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How Deformation Behavior Controls Product Performance After Twin Screw Granulation With High Drug Loads and Crospovidone as Disintegrant

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ABSTRACT

This study addresses the quantitative influence of 12 different materials (active pharmaceutical ingredients and excipients as surrogate active pharmaceutical ingredients) on the critical quality attributes of twin screw granulated products and subsequently produced tablets. Prestudies demonstrated the significant influence of the chosen model materials (in combination with crospovidone) on the disintegration behavior of the resulting tablets, despite comparable tablet porosities. This study elucidates possible reasons for the varying disintegration behavior by investigating raw material, granule, and tablet properties. An answer could be found in the mechanical properties of the raw materials and the produced granules. Through compressibility studies, the materials could be classified into materials with high compressibility, which deform rather plastically under compression stress, and low compressibility, which display breakages under compression stress. In general, and apart from (pseudo)-polymorphic transformations, brittle materials featured excellent disintegration performance, even at low resulting tablet porosities <8%, whereas plastically deformable materials mostly did not reveal any disintegration. These findings must be considered in the development of simplified formulations with high drug loads, in which the active pharmaceutical ingredient predominantly defines the deformation behavior of the granule.

Introduction

Twin screw granulation (TSG) is a relatively new technique, which offers the possibility of conducting wet- or melt granulation continuously. In recent years, numerous research groups and companies have committed their efforts to this topic.[1-7] Most of the studies examined process analytical tools for TSG or the influence of process parameters on critical quality attributes (CQAs) of granules or subsequently produced tablets.[8-14] In these studies, the pharmaceutical formulations were often kept constant, resulting in little data on formulation dependencies of the process. Some studies dealt with formulation changes at constant process parameters and used different batches, polymorphs, or qualities of the same substance,[15-18] or varied the hydrophobicity of the formulation by the mass ratio of the applied excipients.[19] All these studies were of major importance for the understanding and improvement of the TSG process as well as the elucidation of underlying granulation mechanisms. Hitherto, however, there was little information about distinctively different raw material behavior (e.g., compactibility, compressibility) and the influence on resulting product characteristics at constant process conditions. The importance of this must not be neglected, because previous studies observed an oppositional influence of formulation parts on the resulting CQAs.[4,20] Simplified formulations with high drug loads for use in TSG processes were developed in order to decrease the number of used excipients, and to allow a reduction in the number of applied powder feeders within a continuously running environment. The simplified formulations contained approximately 87% of active pharmaceutical ingredient (API), 10% of disintegrants, 3% of binder, and were compressed to tablets after wet granulation and drying. The aim was to produce tablets with disintegration times, according to the pharmacopeial definition of uncoated tablets (<15 min) with sufficient strength. Resulting tablets containing ibuprofen (Ibu) and hydrochlorothiazide (Hyd) acted differently in terms of disintegration performance. The Ibu-containing tablets did not demonstrate any disintegration at all, whereas the Hyd-containing

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Table 1
Characteristics of Applied Model Materials and L/S Ratio, Used During Wet Granulation

Material	Abbreviation	x_{25} (μm)	x_{50} (μm)	x_{75} (μm)	T_{melt} (°C)	Solubility (mg/L)	L/S Ratio
Lidocaine-HCl	Lid	20	48	107	76	656,000	0.075
Dimenhydrinate	Dim	19	41	81	104	6755	0.075
Ibuprofen	Ibu	18	36	61	76	37.4	0.3
Ketoprofen	Ket	3	6	19	93	159	0.3
Phenylbutazone	Phe	6	14	37	106	40.8	0.3
Paracetamol	Par	10	29	92	169	17,339	0.3
Caffeine	Caf	4	12	33	235	21,577	0.3
Hydrochlorothiazide	Hyd	25	42	67	267	690	0.3
Furosemide	Fur	2	3	6	221	25.6	0.3
Sorbitol	Sor	85	194	296	95	2,350,000	0.04
Sodium chloride	NaCl	310	409	534	801	358,000	0.14
Dicalcium phosphate	Dcp	4	9	16	356	100	0.3
Caffeine monohydrate	Caf-hyd	69	175	428	–	–	–

tablets featured fast disintegration times, despite equal experimental conditions and comparable tablet porosities. There was no explanation for the contradictory performance of both formulations. Consequently, the aim of this study is to elucidate possible reasons for this dissimilar disintegration time. Therefore, 9 APIs and 3 excipients are presented as model materials within this study to conduct both TSG and the tableting of the respective formulations. Various properties of the pure model materials, the finished granules, and the tablets are investigated in order to ascertain a rationale for the material-dependent behavior of these crospovidone-containing formulations.

Materials and Methods

Materials

The formulations for the granulation experiments consisted of 3% (wt/wt) povidone 17 (Kollidon 17; BASF, Ludwigshafen, Germany) as binder, 10% crospovidone (Kollidon CL; BASF) as disintegrant, 1% colloidal silica (Aerosil 200; Evonik, Darmstadt, Germany) as glidant, and 86% of the following model materials, which were APIs as well as excipients: Ibu (BASF), Hyd (Unichem Laboratories, Mumbai, India), furosemide (Fur; Sri Krishna Drugs Limited, Bollaram, India), ketoprofen (Ket; Andenex Chemie, Hamburg, Germany), phenylbutazone (Phe; Kraemer und Martin Pharma Handels GmbH, Krefeld, Germany), lidocaine-hydrochloric acid (Lid; Moehs Catalana S.L., Barcelona, Spain), dimenhydrinate (Dim; Pharma Roth, Wiesbaden, Germany), caffeine anhydrate (Caf; BASF), paracetamol (Par; Atabay, Istanbul, Turkey), sodium chloride (NaCl; Fisher Scientific GmbH, Schwerte, Germany), sorbitol (Sor; Caelo, Hilden, Germany), and dicalcium phosphate (Dcp, Dicafos A12; Chemische Fabrik Budenheim KG, Budenheim, Germany). In a single experiment, sodium dodecyl sulfate (SDS; SERVA Electrophoresis GmbH, Heidelberg, Germany) was used in 1% concentration within the powder mixtures instead of colloidal silica to assess the effect of a wetting agent. Demineralized water was used as granulation liquid and magnesium stearate (Parteck LUB MST; Merck Millipore, Darmstadt, Germany) was used in 0.5% concentration as lubricant during tableting. Additionally, caffeine monohydrate (MP Biomedicals Germany GmbH, Eschwege, Germany) was used during compressibility analysis. Specifications regarding particle size distributions of the raw materials are provided in Table 1.

Methods

Preparation of Powder Mixtures

Prior to mixing, all materials with the exception of NaCl were passed through a sieve of 500 μm mesh size to breakdown agglomerates. Powder batches with a total mass of 5 kg each were blended for 20 min at 35 rpm in a laboratory scale blender (LM 40; L.B. Bohle, Ennigerloh, Germany).

Particle Size Distributions of Raw Materials

Starting materials were analyzed for particle size distribution via laser diffraction, using a dry dispersion module (Mastersizer 3000; Malvern Instruments Ltd., Malvern, UK). A dispersion pressure of 3 bar was set for all powders. Determinations were done in triplicate.

Solubility Determination of Model Materials

An excessive amount of pure API was added to a flask with 50 mL of distilled water and shaken for 48 h at 25°C. The supernatant was passed through a 0.45 μm filter, diluted with an appropriate volume of distilled water and analyzed in triplicate for API content via UV-spectroscopy (Lambda 25; PerkinElmer, Ueberlingen, Germany). For the solubility of Dcp, Sor, and NaCl, literature values were consulted.[21-23]

Melting Points of Model Materials

The melting points of the applied model materials were detected by differential scanning calorimetry (DSC 821e; Mettler-Toledo, Giessen, Germany) at an underlying heating rate of 10°C/min. The peak onset was evaluated as the melting point. The melting point of NaCl was taken from the literature.[24] The melting point of caffeine monohydrate is not determinable as it showed dehydration below the melting point.

Compressibility Analysis of Model Materials

All model materials were investigated regarding compressibility by analytical powder compression with a Styl'One (Medelpharm, Beynost, France). Compressibility in this context is defined as the ability of a material to decrease its volume under pressure. The Styl'One was equipped with 4 incremental position sensors (8738-DK812R5; Sony Manufacturing Systems Corporation, Kuki-shi, Saitama, Japan) in order to measure the height of the powder bed and the tablet. Approximately 100 mg of powder in the case of APIs and Sor, and 250 mg of powder in the case of the Dcp and NaCl were filled manually into the die. Flat faced tablets 8 mm in size were produced by applying a maximum compaction pressure of 150 MPa. The compression speed was set to the machine's internal value of 25%, which corresponds to a value of 27 mm/s. The sampling frequency was 5 kHz. Prior to compression of each tablet, the punches were lubricated with magnesium stearate using an eyeshadow applicator. After compression, the exact masses of the tablets were measured on an analytical balance. Every material was investigated with $n = 8$. Obtained data were evaluated by the Heckel