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Short communication

The effect of critical process parameters 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. Typically, this type of preparation is a mixture of powders containing an active pharmaceutical ingredient (API) and suitable suspending and dispersing agents. The suspension can simultaneously provide chemical stability and enable the proper use of the liquid dosage form in a large number of patients who prefer liquid to solid pharmaceutical dosage forms. They are easier to swallow, and have the opportunity for greater flexibility in terms of doses to be administered and the ability to mask the unpleasant taste of certain APIs.

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 (Ansel et.al., 2005).

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 a third generation cephalosporin in form of trihydrate in both formulations which is used to treat susceptible Gram negative and Gram positive bacterial infections. It is a low soluble and permeable drug classified as a BCS IV drug. API is used in micronized grade, has low bulk density and low flowability. The manufacturing process used was wet granulation for both formulations and was characterized by 4 sub-batches of pre-blend that enter the final blend. Each pre-blend was subjected to high-shear wet-granulation (Diosna P300, Germany), drying (De Lama II, Italy), screening (Frewitt, Switzerland), mixing (Lodige, Germany) and filling in bottles (Macofar CEM MT6, Italy) processes. Purified water was used as granulating solvent in both formulations. 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.

Particle size distribution (PSD) of the final blends was estimated by analytical sieving (Retsch AS 200 Control), according to the Ph. Eur.10, Method 2.9.12.

Preparation of formulation I - Formulation I was a dry powder for oral suspension 100 mg/5 mL (100 mL final volume after reconstruction). Each pre-blend was characterized by the presence of API in trihydrate micronized form, suspending agent xanthan gum (for increasing viscosity), filler/sweetener - sucrose in the

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form of milled sugar of each granulate. The suspending agent in Formulation I was presented in both, the internal and external phase The quantity of sucrose in the formulation was divided in the inner and outer phase of the granulate approximately 50:50% w/w with different sucrose PSD grade (milled sucrose in the inner phase and crystal sucrose in the outer phase) (Ph. Eur.10, Method. 2.9.38). The four pre-blends were screened, merged and mixed together with the flavoring agent, suspending agent xanthan gum (also present in the outer phase), preservative and filler crystalline sucrose (non-milled) in a ploughshare mixer until a final blend was obtained (Rowe et al., 2003)..

Preparation of formulation II - Formulation II was granules for oral suspension 100 mg/5 mL (100 mL final volume after reconstruction). Each pre-blend was characterized by the presence of API in trihydrate micronized form with coarser grade of quality of PSD compared to the API in Formulation I, than suspending agent xanthan gum (for increasing viscosity) in the inner phase, filler / sweetener - sucrose in the form of milled sugar. The whole quantity of the suspending agent was presented only in the internal phase. The quantity of sucrose in the Formulation II was divided in the inner and outer phase of the granulate approximately 70:30% w/w with same sucrose PSD grade (milled sucrose in both phases). The four pre-blends were screened, merged and mixed together with the flavouring agent, preservative and filler milled sucrose in a ploughshare mixer, until a final blend was obtained (Rowe et al., 2003). Sucrose in the inner and outer phase was in milled form.

Macrodosing machine was used for filling of bottles with powders/granules for oral suspension. The principle of operation of the machine was vacuum volume filling under the action of compressed air. At the beginning of the process, the CPPs on the macrodosing machine were adjusted, which were the volume, vacuum and compressed air in order to achieve an average mass of 53 g (+3%) (Ph. Eur.10, Method 2.9.27). The CQA of the filling process i.e. uniformity of mass in bottles was depended on the process parameters and intermediate CQAs from the previous manufacturing step such as PSD of the final blend (Maguire and Peng, 2015)**.** The main dosing unit contained with 8 dosing places were filled with granulate. Under the vacuum, the granules 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

Analysis and monitoring were performed during the filling process on the macrodosing machine of 3 consecutive batches of the two formulations separately. 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) an average mass of 53 g (+3%) per bottle was obtained. The filling process of Formulation I resulted with compressed air of 6.5 bar and a vacuum of 1.5 bar in all three batches, and 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. 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%).

The PSD of final blend of Formulation I is wider compared to PSD of final blend of Formulation II, that resulted in higher various of mass in filling process and more frequent service interventions.

Conclusion

The results of the performed comparison show that the filling process was affected by the differences in the formulation. In the filling process compressed air in both formulations was the same but Formulation I required a higher vacuum to achieve the average prescribed filling weight of 53 g. At the beginning of the process, the CPPs on the macrodosing machine were adjusted with more frequent service interventions for Formulation I.

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 showed a narrow PSD compared to Formulation I which showed a wider PSD and larger mass variations during the filling process.

That confirmed that Formulation II performed better during the filling process and resulted with a product with a better quality.

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