Powder Technology 326 (2018) 292–301

Contents lists available at ScienceDirect

Powder Technology

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

Functionality and performance evaluation of directly compressible co-processed excipients based on dynamic compaction analysis and percolation theory

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ARTICLE INFO

Article history:
Received 1 August 2017
Received in revised form 27 November 2017
Accepted 2 December 2017
Available online 06 December 2017

Keywords:
Critical quality attributes
Functional property
Percolation threshold
Compressibility
Compactibility
Tabletability

ABSTRACT

In the present work functional properties of new, co-processed excipients, Pharmaburst® 500, Parteck® ODT, Ludiflash® and Disintequik™ ODT, intended for direct compression of orally disintegrating tablets (ODTs), were investigated based on dynamic compaction analysis and percolation theory. Tablet disintegration time and mechanical properties have been recognized as critical quality attributes (CQAs) which should be optimized through pharmaceutical development. According to the obtained results, in order to achieve adequate mechanical resistance, excipients exhibiting high compactibility and tabletability are required, while, on the contrary, high porosity excipients with higher extent of elastic deformations, average tabletability and compactibility are necessary to obtain fast tablet disintegration. The results obtained in this study indicate that the most important excipient properties affecting tablet CQAs are porosity, mechanism of consolidation, compactibility and tabletability. Pharmaburst® 500, excipient with the highest elastic recovery, the lowest relative density, average compactibility and tabletability, and remarkably high dilution capacity (69.6% w/w of caffeine or 49.1% w/w of ibuprofen) exhibited favourable performance for ODT direct compression. Dynamic compaction analysis and percolation theory proved to be useful tools which can contribute to identification of the most important excipient functional properties influencing critical quality attributes of the prepared ODTs.

1. Introduction

Orally disintegrating tablets (ODTs) have emerged as one of the novel solid oral dosage forms with a potential to deliver a wide range of drugs and facilitate drug administration in patients with swallowing difficulties [1]. The greatest challenge in ODT formulation development is achievement of fast disintegration, while maintaining the acceptable tablet mechanical strength. Thus, tablet disintegration time and mechanical properties can be recognized as critical quality attributes (CQAs) which should be optimized through pharmaceutical development. In line with the quality by design (QbD) approach, in order to facilitate development of better-controlled, more robust formulations based on scientific understanding of materials and processes employed, it is important to investigate and identify critical material attributes which can affect product CQAs [2–4].

Direct compression is considered as the most cost-effective and efficient way for ODT manufacturing, but excipients which are used must possess good flowability, compressibility, compactibility, tabletability; high dilution capacity and controlled particle size [5–7]. Increasing demands toward production of ODTs meeting the specified requirements influenced development of highly functional co-processed excipients.

Co-processed excipients have been developed as multifunctional, directly compressible combinations of two or more conventional excipients interacting at sub-particle level [8]. Change in fundamental excipients characteristics, such as particle size, shape, morphology, porosity, density and surface area can influence their flowability, compressibility, compactibility, tabletability, and dilution capacity, and thus affect ODT disintegration and mechanical properties [8]. Co-processed excipients used for ODT direct compression usually consist of filler, binder and disintegrant, and, therefore, simple mixing with drug and lubricant, prior compaction, is sufficient [9].

Although there are compendial recommendations for excipients functionality assessment, there is no unique approach how to accomplish this [10,11]. Taking into consideration complex influence of manufacturing process employed, drug load and its physicochemical characteristics, it has been emphasized that excipient functionality can only be properly estimated in the context of finished drug product [4,12]. This is also more obvious in the case of new, multifunctional excipients.

Comprehensive testing of pharmaceutical powders based on dynamic compaction analysis may contribute to evaluation of their performance [13,14]. Compact attributes that have been identified as being of

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https://doi.org/10.1016/j.powtec.2017.12.021
0032-5910/

particular importance are: solid fraction (i.e.relative density), compaction pressure and tensile strength. The relationship between these attributes has been established and corresponds to: (i) compressibility (solid fraction vs compaction pressure); (ii) compactibility (tensile strength vs solid fraction), and (iii) tabletability (tensile strength vs compaction pressure) of the pharmaceutical powders [15,16].

Percolation theory is introduced in the pharmaceutical field as multidisciplinary theory providing better understanding of internal structure and component distribution in disordered and chaotic, geometrically complex, multiparticulate solid systems (such as tablets) [17–19]. It is considered as a useful tool for determination of the formulation component volumetric ratio (percolation threshold) at which sudden and significant change in structure and, consequently, physicochemical properties of the system, such as drug release rate, percentage of drug released, disintegration time or mechanical strength, occur [20–22]. Considering relative simplicity of ODT formulations containing co-processed excipients, it may be assumed that changes in drug load would result in phase transition, and that excipient dilution capacity should be determined as its most important functional characteristic.

The objective of the present work was to investigate functionality and performance of different co-processed excipients used for ODT direct compression based on dynamic compaction analysis and percolation theory. Two widely used model drugs (caffeine anhydrous and ibuprofen) have been selected and their influence on ODT critical quality attributes and the performance of co-processed excipients has been evaluated.

2. Materials and methods

2.1. Materials

Pharmaburst® 500 - P.500 (SPI Pharma, New Castle, USA), Ludiflash®-LF (BASF, Ludwigshafen, Germany), Disintequik™ ODT - D.ODT (Kerry, Beloit, WI USA) and Parteck® ODT - P.ODT (Merck, Darmstadt, Germany) were investigated as multifunctional co-processed excipients. The composition of the investigated commercially available co-processed excipients is listed in Table 1. Caffeine anhydrous - CAF (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) and ibuprofen - IBU (BASF AG, Ludwigshafen, Germany) were used as model drugs. Sodium stearyl fumarate (Pruv®, JRS Pharma, Rosenberg, Germany) was used as lubricant. Sodium chloride (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), potassium phosphate monobasic (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), disodium hydrogen phosphate (Sigma-Aldrich Chemie GmbH, Steinheim, Germany), and hydrochloric acid (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) were used for preparation of simulated salivary fluid (SSF) pH 6.75 (prepared according to Peh and Wong [23]).

2.2. Methods

2.2.1. Characterization of co-processed excipients and model drugs

2.2.1.1. Model drug solubility. Solubility of the investigated model drugs was estimated in simulated salivary fluid (SSF) and purified water. Excess amounts of CAF or IBU were added to proper solvent in glass tubes with stoppers. The tubes were shaken constantly in a temperature-controlled water bath at 37 ± 0.5 °C (Grant LSB 18, Grant Instruments, Cambridge, UK). After 48 h, samples were withdrawn, centrifuged, properly filtered, diluted and analyzed spectrophotometrically (Cary 50, Varian, Santa Clara, CA) at 273 nm for CAF and 220 nm for IBU in the case of water, or at 245 nm for CAF and 220 nm for IBU in the case of SSF. Each sample was analyzed in triplicate and results are shown as the mean with standard deviation.

Table 2
Characteristics of the investigated co-processed excipients and model drugs.

	True density[a] (g/cm^3)	Carr index[a] (%)	Hausner ratio[a]	D (v, 0.5) [a] (μm)	SPAN[a]
P.500	1.462 ± 0.004	16 ± 2	1.19 ± 0.03	98.4 ± 0.7	0.642
P.ODT	1.528 ± 0.003	18 ± 2	1.22 ± 0.03	103.5 ± 11.4	1.063
LF	1.483 ± 0.004	21 ± 1	1.26 ± 0.02	70.4 ± 4.3	1.252
D.ODT	1.535 ± 0.002	23 ± 1	1.31 ± 0.03	67.1 ± 5.5	0.969
CAF	1.433 ± 0.005	32 ± 1	1.47 ± 0.02	n/a	n/a
IBU	1.106 ± 0.000	26 ± 0	1.35 ± 0.00	n/a	n/a

[a] Mean ± standard deviation.

2.2.1.2. Powder density. True densities of co-processed excipients and model drugs were investigated by helium picnometer (Accupyc 1330, Micromeritics, Norcross, Ga., USA) at 25 ± 0.5 °C. The measurements were performed in triplicate.

Bulk densities (ρ_{bulk}), and tapped densities (ρ_{tapped}) of the investigated co-processed excipients and model drugs were measured in triplicate following European Pharmacopoeia recommendations [General Chapter <2.9.15>, 10] using 100 ml graduated measuring cylinder and volumeter (StaV 2003, J. Engelsmann AG, Ludwigshafen, Germany). Hausner ratio and Carr index were calculated using the Eq. (1), and Eq. (2), respectively:

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}} \quad (1)$$

$$\text{Carr index}\ (\%) = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right) \quad (2)$$

2.2.1.3. Powder morphology and particle size distribution. Scanning electron microscopy - SEM (J.S.M. 840A, JEOL, Tokyo, Japan) was used to visualize the shape and surface of the investigated excipients particles. Samples were placed in the microscope holder and images were taken at a suitable magnification. Particle size distribution of co-processed excipients was determined using the dynamic image analyzer (Camsizer XT, Retsch Technology GmbH, Haan, Germany) equipped with the x-jet module, under the dispersion pressure of 100 kPa. X_{cmin} diameter, the shortest chord of a particle projection, was used for particle diameter evaluation. The volume median diameter D (v, 0.5) and SPAN value were presented to express the particle size and the range of particle size distribution. The SPAN value was determined as a quotient of difference between the particle sizes corresponding to the D (v, 0.75) and D (v, 0.25) and volume median diameter. Each sample was tested in triplicate.

Table 1
Composition of the investigated co-processed excipients.

	Pharmaburst® 500	Parteck® ODT	Ludiflash®	Disintequik™ ODT
Diluent	Mannitol Sorbitol	Mannitol	Mannitol	Mannitol Lactose monohydrate Glucose monohydrate
Binders			Polyvinyl acetate dispersion	
Disintegrants	Crospovidone	Croscarmellose sodium	Crospovidone	Crospovidone
Glidants	Silicon dioxide, precipitated			