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Evaluation of the ability of powdered milk to produce minitablets containing paracetamol for the paediatric population

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ABSTRACT

The work aims at evaluating the usefulness of powdered milk as a drug matrix for the production of minitablets specifically designed for children. Mixtures made of powdered milk, paracetamol, mannitol, sodium croscarmellose and magnesium stearate (evaluated for flow properties, cohesiveness and caking tendency) were compacted into beams (evaluated for deformation, elasticity and stiffness) and minitablets (evaluated for uniformity of mass, thickness, tensile strength and paracetamol mean dissolution time) and a 2^3 factorial design performed. The increase on milk fraction in the formulation improved the compressibility of paracetamol and hardness of compacts, reducing weight variation and paracetamol release. A marked decrease on the dissolution time was observed as sodium croscarmellose was added to the milk rich formulations. The increase of the compression force resulted in the production of thinner compacts but had little effect on dissolution time. The production of beams has shown that deformation, bending strength and stiffness increased with both milk and compaction pressure, and decreased with sodium croscarmellose, whereas elasticity decreased when all variables increased. Tensile strength and mean dissolution time described minitablets well, unlike compaction force. The study has proved that powdered milk is suitable for the production of minitablets by direct compression of poor compressible drugs.

1. Introduction

Over the years paediatric patients have been medicated by compounding or manipulating medicines designed to the adult population to obtain the required dose or to aid administration (Richey et al., 2012). In recent years the need to reconsider the dosage forms available in order to make them child-friendly has resulted in the publication of European Union (EMEA/CHMP/PEG/194810/2005, 2006, EMA/CHMP/QWP/180157/2011, 2011) and World Health Organization (WHO) guidelines concerning medicines designed for children (WHO, 2010) and essential medicines for children (WHO, 2013), thus increasing awareness and encouraging research on the paediatrics' drug delivery field. These guidelines assert that solid dosage forms are the first choice when developing new medicines for children.

Paediatric patients represent a very heterogeneous group in need of individualized dosing and ease of administration of palatable medicines. Difficulties in swallowing encountered by the youngsters often result in administration of liquid

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formulations which, in comparison to solid dosage forms, present disadvantages namely, reduced stability, difficulty to find non-toxic excipients/preservatives (Krause and Breitkreutz, 2008) and to ascertain the measurement/administration of the right dose by the caretaker. In contrast, minitablets (Thomson et al., 2009; Stoltenberg and Breitkreutz, 2011), pellets (Kayumba et al., 2007) and granules (Mambrini and Kibleur, 2013) may be preferred alternatives when formulating new dosage forms for children providing the required drug stability, and dose accuracy as well as flexibility. Some children seem to prefer uncoated tablets to suspensions, syrups or powders (van Riet-Nales et al., 2013) but the age at which they are able to swell minitablets (2–3 mm diameter (Lennartz and Mielck, 1998)) remains undetermined and probably varies with the individual. Recent studies showed that round uncoated tablets are well accepted by 1–4 year old children (van Riet-Nales et al., 2013), while others deemed their usage safe in children as young as 2 years old (Thomson et al., 2009). Small-sized multiparticulates, on the other hand, can be swallowed by children over 6 months of age when dispersed in soft food or liquid beverages (Krause and Breitkreutz, 2008) if an adequate delivery device (e.g. dosing spoon or a counting device) is considered (Walsh et al., 2011).

Direct compression of powder blends has some advantages (e.g. fewer processing steps, increasing productivity, reduced costs and elimination of heat and moisture effects on the final product (Martinello et al., 2006)) but it requires a good flow (for consistent tablet weight) and the right balance between brittle fracture and plastic behaviour of the mixture components (Thoorens et al., 2014; Jivraj et al., 2000). Factors such as the characteristics of individual particles, applied pressures and environmental conditions affect the powder mixture and tablet performance (appropriate site of action, stability and palatability). Thus, optimal flow properties, at the expense of adjuvants, are often required for reliable design and proper manufacture operation (Sinka et al., 2009; Leturia et al., 2014) and these excipients have to be carefully considered when developing new paediatric solid dosage forms. Excipients, which are innocuous to adults, may pose a risk to the different age groups within the paediatric population (Salunke et al., 2012) and, therefore, powdered milk a complete, universally accepted food is an innovative and attractive excipient in formulating dosage forms for children. Due to its complex composition, milk has been proposed as a vehicle for physiologically active entities (Fox and McSweeney, 1998; Meurant, 1995; Livney, 2010) and resulted in a wide variety of novel applications in milk technology, namely as a solubilizing/dispersing agent for oral drugs (Charkoftaki et al., 2010; Kytariolos et al., 2013). Paracetamol is regarded as a very effective drug for the relief of pain and fever in adults and children (Bosch et al., 2006), considered by WHO palliative in care of children (WHO, 2013).

When developing new dosage forms an experimental design (factorial design) approach is advisable to collect as much as possible information from experimental data using a small number of trials, thus minimizing costs, saving time and improving the properties of the resulting products (Djuris et al., 2013). To that end, it is crucial to identify the variables that most affect the quality of the final product. In this study a full factorial design (Lewis et al., 1998) was employed to identify the variables (both formulation and manufacturing) and their interactions with significant impact on selected properties of minitablets made of paracetamol and powdered milk and produced by direct compression. Thus, the study aims at assessing the feasibility of using powdered milk in the oral delivery of drugs to children in minitablets based on a factorial design (Lewis et al., 1998) to optimize both the process and the formulation parameters.

2. Materials and methods

2.1. Materials

Powdered milk (Nido®, Nestlé Portugal, Oeiras, Portugal), paracetamol (Lusifar, Lisbon, Portugal), sodium croscarmellose (Ac-Di-Sol®, FMC BioPolymer, Philadelphia, USA), D-mannitol (Carlo Erba, Cornaredo, Italy) and magnesium stearate (Sigma-Aldrich, Munich, Germany) were used in the different formulations.

2.2. Experimental design and statistical analysis

To investigate the properties of powder mixtures and compacts (beams and minitablets), full factorial designs were considered (Tables S1 and S2, Annex 1). The factorial design was constructed based on preliminary experiments (results not shown), which have revealed that the milk/drug ratio and disintegrant fraction in the formulation, and the compression pressure applied were critical to the manufacture of the minitablets, as assessed for weight and thickness variations, mechanical strength and paracetamol dissolution time. The milk/paracetamol ratio (m/M), the fraction of disintegrant in the mixtures (d/D) (2^2 factorial design), plus the compression pressure (p/P) on the manufacture beams and minitablets (2^3 factorial design) were considered as independent variables.

The dependent variable(s) for the powders' analysis were flowability (i.e., cohesion coefficient and index, flow rate dependency, the coefficient of compaction and the caking tendency), for the beams mechanical properties (i.e., bending strength, elasticity, deformation and stiffness) and for the minitablets uniformity of weight, thickness, tensile strength and release of paracetamol.

Results were analyzed by ANOVA to identify the significant ($p < 0.05$) variables and interactions, and determine their impact on the properties of powders, beams or minitablets. The statistical analysis (IBM SPSS Statistics, IBM Corporation, Endicott, NY, USA) proceeded by application of multiple linear regressions to identify the relationships between each response and the variables studied, and their respective interactions (Zhan et al., 2013; Juslin et al., 1995). The inclusion, or exclusion, of variables in the equations was based on the significance ($p < 0.05$) of each variable, examination of the residuals (expressed as the root mean square error, RMSE), adjusted coefficient of correlation (R^2_{adj}), mean square error (MSE) and significance based on the F-test (Pinto et al., 1997). Linear relationships between the independent and dependent variables were established according to the following general equation (Pinto et al., 1997).

$$y_i = c + X_i^T \cdot b_i$$

where, y_i is any dependent variable, c is the interception, X_i^T is the transposed factor matrix of the influencing independent variables and b_i is the vector of the regression coefficients.

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