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Short communication

Key aspects in process design & scale up of semi-solid dosage forms from pilot to commercial batch size

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Introduction

Topical semi-solid dosage forms are one of the fastest growing product markets globally. As the skin is the largest organ in the human body and the primary side of action of this type of products, quality assurance is a primary tool in guaranteeing their acceptable performance (Sarika et al., 2020). As eye corneal permeability favours lipophilic compounds that often have a low aqueous solubility, the ocular drug delivery is solved with development of semi-solid suspension products. The knowledge of the critical parameters is basis for successfully scale up the process, where similarity principle can be adopted (Davies et al., 2000). Geometric similarity means that equipment shape and dimensions are proportional from one production scale to another. Thus, this similarity would ensure results that are independent of scale. Unfortunately, pharmaceutical process in manufacturing of semi-solid dosage forms can vary with scale even when the equipment uses the same operating principle (e.g., low-shear mixer) and the same design characteristic. Processes are dependent on volume and area. For a given linear change in scale, the effect on area or volume is different. At small production scales, area is more prominent than volume. At larger production scales, volume is far more prominent than area. For example, controlled process such as heat transfer, particle dispersion or surfactant adsorption at interfaces during emulsification are area-depended process. As scale increases, the area relative to the volume decreases and efficiency of the process can be significantly declined. Heat-exchange provisions (e.g., jacket equipment) that are adequate at a small scale may be inadequate at a larger scale. Hence, a key aspect of scaling up or down requires changes in the controlling mechanism in a process. As Tatterson points out, 'It is unwise to scale a process without knowing the controlling mechanisms' (Tatterson et al., 1994).

Simple ointments are solid suspensions where the drug is suspended in a heated petrolatum base and then slowly cooled and mixed until a homogenous mass is formed. During manufacturing, care must be taken to get drug suspended properly without incorporation of excess air, which can affect viscosity, appearance, uniformity of dosage units and stability. It is more important to maintain the temperature rang properly during the cool-down steps to prevent the sedimentation.

Following the transfer of technology of an eye ointment performed on one pilot batch of 50 kg it was proposed increasing of the batch size (scale up to 100 kg), as the air entrapment is more likely to occur in smaller batches, taking into account the capacity of equipment.

Materials and methods

Materials

Antiviral micronized active substance with poor aqueous solubility provided by Quimica Sintetica, S.A. was used as a drug (PSD quality: 100% less than 24 µm; 90% less than 12 µm; BSC Class III / IV) and paraffin, white soft, Ph. Eur., Type CD 806 as ointment base provided by Parafluid GmbH.

Preparation of scale up batches

Both ingredients used in the study are approved for use in the pharmaceutical industry. The ointment was prepared by melting of the ointment base i.e. dispersion of the active substance by mixing and homogenization followed by continuous cooling. Manufacturing process was performed in double jacket mixing vessel with

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capacity of 150 L (Olsamix PH 150B, Italy), equipped with central impeller, peripheral impeller and flexible scraper blades to remove mass from internal walls of the tank into the center of mixing. The physico-chemical properties of bulk product were met immediately after end of manufacturing process. Samples were taken from 9 locations for testing the control parameters: *appearance, colour, PSD* and *assay*.

Physical characterization of the ointment

Homogenous distribution of the active substance particles was confirmed with PSD test of the bulk product. Particle size distribution of the ointment was analyzed on samples taken after producing the bulk product by phisico-chemical method: optical microscopy (Morphologi G3S, Malvern, UK). Determination of the particle size was performed with scanning under the microscope.

Identification and assay of active ingredient

Identification and content determination of the active substance in the drug product were carried out by HPLC method. The content was calculated from the ratio of the obtained peak areas of the API in the test and standard solution at wavelength of 254 nm.

Results and discussion

After manufacturing of pilot batch size with prescribed homogenizer speed of 1400 rpm and vacuum range from - 0.3 to - 0.5 bar, air entrapment was noticed in the bulk product. Thus, this batch size is considered to be insufficient load for capacity of Olsamix 150, nonetheless the vacuum should be higher from -0.6 to -0.8 bar during homogenization by mixing and cooling.

Optimizing of the mixing speed and time was directly dependent of rheological properties of the bulk product, batch size and percentage loading of the vessel. During the preparation of scaled batch of 100 kg, there was used homogenizer three times under higher vacuum pressure to ensure uniform dispersion of particles. Additionally, it guarantees removal of air pocket from the formulations giving smoothness of the mass. For ointments, it is known that their rheological behavior is complex and highly temperature dependent (Sarika et al., 2020). Establishing suitable temperature ranges (65-80^{0}C; 45-55^{0}C; 29-33^{0}C), higher than used during the production of pilot batch size, as well as properly rate of heating and cooling in all the production phases in order to avoid precipitation of the API in melted base and grittiness from the mass after dispersion, was done. The viscosity of the ointment base is determined as a function of temperature and therefore it can be considered as an indicator for the feasibility of a product (Anton et al., 2018).

Another key aspect during phase of forming primary dispersion is to establish turbulent-flow regime with moving the central impeller and peripheral impeller in reverse direction. On the other hand, during the cool-down phase when solidified homogeneity mass is forming, it is important to achieve laminar-flow regime by setting the scraper blades and paddle blades to move in the same direction. The obtained results for assay were satisfactory for both batch sizes with all individual values within the limits of 95.0-105.0% and low RSD values. Thus, content uniformity of the bulk product was properly achieved with established process parameters.

The whole mass of the ointment was smooth, white and homogenous without visually noticed air bubbles. The optical microscopy during the first scanning at a small magnification (at 400 µm) identified the particles which conforms the criteria in Ph. Eur test for particle size in semi-solid eye preparations (Ph. Eur. 10.8, 2022) as well as interrupted air bubbles in the samples by pilot batch of 50 kg. From the microphotographs at a larger magnification (at 100 µm) there were detected the shapes of larger particles with measured dimensions around 20 µm. The interrupted air bubbles were not found in the samples from scaled batches of 100kg.

Conclusion

Based on the evaluated results, it can be concluded that successful scale up of the suspension semi-solid drug products requires optimizing the batch size as well as suitable ranges of process parameters, taking into account prior knowledge of the manufacturing process.

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