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Short communication

Applicability of *Expert System for Drug Development* as a tool for co-processed excipients formulation development

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Introduction

Expert System for Drug Development, i.e. SeDeM Expert System (Span. *Sistema Experto para DEsarrollo de Medicamentos*) represents a method intended for evaluation of powder properties affecting processability, particularly compression behavior (Pérez et al., 2006). Additionally, it is recognized as useful formulation tool, since it provides identification of impaired powder properties and facilitates formulation development suitable for direct compression, based on mathematical equations. Relevant parameters described in SeDeM Expert System are divided into 5 groups and denoted as "incidence factors", namely: *Density*, *Compression*, *Flowability*, *Particle Size* and *Stability* (Aguilar-Díaz et al., 2014).

The aim of this work was to investigate mannitol- and lactose-based co-processed excipients, based on SeDeM Expert System methodology, and assess its suitability for compressible formulation development.

Materials and methods

Six co-processed excipients were used in the study: i) lactose-based: CombiLac® (Meggle Pharma), MicroceLac® 100 (Meggle Pharma) and StarLac® (Meggle Pharma), and ii) mannitol-based: Disintequik™ ODT (Kerry), Ludiflash® (BASF), Pharmaburst 500® (SPI Pharma), as well as two model drugs: caffeine and ibuprofen.

Investigated powders were characterized in terms of relevant SeDeM Expert System incidence factors: i) *Density*: bulk and tapped density, ii) *Compression*: inter-particle porosity (calculated from bulk and tapped density values), Carr index, tensile strength of compacts obtained at 500 kg compression load (calculated from compact hardness, diameter and thickness), iii) *Flowability*: Hausner ratio, angle of repose, iv) *Particle Size:* fines fraction, i.e. fraction of particles smaller than 45 μm, and v) *Stability*: moisture content. Each parameter was mathematically transformed into corresponding radius parameter, ranging from 0 (not acceptable) to 10 (perfect for compression), according to SeDeM Expert System.

Comprehensive excipients' and model drugs' characterization was used for powder comparison and excipients' assessment for compressible formulation development, according to Equation (1):

$$EC = 100 - \frac{ER-5}{ER-MR} \cdot 100 \quad (1)$$

where EC represents concentration of excipient to be added, ER represents relevant excipient radius parameter, MR is relevant model drug radius parameter and 5 represents radius parameter limit value, i.e. minimal acceptable parameter value (Aguilar-Díaz et al., 2014).

The obtained excipient-model drug blends were also characterized based on SeDeM Expert System methodology. Additionally, compacts (6 mm diameter) were prepared and investigated in terms of disintegration time, according to European Pharmacopoeia.

Results and discussion

Co-processed excipients' characterization

The investigated co-processed excipients exhibited comparable and, generally, favorable characteristics. All excipients exhibited acceptable density-related parameters (*Density* incidence factor values 4.30-6.59), apart from Pharmaburst 500, with somewhat lower bulk and tapped density (0.38 and 0.48 g/mL, respectively). In terms of *Compression,* mannitol-based excipients were favorable to lactose-based excipients (*Compression* incidence factor values 4.36-5.48 and 5.53-6.38, for mannitol- and lactose-

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based excipients, respectively). Tensile strength values of the prepared compacts were generally higher than 1 MPa, considered as the acceptable value.

The most notable difference among excipients was evident regarding parameters describing powder flowability. Lactose-based excipients exhibited favorable flowability-related parameters (*Flowability* incidence factor values from 7.90 to 8.40) in comparison to mannitol-based excipients (*Flowability* incidence factor values 2.45-6.14). The obtained *Particle Size* and *Stability* incidence factors were high (higher than 7), indicating low fines fraction and low moisture content, which is suitable for direct compression.

Model drugs' characterization

Both investigated model drugs exhibited acceptable compression-, particle size- and stability-related parameters, while *Flowability* incidence factor values were low (0.41 and 1.50, for caffeine and ibuprofen, respectively). The obtained Hausner ratio values were 1.47 and 1.35, for caffeine and ibuprofen, respectively, while angle of repose was around 45%, classifying the investigated model drugs into powders with very poor flow, according to Pharmacopoeial criteria. Additionally, ibuprofen *Density* incidence factor was 3.97, which is lower than 5, suggested as acceptable in SeDeM Expert System. Caffeine showed somewhat advantageous *Density*, *Compression* and *Flowability* incidence parameters in comparison to ibuprofen.

Formulation development based on SeDeM Expert System

It was determined that the suitable excipients should exhibit high *Flowability,* and *Density* and *Flowability* parameters, to improve the characteristics of caffeine and ibuprofen, respectively. In order to obtain compressible formulations, caffeine was mixed with CombiLac® (57.4%), while StarLac® (50.7%) was selected for formulation with ibuprofen. Prepared powder blends exhibited improved density- and flowability-related parameters in comparison to model drug characteristics. Powder blend *Compression* incidence factors decreased in comparison to model drugs', which is contributed to high flowability of lactose-based excipients and less tendency to sticking. The prepared compacts exhibited high tensile strength (3.10 and 1.13 MPa, for compacts with caffeine and ibuprofen, respectively) and disintegrated very quickly, in less than 2 minutes (disintegration time 116 s and 16 s, for compacts with caffeine and ibuprofen, respectively). Generally, the obtained powder blends' parameters were more similar to excipients, particularly the mixture with StarLac®, indicating high dilution capacity. SeDeM Expert System enhanced the appropriate excipient selection and addition, based on model drug limitations, and enabled compressible formulation development. In spite of mathematical equation, it was not possible to predict the exact parameter values, which is related to complex behavior of powder mixtures, excipient dilution capacity and percolation threshold.

Conclusion

The investigated co-processed excipients exhibited comparable characteristics. Lactose-based excipients were favorable in terms of flowability, while mannitol-based excipients were more suitable for compression.

SeDeM Expert System was found as useful aid for powder assessment and comparison. It facilitated the appropriate excipient selection and addition, for diminishing impaired model drug characteristics, based on mathematical equation. In the case of caffeine, 57.4% of CombiLac® was added, while StarLac® (50.7%) was mixed with ibuprofen. The prepared mixtures exhibited improved density- and flowability-related parameters and the obtained compacts showed high tensile strength (higher than 1 MPa) and short disintegration time (less than 2 minutes). However, SeDeM Expert System simplifies the excipient characteristics, neglects dilution capacity and percolation threshold, which should be taken into account for better understanding of excipient and model drug mixtures' properties.

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