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Evaluation of drug-carrier interactions in quaternary powder mixtures containing perindopril tert-butylamine and indapamide

Adam Voelkel[a,*], Kasylda Milczewska[a], Michał Teżyk[b,c], Bartłomiej Milanowski[b], Janina Lulek[b]

[a] Institute of Chemical Technology and Engineering, Poznan University of Technology, Berdychowo 4, 60-965 Poznan, Poland
[b] Department of Pharmaceutical Technology, Faculty of Pharmacy, Poznan University of Medical Sciences, 6 Grunwaldzka Street, 60-780 Poznan, Poland
[c] Gedeon Richter Polska Sp. z o.o., 5 Ks. J. Poniatowskiego Street, 05-825 Grodzisk Mazowiecki, Poland

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ABSTRACT

Interactions occurring between components in the quaternary powder mixtures consisting of perindopril tert-butylamine, indapamide (active pharmaceutical ingredients), carrier substance and hydrophobic colloidal silica were examined. Two grades of lactose monohydrate: Spherolac® 100 and Granulac® 200 and two types of microcrystalline cellulose: M101D+ and Vivapur® 102 were used as carriers. We determined the size distribution (laser diffraction method), morphology (scanning electron microscopy) and a specific surface area of the powder particles (by nitrogen adsorption-desorption). For the determination of the surface energy of powder mixtures the method of inverse gas chromatography was applied. Investigated mixtures were characterized by surface parameters (dispersive component of surface energy, specific interactions parameters, specific surface area), work of adhesion and cohesion as well as Flory-Huggins parameter χ'_{23}. Results obtained for all quaternary powder mixtures indicate existence of interactions between components. The strongest interactions occur for both blends with different types of microcrystalline cellulose (PM-1 and PM-4) while much weaker ones for powder mixtures with various types of lactose (PM-2 and PM-3).

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1. Introduction

Tablets, the most common solid oral formulation, are mostly manufactured by materials compression previously placed into the die cavity. Increased pressure between upper and lower punches results in tablets formulation.

Powder blends can be prepared using the most basic equipment such as e.g. blenders. The manufacturing process is based on directly combining raw materials or prepared premixes to achieve a uniform distribution of APIs in the whole volume of powder blend. The mixing time and speed must be optimized and validated. It guarantees that the manufacturing process is repeatable and the quality of final product is in accordance with product specification requirements. The main difficulty of processing powder blends is the risk of losing powder mixture homogeneity during processing. It may be a result of the difference in size, shape, and density of interacting particles. To diminished the risk of existence such dangerous phenomena the nature of raw materials and final blends should be investigated to get better understanding of the nature and strength of interactions occurring between APIs and excipients. The concept of quality by design (QbD), introduced by International Council for Harmonisation (ICH) guidelines, presume science-based deep understanding of raw materials attributes, influence of process parameters, identification their interactions and impact on final product critical quality attributes (CQA) (U.S. Guidance for Industry: Q8., 2009; U.S. Guidance for Industry: Q9, 2006; U.S. Guidance for Industry: Q10, 2009). Moreover, this knowledge may help to get a deeper insight into the behavior of direct compression blends during the processing and enable more conscious production process design, based on a better material properties and process understanding.

Characterization of the surface properties, especially the surface free energy (surface energetics), of solid pharmaceutical materials is key to the understanding solid/liquid and solid/solid interactions in processes related to the manufacture of dosage forms (Packham, 2003; Brandyophadhyay and Grant, 2000; Cline and Dalby, 2002; Barra et al., 1996). Surface energetics affect dissolution behaviors of solid dosage forms and their components

* Corresponding author.
E-mail addresses: Adam.Voelkel@put.poznan.pl, adamvoelkel@wp.pl (A. Voelkel), Kasylda.Milczewska@put.poznan.pl (K. Milczewska), mtezyk@grodzisk.rgnet.org (M. Teżyk), bmilan@ump.edu.pl (B. Milanowski), jlulek@ump.edu.pl (J. Lulek).

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(Prestidge and Tsatouhas, 2000). It also plays important role in powder suspension, granulation and coating processes (Planinsek et al., 2000; Zajic and Buckton, 1990). Furthermore surface free energy information can also be used as predictive tool in powder rheology (e.g. in predicting blending of dry powders, powder dispersion, lubricant-powder and powder-powder adhesion-cohesion interactions) (Levinsky, 2003; Breznik et al., 2002; Grimsey et al., 2002; Siaan et al., 1999; Barra et al., 1998; Ahfat et al., 1997; Swaminathan et al., 2006) and to control drug particles wetting properties in crystallization, milling and compaction (Barra et al., 1999; Buckton et al., 1988). Surface energetics of a solid material can be assessed by means of inverse gas chromatography (iGC) (Voelkel et al., 2009a).

1.1. Inverse gas chromatography (iGC)

The term *inverse* indicates that the material of interest is placed in a chromatographic column and the behavior of carefully selected test solutes is studied. Retention parameters and the shape of chromatographic peak of these solutes are affected by the nature and magnitude of interactions between them and the examined material. The application of inverse gas chromatography is easy, cheap and quick (Voelkel et al., 2009a). The basic equations of iGC were derived using the specific retention volume (V_g). Surface of solids is characterized by their activity, acid-based properties, surface area, porosity. Almost all of these properties can be measured by means of iGC (Lloyd et al., 1989).

The values of the dispersive component of surface energy can be estimated using non-polar test solutes. Materials characterized by $\gamma_S^D \leq 20$ [mJ/m^2] can be described as inert. Those with values of $\gamma_S^D > 60$ [mJ/m^2] may be categorized as active. γ_S^D may be determined by two iGC based methods, i.e. Schultz-Lavielle and/or Dorris-Gray methods (Voelkel et al., 2009b; Kołodziejek et al., 2013). All equations used in the determination of iGC derived parameters are presented in Experimental section.

The nature and strength of interactions, occurring in the pharmaceutical powder mixtures between the active substance (API) and excipients, have a significant influence on direct compression blends behavior during the processing. The carrier with potentially best adhesion properties can prevent segregation tendency (loss of blend homogeneity) of the mixture during transport to a tablet press. The carrier with higher surface energy presents higher adhesion properties (Swaminathan et al., 2006). More reactive surface can potentially prevent segregation (loss of homogeneity) of the mixture during transport between individual technological steps.

The aim of the work was to determine interactions occurring between components in the quaternary powder mixtures consisting of perindopril tert-butylamine, indapamide (APIs), carrier substance and hydrophobic colloidal silica. Two grades of lactose monohydrate: Spherolac® 100 and Granulac® 200 and two types of microcrystalline cellulose (**MC**): MC type M101D+ and Vivapur® 102 were used independently as carrier substances. Aerosil® R 972 Pharma, a nano-sized pharma-grade hydrophobic colloidal silica, served as a glidant in each powder mixture. In the preliminary study we determined the size distribution (laser diffraction method), morphology (scanning electron microscopy) and a specific surface area of the powder particles (by nitrogen adsorption-desorption). For the determination of the surface energy of powder mixtures the method of inverse gas chromatography (iGC) was applied. Values of surface parameters describing its dispersive and acid-base properties were determined basing on retention data of test solutes. Experimental data enabled the calculation of the Flory-Huggins parameters as well as the work of cohesion and adhesion that provide information about the strength of the interactions between the active substance and carrier in tested blends (Voelkel et al., 2009a; Lloyd et al., 1989).

2. Experimental

2.1. Materials

Perindopril tert-butylamine (**PER**), 100.7% pure, Glenmark Generics Ltd., India) and indapamide (**IND**), 99.3% pure, Bioindustria Laboratorio Italiano Medicinali S.p.A., Italy) were used as model active pharmaceutical ingredients (APIs). Two grades of lactose monohydrate: Spherolac® 100 ((**SPH**), Meggle, Germany) and Granulac® 200 (**GRA**), Meggle, Germany) and two types of microcrystalline cellulose (MC): MC type M101D+ (**MCM**), Mingtai Chemical Co., Ltd., Taiwan) and Vivapur® 102 (**VIVA**), JRS Pharma, Germany) were used independently as carrier substances. Aerosil® R 972 Pharma ((**A**), Evonik, Germany), a nano-sized pharma-grade hydrophobic colloidal silica was an ingredient of each powder mixture.

2.2. Powder blends

Four different powder mixtures (**PM**) with the same quantitative composition were prepared for trials purpose. Each of blends consists of four ingredients: perindopril tert-butylamine and indapamide (APIs), hydrophobic colloidal silica and a carrier substance: Vivapur® 102 (**PM-1**) or Spherolac® 100 (**PM-2**) or Granulac® 200 (**PM-3**) or MC type M101D+ (**PM-4**). All blends have unique surface properties, which will be presented elsewhere in this manuscript. The qualitative and quantitative composition of powder blends is given in Table 1.

Table 1
Qualitative and quantitative composition of examined materials.

No.	Sample namematerial	Perindopril tert-butylamine [g]	Indapamide [g]	Hydrophobic colloidal silica [g]	Carrier [g]
1	PER	18.2	x	x	x
2	IND	x	5.7	x	x
3	PER-IND	18.2	5.7	x	x
4	A-VIVA	x	x	1.2	74.9
5	A-SPH	x	x	1.2	74.9
6	A-GRA	x	x	1.2	74.9
7	A-MCM	x	x	1.2	74.9
8	PM-1 (carrier: VIVA)	18.2	5.7	1.2	74.9
9	PM-2 (carrier: SPH)	18.2	5.7	1.2	74.9
10	PM-3 (carrier: GRA)	18.2	5.7	1.2	74.9
11	PM-4 (carrier: MCM)	18.2	5.7	1.2	74.9