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Fast dissolving fillers in dry foam formulation

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ABSTRACT

Dry foam technology was developed as alternative granulation technique to overcome insufficient oral bioavailability of poorly soluble and wettable active pharmaceutical ingredients (APIs). In recent studies the type of filler showed to have a distinct influence on dry foam morphology as well as dissolution characteristics. Isomalt for instance improved the initial dissolution rate of fenofibrate dry foam formulation tablets. In this study the hypothesis that fast dissolving low molecular weight fillers improve dissolution rate and alter dry foam morphology should be confirmed with two APIs with different aqueous solubility (indomethacin, orlistat), in three different filler combinations, namely maltodextrin 21D, isomalt and 1:1 mixture of mannitol and maltodextrin 21D. In addition the dissolution behaviour of dry foam tablets was compared to fluid bed granulation formulations with the same drug loading and to an orlistat marketed formulation (Alli® 60 mg capsules) in FaSSIF using USP 2 paddle apparatus and HPLC analysis after filtration.

Dry foams prepared with low molecular weight fillers revealed more compact and less porous structures compared to dry foams containing maltodextrin 21D. Interestingly, their rough surface still resulted in increased surface area compared to the other formulations. The initial dissolution behaviour of indomethacin and orlistat dry foam tablets was improved by using isomalt and the mannitol–maltodextrin mixture as filler. All indomethacin formulations reached complete dissolution of the applied dose, whereas the total amount of dissolved orlistat was increased compared to the fluid bed granule tablets and the marketed formulation Alli® by using low molecular weight fillers in dry foam formulations. The improved dissolution behaviour of Orlistat dry foam tablets using low molecular weight fillers was additionally confirmed in USP monography dissolution medium.

1. Introduction

Insufficient oral bioavailability due to poor solubility and wettability of active pharmaceutical ingredients (APIs) is a major concern in pharmaceutical formulation. As the API in a solid dosage form first must undergo dissolution before it is available for absorption from the gastrointestinal tract, solubility and dissolution rate can be the limiting terms for sufficient bioavailability. Both are considered in the developability classification system (DCS) introduced by Butler and Dressman [1] derivating from the biopharmaceutic classification system (BCS) [2]. It divides the class of poorly soluble drugs with high permeability in a dissolution rate limited (IIa) and a solubility limited group (IIb) taking into account that permeability and solubility can be compensatory. As a result compounds of class IIa can usually still be formulated as a standard oral dosage form from crystalline drug without using solubilization 'methods, whereas for class IIb compounds a solubilized form is inevitable for achieving complete absorption.

Perrie and Rades divide the different approaches to overcome low oral bioavailability due to poor solubility in three groups, namely molecular modification, physical modification and carrier/delivery systems [3]. A broad overview on the state of the art of formulating poorly-soluble compounds is given by Williams et al. in their review on strategies how to address low drug solubility in discovery and development [4]. Common strategies, namely particle size reduction, polymorph change, amorphous solid dispersions, co-crystals, lipid-based systems, salts, cyclodextrins, cosolvents and surfactants are elaborated for toxicological, parenteral and oral formulations. The use of surfactants for improvement of wettability in simple solid dosage forms and to stabilize traditional suspension-based formulations is mentioned briefly. Leuner et al. give an insight on improving drug solubility by solid dispersion in their review [5].

Micronization is the most common method to increase available surface area of the drug and therefore its initial dissolution rate. Unfortunately, micronized drugs have the tendency to agglomerate

Abbreviations: 50%MTL, 1:1 mixture mannitol: maltodextrin 21D; DF, dry foam; DOSS, dodecylsulfate sodium; ER, expansion ratio; FBG, fluid bed granule; IDM, indomethacin; ISM, isomalt; M21D, maltodextrin 21D; SEM, scanning electron microscopy; SSA, specific surface area; THL, Orlistat (Tetrahydrolipstatin); VBT, vacuum belt dryer; VitE, Vitamin E—TPGS; X-ray μ-CT, X-ray microcomputed tomography.

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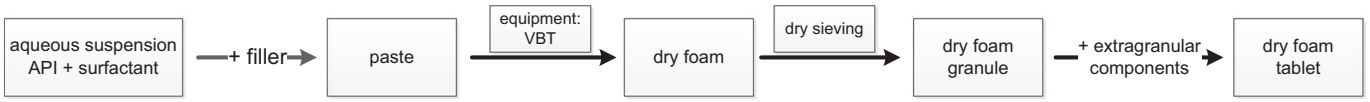

Fig. 1. Dry foam preparation process.

due to their hydrophobicity and electrostatic attraction diminishing the expected effect [6,7]. Formulating these hydrophobic, poorly wettable and agglomerating drugs can be challenging. Different granulation methods are studied in pharmaceutical formulation sciences. Besides the most common wet granulation methods, like high shear and fluid bed spray granulation, dry granulation methods like roller compaction and also melt granulation are of growing interest. The choice of granulation method is adapted to the physico-chemical properties of the API like hygroscopicity, water induced phase transitions, poor powder flow, cohesive properties, high compressibility and crystal morphology [8]. Wetting agents are added to improve the processability and dissolution characteristics of the active compound. The effectiveness of these additives is a result of their distribution and contact area with the API depending on the employed granulation method. In dry granulation contact surfaces of API and solubilization agent only evolve due to mixing and compaction forces. In high-shear granulation commonly the API is premixed with the dry surfactant and other powder components before adding the granulation liquid. A surfactant, which is dissolved in the granulation liquid, can facilitate wetting of the API and the powder mixture. During spray granulation the surfactant is usually added to the granulation liquid and finely sprayed on the API powder mixture providing a better distribution and wetting. Using a foamed surfactant solution these advantages become even more prominent by increasing the available surface area of the surfactant mixture [9]. In dry foam formulation technology as a first step the API is suspended in a surfactant solution and therefore wetted thoroughly. Afterwards the suspended API is embedded in a filler matrix, forming a viscous paste. Sponge-like structures develop due to the vacuum drying process, which can be downstream processed to granules and tablets [10]. Dry foam formulation technology is expected to improve bioavailability by wetting the API and therefore enhancing its initial dissolution rate. Additionally, agglomeration of API particles is hindered steric by the foam matrix [11].

The filler represents the major component of dry foam formulations embedding the API and therefore is thought to affect the drug release crucially. Busson et al. described a variety of embedding materials, such as modified or substituted starch or cellulose derivatives, acacia

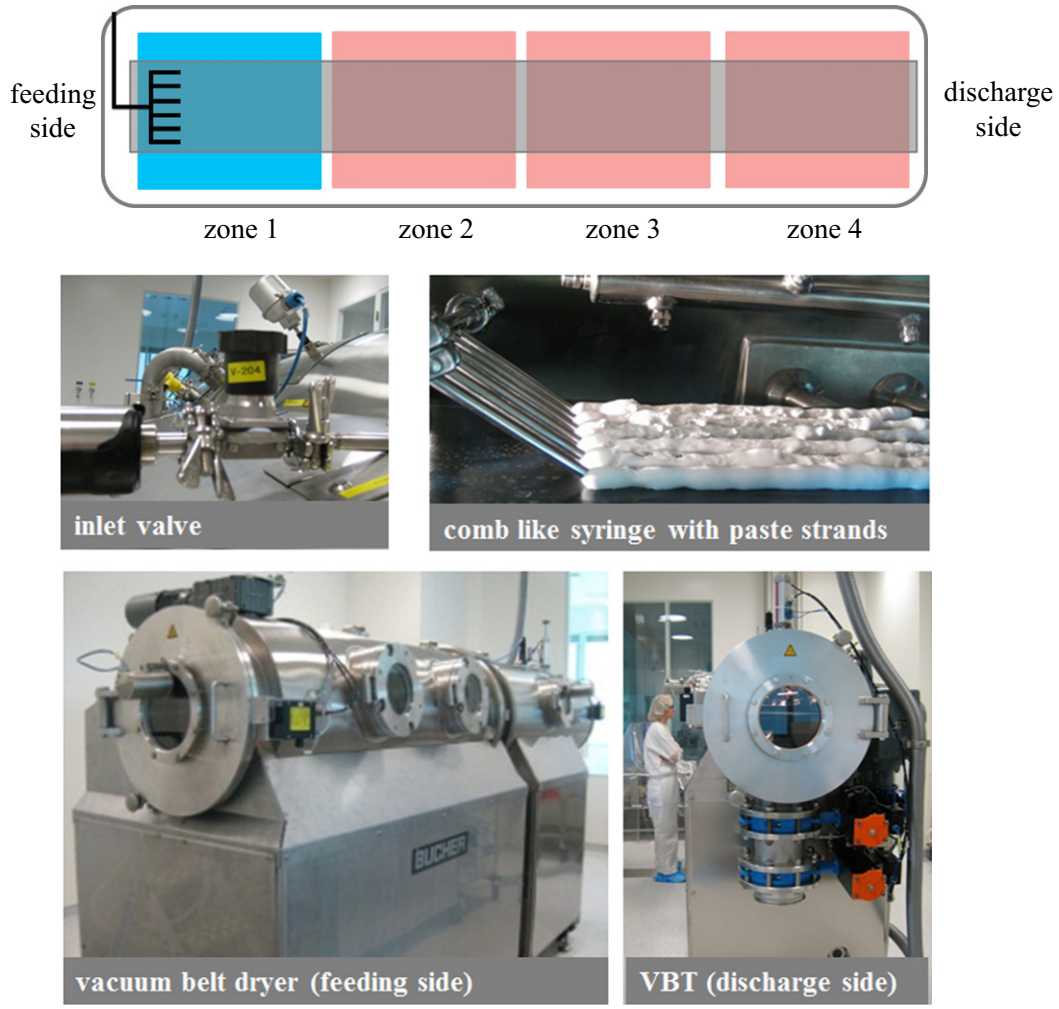

Fig. 2. Scheme (top) and photographs (middle and bottom) of VBT illustrating the dry foam preparation process. VBT scheme is depicted in bird's eye perspective, and paste application is symbolized by the comb like syringe (black) onto the moving belt (grey) passing the 4 temperature zones (blue and red) towards discharge side.