Journal of Pharmaceutical Sciences xxx (2017) 1-13

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Alternative Manufacturing Concepts for Solid Oral Dosage Forms From Drug Nanosuspensions Using Fluid Dispensing and Forced Drying Technology

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ARTICLE INFO

Article history:
Received 27 June 2017
Revised 8 October 2017
Accepted 7 November 2017

Keywords:
solid dosage form
oral drug delivery
individualized drug therapy
formulation
suspension
nanotechnology
excipients
dissolution
processing
drying

ABSTRACT

Flexible manufacturing technologies for solid oral dosage forms with a continuous adjustability of the manufactured dose strength are of interest for applications in personalized medicine. This study explored the feasibility of using microvalve technology for the manufacturing of different solid oral dosage form concepts. Hard gelatin capsules filled with excipients, placebo tablets, and polymer films, placed in hard gelatin capsules after drying, were considered as substrates. For each concept, a basic understanding of relevant formulation parameters and their impact on dissolution behavior has been established. Suitable matrix formers, present either on the substrate or directly in the drug nanosuspension, proved to be essential to prevent nanoparticle agglomeration of the drug nanoparticles and to ensure a fast dissolution behavior. Furthermore, convection and radiation drying methods were investigated for the fast drying of drug nanosuspensions dispensed onto polymer films, which were then placed in hard gelatin capsules. Changes in morphology and in drug and matrix former distribution were observed for increasing drying intensity. However, even fast drying times below 1 min could be realized, while maintaining the nanoparticulate drug structure and a good dissolution behavior.

Introduction

The concept of personalizing medicine regarding dose strength, complex release kinetics, and combination of different drugs into one dosage form receives ever more interest.[1] It is well known that the optimum amount of drug and the optimum type of drug may vary from patient to patient.[1,2] By tailoring drug products for a specific patient or patient population, the efficiency of the medication can be increased while simultaneously reducing the side effects.[3-5]

Pharmaceutical industry strives to develop new manufacturing technologies to facilitate the flexible manufacturing of single drug products for personalized medicine.[1] Different printing and additive manufacturing technologies are considered suitable, such as 3D printing,[6-9] ink-jet printing,[10-12] flexographic printing,[13,14] polypills,[3] microvalve technology,[15,16] and positive displacement systems.[17,18] These technologies could further be used to facilitate the transition from conventional large-scale batch production to continuous manufacturing processes to increase the overall efficiency in the pharmaceutical sector due to increased agility, flexibility, robustness, and lower costs.[11,19,20]

Such technologies are frequently investigated in literature for the manufacturing of film- and tablet-based dosage forms. In contrast to the conventional approach where the drug is directly incorporated into a polymer film,[21-23] placebo polymer films are loaded with drug compound by ink-jet and flexographic printing to manufacture orodispersible films.[10,11,13,14] Tablet-based dosage forms are generally manufactured from scratch by using 3D printing equipment.[7-9] Current research seems to be limited mainly to these 2 dosage form concepts. Alternative concepts have been mentioned conceptually in literature but have not been investigated experimentally so far. For example, the personalization of drug units by dispensing liquid drug formulations directly into hard gelatin capsules,[17,18] the placing of loaded polymer films into hard gelatin capsules,[12,24] or the loading of placebo tablets.[3,25] An exception is the Liquid Dispensing

This article contains supplementary material available from the authors by request or via the Internet at https://doi.org/10.1016/j.xphs.2017.11.007.

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https://doi.org/10.1016/j.xphs.2017.11.007
0022-3549/

Technology from GlaxoSmithKline plc. that is already used to load placebo tablets with drug solutions.[3,25] Even though this technology is currently used at commercial scale,[3] there is a lack of investigations on further facets of this manufacturing concept.

Furthermore, each type of equipment is usually considered for the manufacturing of only one product type. The ability to manufacture various types of solid oral dosage forms with one type of equipment would further increase manufacturing flexibility.

In 2 previous studies, microvalve technology was investigated regarding dispensing performance of different liquids. First, Newtonian fluids were used to systematically characterize the microvalve itself, which was supported by a numerical modeling study.[26] In addition, the dispensing of a set of non-Newtonian drug nanosuspensions with different fluid properties has been conducted, from which a systematic understanding of the dispensing behavior could be established including an operational range for the stable depositioning of drug nanosuspension on a flat and solid substrate.[16] For Newtonian as well as non-Newtonian fluids, the microvalve showed a high accuracy regarding the amount of the dispensed liquid with an relative standard deviation below 1% for most process parameters, showing sufficient accuracy for the manufacturing of dosage forms.

In this study, the feasibility of using microvalve technology for the manufacturing of different types of solid oral dosage forms was explored. Microvalves can handle fluids with a large range of properties and precisely dispense small and large amounts of fluid from a few picoliters up to several hundred microliters per single dispensing event.[16,26] Thereby, the drug can be either distributed over a surface to load edible polymer films or the whole amount of fluid can be dispensed at one position to load tablets or even capsules. The aim of this study was to evaluate the basic feasibility of alternative manufacturing concepts using microvalve technology and to investigate the influence of formulation parameters of the substrate and drug nanosuspension on dissolution behavior. Suitable drug nanosuspensions and process parameters were selected from the previous study.[16]

In addition, drying by convection and radiation was investigated for the fast drying of film-based drug formulations. Typical drying methods for film-based drug formulations used in most studies are leaving the film to dry at ambient conditions,[23,27-30] drying in an oven at elevated temperatures,[31-33] or using convection drying.[14,22,34,35] All these methods are reasonable for research purposes, but the final film and drug properties depend on the utilized drying process. So far, only a limited number of studies reported the investigation of forced drying methods to accelerate the manufacturing process of film-based formulations,[36-38] which is essential for an efficient commercialization.[39] In this study, the feasibility of a forced drying process was investigated by using convection drying and radiation drying technology with different drying parameters. The influence of the drying process on the final dosage form properties regarding dissolution behavior, morphology, and drug and excipient distribution was evaluated.

Materials and Methods

Materials

Naproxen (NAP) was obtained from Bulk Medicines & Pharmaceuticals (Nordstadt, Germany) and micronized to a mean particle size of about 3 μm by jet-milling technology before use. Kollidon® VA64 (CoPVP) from BASF SE (Ludwigshafen, Germany), sodium dodecyl sulfate (SDS) BioUltra ≥99.0% from Sigma-Aldrich, Fluka (St. Louis, MO), and 30% simethicone emulsion USP, quality Q7-2587 from Dow Corning® (Midland, MI) were used as received for the manufacturing of drug nanosuspensions.

Lactose, quality CapsuLac® 60 from MEGGLE (Wasserburg, Germany), mannitol, quality PEARLITOL® 200SD from Roquette Pharma (Lestrem, France), lactose monohydrate spray dried from Kerry Group (Tralee, Ireland), magnesium stearate, quality Eur Phar Vegetable from Brenntag (Basel, Switzerland), polyethylene oxide (PEO), qualities N10 and N80 from DOW (Midland, MI), Tween® 80 from Sigma-Aldrich (St. Louis, MO), and sucrose, quality High Purity (Low Endoxin), USP/NF, EP, JP S-124-1-MC from Pfanstiehl (Waukegan, IL) were used for the preparation of placebo substrates. Hard gelatin ConiSnap® capsule size 0 in transparent and hard gelatin DBcaps® size AA in orange from Capsugel (Morristown, NJ) were used as received. AEROPERL® R 300 Pharma was provided as samples from Evonik Industries (Hanau, Germany). MDPE Coated Release Paper, type 2PE090/1V WH, was a gift from Cotek Papers Ltd. (Gloucestershire, UK).

Wet Media Milling

NAP drug nanosuspensions with drug loads of 10%, 20%, and 30% w/w NAP were manufactured by wet media milling using a wet stirred media mill, model DeltaVita (NETZSCH-Feinmahltechnik, Selb, Germany). As stabilizers, 3% w/w Kollidon® VA64 (CoPVP) and 0.075% w/w SDS were used for each formulation. In addition, 0.05% w/w simethicone was added as an antifoaming agent. For example, NAP20 CoPVP contains 20% w/w NAP and Kollidon® VA64 as stabilizing polymer. The rotor tip speed was set to 7 m/s peripheral velocity, and processing was performed in recirculation mode for 4 h. The milling chamber was filled to 80% v/v with 100-μm YTZ® grinding media (Nikkato Corporation, Tokyo, Japan). The resulting mean particle sizes were in the range of 117-143 nm (see Supplementary Table 1). A detailed characterization of these formulations was performed in a previous study.[16]

Microdispensing System

A noncontact microvalve from Microdrop Technologies GmbH (Norderstedt, Germany), model Nanojet, which was investigated in 2 previous studies,[16,26] was used. In brief, the piezo-actuated microvalve is supplied by a pressurized reservoir and ejects the liquid through a circular nozzle with an inner diameter of about 180 μm. The microvalve is opened and closed by a tappet rod, which is controlled by an electrical trigger pulse. The amount of dispensed liquid was varied by adjusting the reservoir pressure and valve opening time.

Tablet Manufacturing

Placebo tablets were manufactured from spray-dried lactose and 0.5% magnesium stearate using a single-punch tablet-press XP1 (Korsch, Berlin, Germany). Tablets with 7- and 10-mm diameter were prepared with a double flat-punch geometry. By adjusting the compression pressure to 23 MPa and 67 MPa, tablets with 2 different porosities were manufactured for each size.

Film Casting

Edible polymer films were manufactured by solvent casting method using the Labcoater LTE-S (Mathis, Zurich, Switzerland). The polymer solution was cast onto a liner type 2PE090/1V WH (Cotek Papers Ltd., Moreton-in-Marsh, UK) with 360 mm/min casting speed. For the investigated PEO-based formulation, the wet film thickness was 550 μm in order to reach a dry film thickness of 80 μm. The films were dried in the Labcoater LTE-S at 50°C for 40 min with the ventilation set to the minimum value.