THE EFFECT OF CPPs IN MANUFACTURING (FILLING PROCESS) OF DRY POWDERS FOR ORAL SUSPENSIONS

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INTRODUCTION

Dry powders and granules for oral suspensions are pharmaceutical preparations intended to be reconstituted with the prescribed liquid in order to produce a liquid preparation for oral use. APIs that are chemically unstable in solution in the presence of an aqueous vehicle for a long period of time (eg. antibiotics) usually come on the market as a mixture of dry powders that need to be reconstituted before being dispensed to the patient.

This study provides an overview of different characteristics of two formulations with the same API, (third generation cephalosporin in form of trihydrate), batch size, deliverable volume of suspension after reconstitution, same manufacturing process and composition, but different quantities and grades of excipients that affected the filling process. Therefore, the aim of this study was to investigate the differences between two formulations of dry powder and granules for oral suspension with the same API in terms of the filling process in primary packaging materials and their behavior during the filling process taking into consideration the critical process parameters (CPP) and the intermediate critical quality attributes (CQA).

MATERIALS AND METHODS

The API is classified as a BCS IV drug in both formulations which is a low soluble and permeable drug and is used in micronized grade, has low bulk density and low floawability.

	Preparation of formulation I	*Preparation of formulation II*
Description of formulation	dry powder for oral suspension 100 mg/5 ml (100 ml final volume after reconstruction	granules for oral suspension 100 mg/5 ml (100 ml final volume after reconstruction
	API in trihydrate micronized form	API in trihydrate micronized form with coarser grade of quality of PSD
Description of manufacturing process	MIXING and (WET) GRANULATION API and excipients are mixed in a mixer granulator. Blend is granulated in a high-shear mixer granulator with purified water as a granulating solvent. - API - suspending agent - xanthan gum (for increasing viscosity) - filler / sweetener - sucrose (in the form of milled sugar)* Wet granulation by 4 sub-batches of pre-blend that enter the final blend	
	* sucrose 50% w/w	* sucrose 70% w/w
	Drying	
	Screening	
	Homogenization (dry mixing) Screened granulate is mixed with the following pre-sieved ingredients: -preservative -filler crystalline sucrose 50% w/w (non-milled) -flavoring agent -xanthan gum	Homogenization (dry mixing) The preservative is triturated with part of sucrose and mixed with screened granulate: -preservative -sucrose* 30% w/w (milled) -flavoring agent
	FILLING IN BOTTLES The final blend was filled and dispensed into a multidose container - a dark glass bottle with a screw-type aluminium cap with inserted polyethylene seal with a prescribed average filing mass of 53 g in order to obtain deliverable volume of 100 ml suspension. Under a vacuum, the granules from each dosing place were kept in each dosing place until they reached the receiving cup with bottle and then with aid of compressed air the granules were filled in the bottle.	

RESULTS AND DISCUSSION

Throughout the filling process of three batches, in-process control test of the filling mass per bottle was performed by weighing the filling mass of 8 bottles of each dosing place at three time points with adjusting of the CPPs (volume, vacuum and compressed air).

The results from process controls (PC) and control tests (CT) carried out on the samples taken during the filling and sealing process are presented in Table 1 and Table 2.

FORMULATION 1

Table 1a. First batch from formulation I

Parameter	Filling per bottle (g) Acceptance criteria: 53.0g-54.6g		
Batch No: 1			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	53.22	53.36	54.26
2	53.29	53.16	53.40
3	54.01	53.65	53.10
4	54.14	54.15	53.19
5	53.35	53.53	53.36
6	53.76	53.89	53.80
7	53.96	53.18	54.25
8	53.72	53.29	53.40
Descriptive statistics			
average	53.60		
min	53.10		
max	54.26		
stdev	0.38		
RSD	0.71		

Table 1b. Second batch from formulation I

Parameter	Filling per bottle (g) Acceptance criteria: 53.0-54.6 g		
Batch No: 2			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	53.81	53.47	53.40
2	53.34	54.41	53.80
3	54.25	54.17	53.70
4	53.43	53.32	54.12
5	54.12	54.02	53.52
6	53.59	54.05	53.85
7	54.24	54.16	53.76
8	53.82	54.22	53.61
Descriptive statistics			
average	53.84		
min	53.32		
max	54.41		
stdev	0.33		
RSD	0.61		

Table 1c. Third batch from formulation I

Parameter	Filling per bottle (g) Acceptance criteria: 53.0-54.6 g		
Batch No: 3			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	53.74	53.51	53.73
2	53.77	53.63	53.33
3	53.52	53.33	53.40
4	53.84	53.21	53.50
5	53.68	53.26	53.50
6	53.67	53.66	53.45
7	53.40	53.39	53.63
8	53.84	53.51	53.39
Descriptive statistics			
average	53.54		
min	53.21		
max	53.84		
stdev	0.18		
RSD	0.55		

Formulation I resulted with compressed air of 6.5 bar and a vacuum of 1.5 bar in all three batches. More frequent service interventions at the beginning of the process for adjusting all 8 dosing pleases were present in Formulation I due to mass variations to achieve an average mass of 53 g (+3%).

FORMULATION 2

Table 2a. First batch from formulation II

Parameter	Filling per bottle (g) Acceptance criteria: 53.0-54.6 g		
Batch No: 1			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	54.0	54.2	53.3
2	53.7	54.4	54.0
3	54.0	53.9	53.4
4	54.5	53.1	53.7
5	54.0	54.2	53.5
6	53.9	54.5	53.6
7	54.3	54.0	53.9
8	54.2	53.2	53.4
Descriptive statistics			
average	53.9		
min	53.1		
max	54.5		
RSD	1.2 %		

Table 2b. Second batch from formulation II

Parameter	Filling per bottle (g) Acceptance criteria: 53.0-54.6 g		
Batch No:2			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	53.7	54.0	53.8
2	53.8	53.9	53.7
3	53.7	53.6	54.3
4	53.3	53.3	53.4
5	53.8	53.8	53.6
6	53.3	53.4	53.6
7	53.4	53.2	53.6
8	53.2	54.3	54.2
Descriptive statistics			
average	53.7		
min	53.2		
max	54.3		
RSD	0.6		

Table 2c. Third batch from formulation II

Parameter	Filling per bottle (g) Acceptance criteria: 53.0-54.6 g		
Batch No: 3			
Sample No.	Beginning of filling	Middle of filling	End of filling
1	53.8	53.9	53.3
2	54.2	53.4	53.2
3	53.8	53.5	53.4
4	53.1	53.4	53.5
5	53.6	54.1	53.4
6	53.4	53.7	53.3
7	53.4	53.5	53.8
8	53.7	53.8	53.3
Descriptive statistics			
average	53.6		
min	53.1		
max	54.1		
RSD	0.5		

Formulation II resulted with compressed air of 6.5 bar and a very low vacuum value of about 0.15 bar in all three batches

Photo 1 .PSD on the final blend (%)- Formulation I

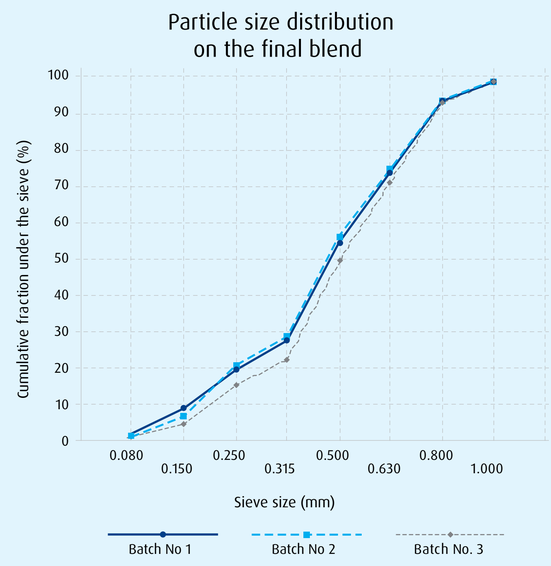
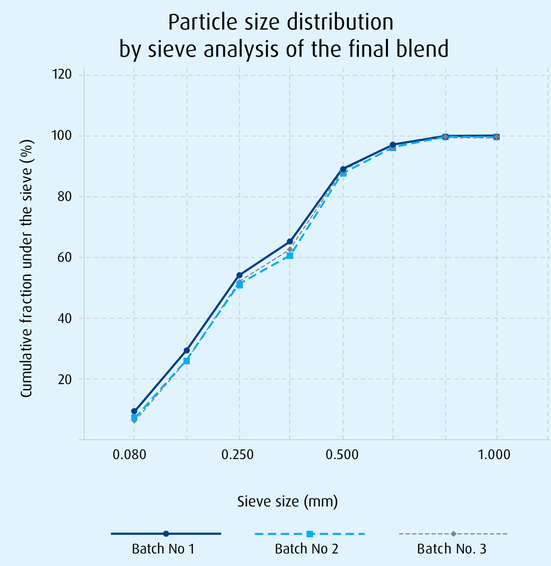


Photo 2 .PSD on the final blend (%)- Formulation II



CONCLUSION

The results of the performed comparison show that the filling process was affected by the differences in the formulation. The filling process of the final blend with average mass of 53g (+3%) per bottle was directly affected by PSD as intermediate CQA of the two formulations. Formulation II performed better during the filling process and resulted with a product with a better quality.

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