablet attributes			
				Weight	Friability	Hardness	Drug release
Glycerides	High	High	High	High	High	High	High
Particle size	High	High	High	High	Low	High	High
Melting range	Low	Low	Low	Low	Low	Low	Low
Fatty acids	Low	Low	Low	Low	Low	Low	Low
Acid value	Low	Low	Low	Low	Low	Low	Low
Peroxide value	Low	Low	Low	Low	Low	Low	Low
Water content	Low	Low	Low	Low	Low	Low	Low
Free glycerol	Low	Low	Low	Low	Low	Low	Low

Effect of glyceride content

The composition of the different Compritol® 888 ATO batches had no significant impact on the physical properties of the tablets. Statistical analysis gives evidence that all tablets were equal to the target weight with 334.1 ± 2.0 and 1001.7 ± 6.9 mg for theophylline and metformin HCl respectively (α 0.05). Friability was 0.14 ± 0.02 and 0.26 ± 0.04%, and no significant differences were observed for tablet hardness with 86.8 ± 4.0 and 116.8 ± 5.5 N. Drug release was considered similar and independent of the glyceride concentrations with f2 values above 80 for both drugs (Figure 2a, example theophylline).

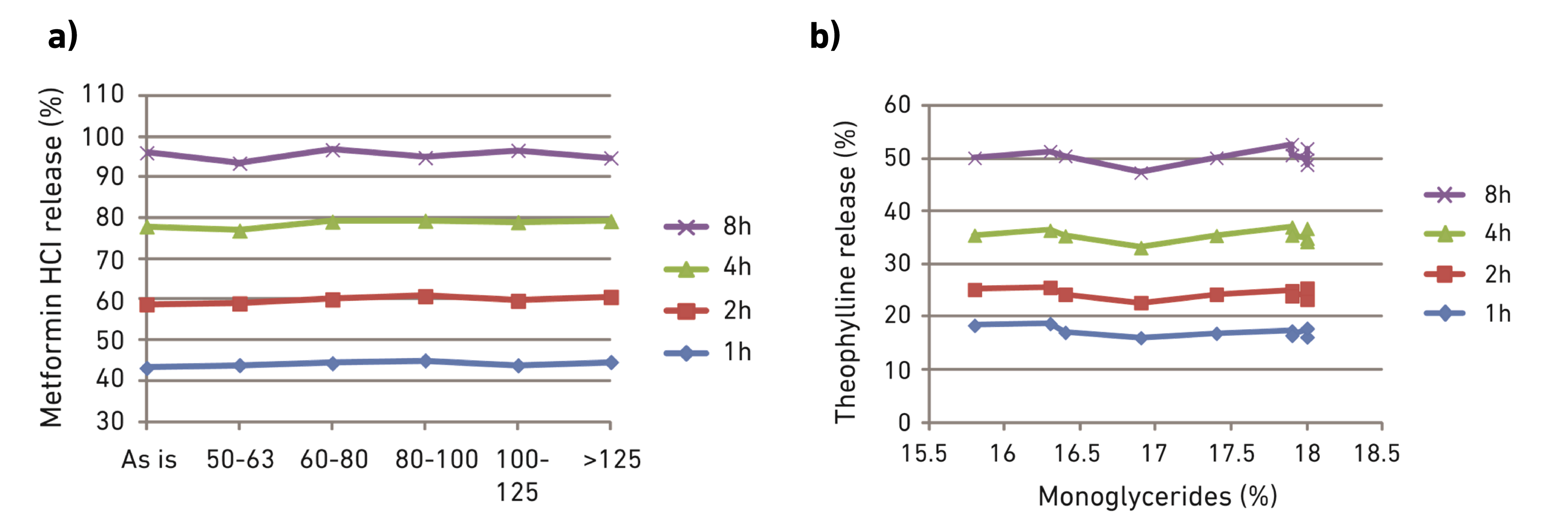

Figure 2: Effect of: a) particle size and b) monoglycerides on drug release

Effect of particle size

The sieved particle size fractions were compared to pure Compritol® 888 ATO that had a mean particle size of 56.1 ± 32.8 µm. All sieved cuts provided tablet weight and hardness variances equal to the mean particle size of Compritol® 888 ATO indicating that particles above the normal mean did not affect the final drug product performance. Drug release kinetics from the size fractions was concluded similar with f2 values above 85 for theophylline and metformin HCl respectively (Figure 2b, example metformin HCl).

CONCLUSION

Within the scope of providing robust and high quality drug products Compritol® 888 ATO was evaluated for its critical material attributes in a direct compression process. The results from this study revealed that different mono-, di- and triglyceride concentrations and size variations greater the mean of Compritol® 888 ATO had no significant impact on the properties of tablets. Weight uniformity, hardness and friability of tablets were similar and drug release kinetics was not affected. Glyceride composition and particle size were therefore not considered critical material attributes of Compritol® 888 ATO when used as sustained release agent in matrix tablets produced by direct compression.

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