International Journal of Pharmaceutics 530 (2017) 79–88

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Dual centrifugation – A new technique for nanomilling of poorly soluble drugs and formulation screening by an DoE-approach

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ARTICLE INFO

Article history:
Received 22 May 2017
Received in revised form 3 July 2017
Accepted 15 July 2017
Available online 18 July 2017

Keywords:
Nanomilling
Design of experiments
Dual centrifugation
Nanosuspension
Wet ball milling
Nanocrystalline suspension
Nanoparticles

ABSTRACT

The development of nanosuspensions of poorly soluble APIs takes a lot of time and high amount of active material is needed. In this publication the use of dual centrifugation (DC) for an effective and rapid API-nanomilling is described for the first time. DC differs from normal centrifugation by an additional rotation of the samples during centrifugation, resulting in a very fast and powerful movement of the samples inside the vials, which – in combination with milling beads – result in effective milling. DC-nanomilling was compared to conventional wet ball milling and results in same or even smaller particle sizes. Also drug concentrations up to 40% can be processed. The process is fast (typical 90 min) and the temperature can be controlled. DC-nanomilling appears to be very gentle, experiments showed no change of the crystal structure during milling. Since batch sizes are very small (100–1000 mg) and since 40 sample vials can be processed in parallel, DC is ideal for the screening of suitable polymer/surfactant combinations. Fenofibrate was used to investigate DC-nanomilling for formulation screening by applying a DoE-approach. The presented data also show that the results of DC-nanomilling experiments are highly comparable to the results obtained by common agitator mills.

1. Introduction

The increasing focus of drug screening towards more lipophilic targets has led to a significant higher number of potential new active pharmaceutical ingredients (APIs), which are characterised as poorly soluble in accordance to the established BCS system (Amidon et al., 1995). Almost 90% of APIs in current development studies can be classified as poorly soluble (Loftsson and Brewster, 2010), which reduces their suitability for oral application in many cases. However, oral delivery of drugs offers several advantages and is clearly the preferred route of drug application.

Orally administered APIs have to be dissolved in the gastrointestinal tract to be passively absorbed (Liversidge and Conzentino, 1995) or to be delivered by a transporter system. To increase the solubility of poorly soluble compounds one of the suitable technologies is to reduce their particle size, thus increasing the effective particle surface area, which leads to a higher rate of dissolution and an oversaturation effect (Noyes Whitney-Equation (Buckton and Beezer, 1992)). The resulting increase of bioavailability allows a faster dissolution (decrease of t-max), higher AUC (Area under Curve) and therefore lower doses, which helps to reduce adverse effects as well as food effects (Liversidge and Conzentino, 1995; Juenemann et al., 2011; Jinno et al., 2006; Junghanns, 2008).

One approach to produce small drug particles is to mill an aqueous suspension containing the poorly soluble drug, as well as polymer(s) and surfactant(s) for stabilization by avoiding agglomeration. Since the milling process is usually supported by milling beads, it is often called wet ball- or pearl milling (Junghanns, 2008). The advantages of wet ball milling technique are a water based approach (no organic solvents) and low batch to batch variations (Chin et al., 2014). There are several FDA approved products on the market which have been produced by this technique (e.g. Rapamune® (Sirolimus, Wyeth), TriCor® (Fenofibrate, Abbott) and Megace® ES (Megestrol acetate, Par Pharmaceuticals))(Kesisoglou et al., 2007).

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http://dx.doi.org/10.1016/j.ijpharm.2017.07.047
0378-5173/

After wet ball milling, the resulting nanosuspensions should be converted into a dry state to prevent Ostwald ripening and subsequent agglomeration or chemical changes by hydrolysis. Therefore, the suspensions have to be transferred into a solid form via lyophilisation, spray-/freeze drying, layering or granulation (Van Eerdenbrugh et al., 2008) to finally achieve solid dosage forms like tablets, capsules or stick packs in case of granulates or pellets as interim step.

The development of a suitable suspension of (nano-) particles (nanosuspensions) of a poorly soluble drug stabilized by an optimal combination and ratio of different co-polymers and surfactants is very time-consuming. For every drug compound a high number of different combinations/ratios of polymers and surfactants have to be tested by milling and at least the particle size distribution (PSD) and the particle stabilities with respect to agglomeration of each combination have to be measured.

However, what makes screening moreover time-consuming is that a lab-milling procedure has to be applied which is predictive and comparable to the milling process which is used later in the large scale drug manufacturing process. Thus, planetary wet ball milling is used very often (Malamatari et al., 2015; Laaksonen et al., 2011; Palo et al., 2015; Tuomela et al., 2015). Most planetary ball mills (e.g. Pulverisette 7, Fritsch) are equipped with milling zirconium oxide bowls. Using these devices, it is necessary to mill mixtures of water, drug, polymer(s) and surfactant(s) and milling beads over several hours if API concentrations of 10% or higher are used. Since this device has no cooling system, the process has to be interrupted by several breaks to allow the suspensions to cool down to room temperature. Thus, the screening is very time-consuming, only a small number of different formulations can be tested in a certain time.

In addition, even small planetary ball mills (if not modified with special inserts) need minimum batch sizes of 10 ml, which makes a broad screening of formulations containing expensive APIs almost impossible – or at least limits the number of formulations which can be tested. In literature further milling approaches are mentioned, e.g. (Möschwitzer, 2015) in which suspensions are stirred with an simple magnetic stirrer in 20 ml bottles or (Romero et al., 2015) in which group stacked stirring bars (3 bar) plus milling beads are used in 2 ml glass vials for up to 120 h. Also screening procedures using a 96-well plate were already described (Van Eerdenbrugh et al., 2009). Here, 0.5-mm yttrium-stabilized zirconium milling beads were added and the plate was shaken over 24 h. Although these systems allow the processing of a high number of samples, they have disadvantages like a maximum drug load of 5% and/or long milling times. Therefore the resulting particles sizes are not comparable with those resulted from the agitator mills used in large scale drug production.

Dual centrifugation (DC) is to a certain extent related to the wet ball milling. DC differs from normal centrifugation by an additional rotation of the samples during the centrifugal process. Thus, the direction of the strong centrifugal forces inside the vials changes continuously. The resulting powerful movement of the samples inside the vials finally results in their rapid homogenization or milling.

DC-based-processes has so far been used for preparation of lipid nanoparticles like liposomes (Massing et al., 2008) by homogenizing aqueous phospholipid-drug-mixtures in small containers using the same zirconium oxide beads as used for the production of drug-nanosuspension in common ball mills. Beside its extremely high power, the most important advantage of DC is that all homogenisation, mixing and milling processes can be done in closed disposable containers of different volumes, very small ones included. In addition, up to 40 vials (2 ml) can be processed in one run and due to the high input of energy the resulting milling time is very short. Furthermore, the most actual DC-device allows efficient cooling of the samples during the DC-process which allow continuous milling without the need of cooling breaks.

Thus, DC is as a promising tool for a very rapid and broad screening of suitable polymers and surfactants for nanomilling of poorly soluble drug compounds. In this article, the development of a nanomilling screening protocol using the new DC-apparatus ZentriMix 380R (Andreas Hettich, Tuttlingen, Germany) for simultaneous milling of 40 samples in small disposable containers (2 ml) is described. Furthermore, nanomilling using the new DC-system as well as a conventional ball mill is compared. For handling of the high number of data points resulting from the DC-nanomilling approach a design of experiment (DoE) approach was utilized to classify and quantify all the critical formulation variables with respect to the gained particle size distributions (PSD). Afterwards, design spaces were obtained in which particle sizes can be predicted.

2. Materials and methods

2.1. Materials

HPMC 3 mPas was purchased from Shin-Etsu Chemical (Tokyo, Japan). PVP 25 K, PVP VA 64, Poloxamer and SDS were purchased from BASF SE (Ludwigshafen, Germany). Tween 80 was ordered from Merck (Darmstadt, Germany) and Sodium-Docusate (DOSS) from Cytec (New Jersey, USA). As milling beads (for DC-milling as well as planetary wet ball milling) Yttrium oxide-stabilized zirconium oxide beads (0.1–0.2 mm, Sigmund Lindner GmbH, Warmensteinach, Germany) were used. Highly stable 2 ml DC-Twist-Top-vials were purchased from Andreas Hettich GmbH & Co KG, Tuttlingen, Germany.

2.2. Preparation of API-suspensions

The API-suspensions for the milling experiments were prepared as follows: weigh milling beads and API in the DC-Twist-Top-Vial or the planetary ball milling bowls. Polymer and surfactant are pre-dissolved in purified water and added. Afterwards the suspensions were further diluted with purified water. Sample preparation for the investigation of the DC-system and the planetary ball mill differed only in the batch size. All amounts of the formulation components are given as percentage by mass (%w/w).

2.3. Dual centrifugation (DC)

DC was performed using a ZentriMix 380 R (Andreas Hettich GmbH und Co KG, Tuttlingen, Germany). Milling parameters are given in the corresponding chapters. For every milling trial the cooling device was set to 0 °C (measured in the rotating chamber, which results in sample temperatures of approx. 18 °C after 90 min milling at 2000 rpm/1000 mg milling beads). Since this is the maximum DC-speed and milling time used in this investigation, it can be assumed that the process temperature was always below 18 °C in all experiments.

2.4. Planetary wet ball milling

Planetary ball milling was done with a Pulverisette 7 (Fritsch GmbH, Idar-Oberstein, Germany). For each milling trial two 45 ml bowls (Fritsch GmbH, Idar-Oberstein, Germany) each filled with 10 g of API-suspension were used. This is the minimum reasonable batch size for this equipment using the mentioned 45 ml bowls (note: smaller bowls are available as well). Milling conditions were 750 rpm over 14 cycles of 30 min interrupted by cooling breaks of 5 min (total milling time: 7 h). The defined parameters reflect a standard process often used in industry as well as academia.