Process Development and Industrial Manufacturing of Nanotechnology-Based Pharmaceuticals

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ABSTRACT

Process design and development of oral, topical and parentral nanotechnology-based pharmaceuticals are presented. Factors affecting process output and scale-up choices for various dosage forms are discussed with emphasis on critical parameter control and optimization. For example, effect of process variables on nanoparticles crystal form, shape, size, as well as nanoparticles stabilization, purification and yield are elaborated. Quality control testing and design of accelerated stability studies for nanoparticles-containing pharmaceuticals are detailed.
Finally, integrating nanoparticles manufacturing equipment into conventional equipment trains used for large scale production of tablets, capsules as well as parentral and topical suspensions are demonstrated using selected model drugs.
Keywords: nanoparticles, nano-emulsions, process development, scale-up

1 INTRODUCTION

Regardless of how innovatively nanoparticles are designed or made, they must end in one of the standard dosage forms approved by regulatory agencies such as FDA or EMEA. Among the various nanotechnology-based drug delivery systems, solid oral dosage forms containing solid drug nanoparticles are of great interest because of their novelty and manufacturing complexity, relative to standard manufacturing methods of tablets or capsules. Similarly, process development and manufacturing of nanoparticles-containing topical or parentral preparations require modified methodologies to address the physical and chemical characteristics of those drug delivery systems.

2 DEFINITIONS

Nanoparticles are referred to as particles that: A. Are 200nm or less in diameter and B. Possess superior physical properties when compared to those of the bulk materials, due to their reduced size.

In-Process Testing is defined as a quality-related test of intermediate materials, whose results are required before further material processing can be performed.

3 PROCEDURES

3.1 Process Development of Nanoparticles

Solid drug nanoparticles (SDN) are manufactured by simple particle size reduction in presence of surface active agents (wet milling) (1) or by precipitating nanoparticles from solutions (2) or emulsions (3). All manufacturing techniques share the need for high energy possibly generated from different sources such as high pressure fluidization or ultrasonic waves. While the type and amount of force appear determinant to nanoparticles size, type of vehicle, surfactants as well process conditions such as temperature and equipment configuration play critical role in the stability of the formed nanoparticles. By default, the resultant highly energetic surface of nanoparticles dictates In-process evaluation of nanoparticles to determine quality and the holding time allowed prior to further processing. Tests such as particle size analysis and crystal form identification become necessary tests to ensure product quality.

3.2 Incorporation of Nanoparticles into Standard Dosage Forms

SDN were incorporated in oral tablet formulations using wet granulation of drug nanoparticles concentrate followed by drying and compression.

SDN were also prepared as powder for injection whereas topical nano-emulsions were prepared by diluting self emulsifying nanosystems with various gel matrices.

3.3 Accelerated Stability Testing of Nanoparticles-Containing Dosage Forms

Accelerated stability for SDN as dried nanoparticles concentrates as well as in the finished products containing SDN were performed at 40C/75% RH for up to three months.

4 RESULTS AND DISCUSSION

Table 1: summarizes manufacturing process variables for SDN made from nano-emulsions.

Table 1: Manufacturing process variables for SDN

Process	Equipment	Independent Variable(s)	Affected response
Pre-emulsion formation	Homogenizer	Internal phase and external phase ratio	Emulsion stability
Nanoemulsion formation	High pressure homogenizer/Ultrasonicator	Mixing time Temperature Viscosity	globule size integrity
Emulsion decay /nanoparticles formation	Mixer	Mixing rate Mixing time	Particle size distribution Aggregate formation Dissolution rate
Concentration of Nanoparticles suspension	Centrifugation/Ultrafiltration	Speed and time	Yield Aggregate formation Process time Crystal formation
Drying of nanoparticles concentrate	Fluid bed processor	Drying time	Micromeritic properties

Table 2: shows various In-process tests applied while manufacturing SDN from nano-emulsions. Amorphous SDN of approximately 100nm-200nm were manufactured. SDN are considered intermediate bulk materials and their processing into finished product was designed to preserve their functional integrity. For example, incorporation of SDN into oral tablets did not affect the nanoparticles dissolution or loss of amorphous character of the API. The most challenging task was to inhibit the transformation of amorphous nanoparticles into drug crystalline form during drug nanoparticles concentration and drying. That challenging task was expected as concentrating nanoparticles causes: A. Formation of a saturated drug solution and B. Particle aggregation. Moreover, nanoparticles compression was possible without affecting drug dissolution rate. In that aspect, selection of adjuvants and drug to adjuvants ratio were of utmost importance to preserve high dissolution rate of compressed tablets.

Similarly, SDN made for parenteral administration kept their amorphous nature for more than 6 months at room temperature in the dry state with reversible aggregation.

Table 2: In-Process Testing of SDN

Process	Testing Parameters
Pre-emulsion formation	Microscopic evaluation Globule size distribution
Nanoemulsion formation	
Emulsion decay and Nanoparticles formation	Microscopic evaluation Particle size analysis crystal
Concentration of nanoparticles suspension	Microscopic evaluation Assay Drug release
Drying of nanoparticles concentrate	Moisture content Density Sieve analysis Assay

5. REFERENCES

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