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Simplified formulations with high drug loads for continuous twin-screw granulation

R. Meier [a], M. Thommes [a,b], N. Rasenack [c], M. Krumme [c], K.-P. Moll [c], P. Kleinebudde [a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Duesseldorf, Germany
[b] Faculty of Bio- and Chemical Engineering, Technical University Dortmund, Emil-Figge-Str. 68, 44227 Dortmund, Germany
[c] Novartis AG, 4002 Basel, Switzerland

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ABSTRACT

As different batches of the same excipients will be intermixed during continuous processes, the traceability of batches is complicated. Simplified formulations may help to reduce problems related to batch intermixing and traceability.

Twin-screw granulation with subsequent tableting was used to produce granules and tablets, containing drug, disintegrant and binder (binary and ternary mixtures), only. Drug loads up to 90% were achieved and five different disintegrants were screened for keeping their disintegration suitability after wetting.

Granule size distributions were consistently mono-modal and narrow. Granule strength reached higher values, using ternary mixtures. Tablets containing croscarmellose-Na as disintegrant displayed tensile strengths up to 3.1 MPa and disintegration times from 400 to 466 s, resulting in the most robust disintegrant. Dissolution was overall complete and above 96% within 30 min. Na-starch glycolate offers tensile strengths up to 2.8 MPa at disintegration times from 25 s to 1031 s, providing the broadest application window, as it corresponds in some parts to different definitions of orodispersible tablets. Tablets containing micronized crospovidone are not suitable for immediate release, but showed possibilities to produce highly drug loaded, prolonged release tablets.

Tablets and granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to requirements of the authorities.

1. Introduction

Granulation is a commonly used particle enlargement technique to improve material properties such as flowability, tabletability or powder segregation (Kristensen and Schaefer, 1987). As granulation can be conducted by dry or wet processes, several different machines and techniques are available like roll compaction, fluidized bed granulation, high shear wet granulation or twin-screw granulation. The twin-screw granulation stands out because of the short residence times, its design flexibility, adjustable throughput ranges and intimate mixing and kneading processes on a relatively short process-distance (El Hagrasy et al., 2013; Vercruysse et al., 2014; Vervaet and Remon, 2005). Twin-screw granulators can be implemented as central elements into continuous production lines as demonstrated by the ConsiGma system (Fonteyne et al., 2013).

At some point of continuous processes new batches of utilized excipients have to be introduced into the process. Besides regulatory considerations, the change of batches during the process will not cause any problems for drugs and excipients that feature a high batch to batch conformity. Considering biopolymers or semi-synthetic polymers, e.g. microcrystalline cellulose, the batch to batch conformity can be problematic. Changing properties such as the water binding behavior, caused by differing degrees of crystallinity (Fonteyne et al., 2015), can influence and alter a running wet granulation process completely. Different batches of the same polymer may vary in molecular weight distribution and lead to variations in porosity, specific surface area or water content. Consequently, problems related to batch to batch inconformities can cause major issues in controlling a continuous manufacturing process.

* Corresponding author. Tel.: +49 2118114220; fax: +49 2118114251.
E-mail addresses: Robin.Meier@hhu.de (R. Meier), Markus.Thommes@bci.tu-dortmund.de (M. Thommes), Norbert.Rasenack@novartis.com (N. Rasenack), Markus.Krumme@novartis.com (M. Krumme), Klaus-Peter.Moll@novartis.com (K. -P. Moll), Kleinebudde@hhu.de (P. Kleinebudde).

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The residence times of the material inside the twin-screw granulator depend on throughput, screw configuration, barrel length, type of extruder etc. and are in the range of seconds (Dhenge et al., 2010; El Hagrasy et al., 2013; Kumar et al., 2014; Lee et al., 2012; Vercruysse et al., 2013; Li et al., 2014). Thus, the probability of an intermixing of powder from different batches inside the granulator is minimal.

However, inside powder feeders an intermixing of different batches definitely will take place. To ensure a homogenous and constant feed-rate and to keep a continuous process running, powder feeders need to maintain a constant filling degree and are frequently refilled (Hopkins, 2006). Mixing devices, such as blades or stirrers are implemented in the feeders to keep the primary powder in motion as well as to prevent demixing, bridge formation or consolidation of the powder (Cartwright et al., 2013; Hopkins, 2006), as the powder is usually very cohesive. The comparably slow mixing process causes unknown and prolonged residence times but also unknown residence time distributions of powder inside the feeder. Thus, different batches of the same excipients are blended within the powder feeder.

In batch processes a defined amount of excipients is employed, which is usually part of one batch. By implementation of continuous systems the aspect of traceability arises (Myerson et al., 2015). The number and the diversity of the applied excipients lead to drawbacks of batch intermixing and thus quality issues of unknown magnitudes.

To reduce the problems related to traceability of different batches, residence time issues and batch to batch inconformities, the formulations need to be simplified. Simplified formulations contain as few different excipients as possible. By simultaneously keeping the drug load of the produced granules as high as possible, the influence of batch-related problems is further decreased. Several obstacles related to high drug loads have to be overcome namely the poor compression properties (Gohel and Jogani, 2005) and the hydrophobicity of several drugs (Hapgood and Khanmohammadi, 2009). These could cause mechanically weak and poorly disintegrating tablets. Hence, the simplified formulations in wet granulation should contain at least binder and disintegrant as excipients.

An additional benefit of simplified formulations can be seen, when considering a completely continuous twin-screw granulation and tableting process. In such a process, different excipients may separately be fed by different powder feeders and blended in a continuous blender or the twin-screw granulator. Simplified formulations could contribute to an optimized production of those blends, because of the requirement of less powder feeders and the generation of less complex powder blends.

When tablets are produced after twin-screw granulation, the addition of the disintegrant usually takes place after the wet granulation, drying and milling steps, to prevent a possible loss of disintegration power after initial wetting (Gordon et al., 1993; Zhao and Augsburger, 2006). To investigate this assumption, in the present study several different disintegrants were incorporated intragranularly and examined for maintaining their disintegration ability after wet granulation and tableting. If successful, a mixing step prior tableting could be skipped and a continuous process could be simplified further.

The aim of this study was to screen for highly drug loaded and simplified formulations, containing ibuprofen as model drug, for a continuous twin-screw granulation process. Formulations containing drug, disintegrant and binder or drug and disintegrant only should be used for this purpose. The concept of reducing the number of excipients for manufacturing should be proven. Granules should offer sufficient mechanical strength and adequate compression properties. Resulting tablets need to be mechanically strong and need to disintegrate within the pharmacopeial limits. Additionally, the release of the incorporated drug has to be ensured.

2. Materials and methods

2.1. Materials

2.1.1. Twin-screw granulation

Ibuprofen 50 ff (BASF, Ludwigshafen, Germany) was used as model drug in 90% (w/w) concentration within all powder blends. The following disintegrants were included in 10% (w/w) concentrations in the respective powder mixtures: polacrilin potassium (Amberlite IRP88, Rohm and Haas France SAS, Chauny, France), crospovidone and micronized crospovidone (Kollidon CL and Kollidon CL-M, BASF, Ludwigshafen, Germany), croscarmellose sodium (Ac-Di-Sol FMC BioPolymer, Wallingstown, Ireland) and sodium starch glycolate (Explotab, JRS Pharma, Rosenberg, Germany). Either a 10% (w/w) solution of povidone (Kollidon 17, BASF, Germany) in demineralized water or pure water were used as granulation liquid. For each powder blend both liquids and different liquid to solid ratios (L/S) were applied. Using the PVP solution as granulation liquid, the PVP concentrations within the granules changed simultaneously by varying the L/S-ratio.

2.1.2. Tableting

During compression of the granules magnesium stearate (Bärlocher, Unterschleissheim, Germany) was applied as lubricant.

2.1.3. Dissolution experiments

As buffer substance for the dissolution experiments potassium dihydrogen phosphate (AppliChem GmbH, Darmstadt, Germany) was used. To adjust the pH of the buffer a 1 M solution of sodium hydroxide (AppliChem GmbH, Darmstadt, Germany) was applied. Distilled water was used as solvent.

The mobile phase for the HPLC measurements consisted of acetonitrile (VWR, Fontenay-sous-Bois, France), 85% (m/m) orthophosphoric acid (Carl Roth GmbH + Co., KG, Karlsruhe, Germany) and distilled water. All reagents were of analytical grade.

2.2. Methods

2.2.1. Blending

Powder batches of 4 kg total mass were blended for 20 min at 35 rpm in a lab-scale blender (LM 40, L.B. Bohle, Ennigerloh, Germany).

2.2.2. Powder feeding

Premixed powders were manually transferred to a loss-in-weight powder feeder (K-CL-24-KT 20, K-Tron, Niederlenz, Switzerland), which fed the powder to the extruder barrel by a set feed-rate of 20 g/min during all experiments.

2.2.3. Liquid feeding

Granulation liquids were added by a micro annular gear pump (MZP 7205, HNP-Mikrosysteme, Schwerin, Germany) through an own built nozzle with an inner diameter of 0.12 mm into the extruder barrel, directly on the flight of one of the screws in front of the first kneading zone. The micro gear pump works by a positive displacement principle and generates differential pressures of up to several bars through a 6/7-tooth-ratio of an inner and an outer rotor. This setup, combined with high rotational speeds of the rotors of up to 6000 rpm, leads to a pulsation-free transport of the liquid. Through the small nozzle diameter and the subsequent high flow velocities, a thin and constant stream of liquid leaves the nozzle and prevents the liquid addition port to get blocked by powder (Muehlenfeld and Thommes, 2011, 2014). The pump was