EVALUATION OF POWDERED MILK MINI-TABLETS CONTAINING PARACETAMOL

J. T. Pinto[1], M. I. Brachkova[1], A. I. Fernandes[1], J. F. Pinto[2*]

[1]CiiEM, Instituto Superior de Ciências da Saúde Egas Moniz, Monte de Caparica, 2829-511 Caparica, Portugal
[2]*iMed.ULisboa*, Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003, Lisboa, Portugal

INTRODUCTION

In recent years the development of medicines for paediatric use have gained increase interest. Small, flexible solid dosage forms, such as mini-tablets, are an attractive choice when developing new medicines for children [1]. Excipients, though innocuous in adults, may pose a threat to the different paediatric age groups [2] and, therefore, milk, a complete, universally accepted food, used in children's diet since birth, seems to be an innovative and attractive excipient when formulating for the aforementioned population. In this study a full factorial design was employed to identify the variables (both formulation and manufacturing) and their interactions with significant impact on selected properties of mini-tablets, containing paracetamol and powdered milk, produced by direct compression.

MATERIALS AND METHODS

Materials

Whole milk powder (Nestlé, Portugal), paracetamol (Lusifar, Portugal), sodium croscarmellose (FMC BioPolymer, USA), D-mannitol (Carlo Erba, Italy) and magnesium stearate (Sigma-Aldrich, Germany) were used in the different mini-tablets formulations.

Experimental design

The influence of the independent variables (milk/paracetamol ratio, disintegrant fraction and compression force) and their interactions on mini-tablets' mass and thickness variations, tensile strength and paracetamol dissolution rate were evaluated using a 2^3 full factorial design, as described in Table 1.

Table 1: Independent variables and their levels in the full factorial design.

Factor	Variables	Levels	
		Low (-)	High (+)
Milk / Paracetamol ratio	m/M	20/80	80/20
Disintegrant (%)	d/D	1	5
Compression pressure (MPa)	f/F	73	178

Formulation and production of the mini-tablets

Tablets were manufactured according to a design matrix. Powder milk, paracetamol, mannitol and sodium croscarmellose were blended in a cube mixer (Erweka, Germany) for 10 min, prior to the addition of magnesium stearate and mixing for another 5 min. All formulations were compressed at a 5 mm/min rate, in a mechanical press (LR 50K, Lloyds Instruments, UK) equipped with flat faced punches and dies (2.5 mm diameter).

Characterization of the mini-tablets

Uniformity of mass: The uniformity of mass of the mini-tablets (*n*=20) was carried out according to the British Pharmacopoeia.

Tensile strength and thickness: All mini-tablets were stored for at least two weeks, at room temperature (21°C) and 65% relative humidity, prior to evaluation. Mini-tablets (*n*=6) of each batch were evaluated for thickness (calliper), diametric crushing strength (Texture Analyzer, TA-XT Plus, Stable Micro Systems, UK) and tensile strength (σ);

Dissolution test: Paracetamol release from the mini-tablets was evaluated by dissolution testing (*n*=12) in conformity with the BP (paddle apparatus, at 50 rpm in phosphate buffer solution, pH=5.8; AT7, Sotax AG, Switzerland). The quantification of paracetamol in the samples was carried out by high pressure liquid chromatography (HPLC, Merck–Hitachi LabChrom,L-7100pump, a L-7200 auto-sampler and a L-7450 diode array detector, Tokyo, Japan) with a C-18 reverse-phase column (Purospher®, Merck, Germany).

RESULTS

Uniformity of mass

Results (Figure 1 a) show a direct correlation between: i) the amount of powdered milk, *'M'*, and ii) the percentage of disintegrant, *'D'*, in the formulation, and the mass of mini-tablets. The addition of higher fractions of sodium croscarmellose to milk rich formulations, *'MD',* decreased uniformity of mass.

Thickness

The increase of powdered milk, *'M',* in the formulations and the use of higher compression loads, *'F'*, clearly produced thinner compacts (Figure 1 b). In contrast, the increase of *'D'* showed a very small effect on compacts' thickness. For the formulations containing higher powdered milk loads it was possible to determine that increasing compression forces caused a reverse effect on compacts' thickness, *'MF'*.

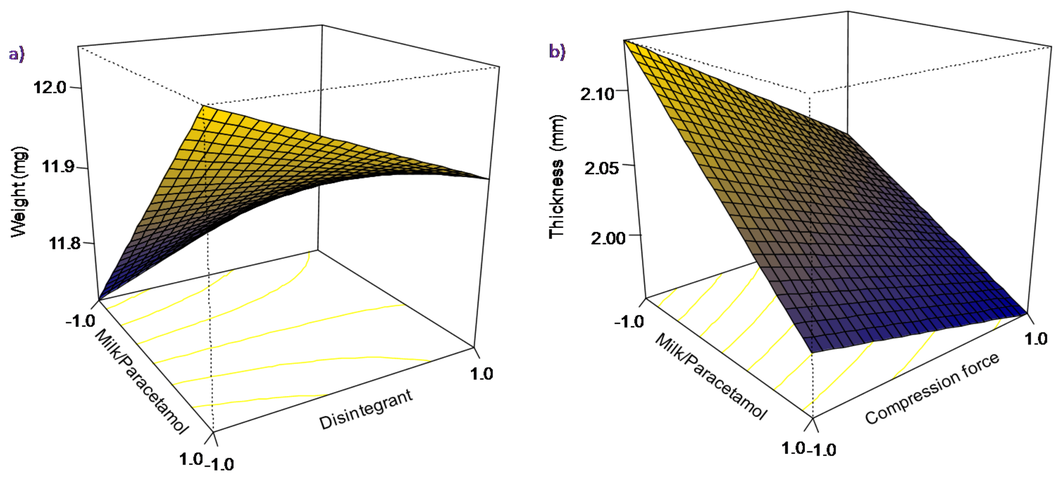

Figure 1: Graphical representation of the multiple linear regression equations for a) mass uniformity and b) thickness.

Tensile Strength

The crushing resistance test and, consequently, tensile strength results (Figure 2 a) demonstrated that the addition of increasing powdered milk quantities, *'M'*, to the compressed formulations produced a huge raise in mini-tablet's mechanical strength.

Mean dissolution time

Dissolution tests show that milk rich tablets disintegrate at a much slower rate than those with higher fractions of paracetamol; furthermore a significant difference is observed when 1% or 5% of disintegrant was used (Figure 3). In fact, multivariate analysis (Figure 2 b) showed that greater fractions of powdered milk, *'M'*, in the formulations delayed the paracetamol in mini-tablets' dissolution, increasing t_{50}. In contrast, the presence of higher fractions of sodium croscarmellose, *'D',* promoted a quicker disintegration of the tablets, thus decreasing t_{50}, as expected.

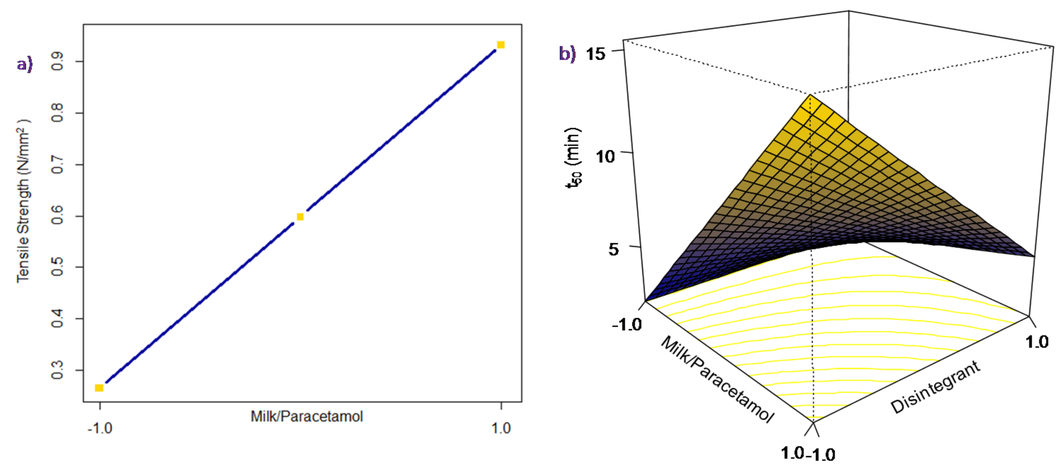

Figure 2: Graphical representation of the multiple linear regression equations.

a) tensile strength and b) mean dissolution time.

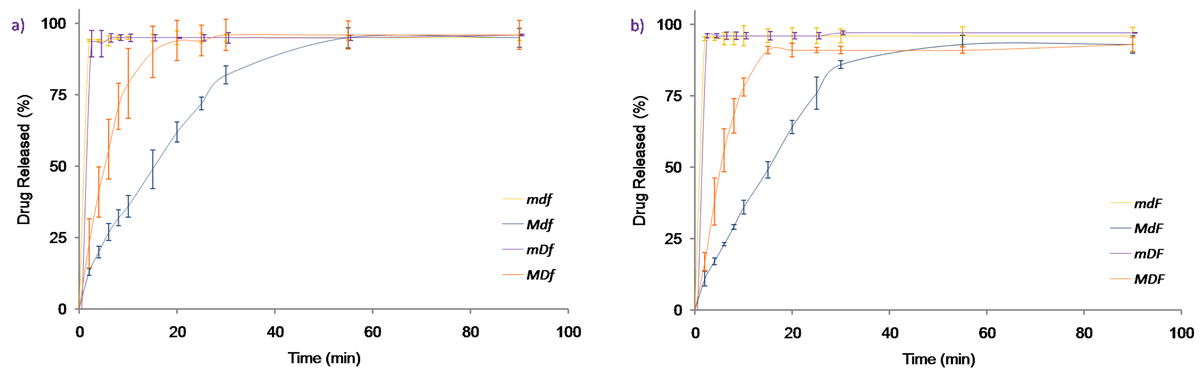

Figure 3: Dissolution profiles of the different batches of mini-tablets.

a) mini-tablets produced using 73 MPa and b) mini-tablets produced using 178 MPa.

DISCUSSION

The increase of the powdered milk fraction in the formulation improved the compressibility of paracetamol with a decrease on mass variation. Thinner and harder compacts, with slower paracetamol release, were also obtained. These observations are not surprising if powdered milk composition is taken into consideration: milk proteins, lactose (widely used as diluent) and lipids (often used as binders, lubricants and taste masking agents), which individually, or in combination, facilitate the production of tablets [3]. A marked decrease in the dissolution time was observed as sodium croscarmellose was added to the milk rich formulations, as anticipated. The increase of the compression force resulted in the production of thinner compacts with slightly higher tensile strengths, but had little effect on the mean dissolution time.

CONCLUSIONS

Results show that powdered milk is a promising system for the mini-tabletting of poor compressible drugs. The predictive mathematical models produced, allow the choice of optimal production parameters and drug delivery outcomes from powdered milk mini-tablets.

REFERENCES

[1] S.A. Thomson, C. Tuleu, I.C. Wong, S. Keady, K.G. Pitt, A.G. Sutcliffe (2009) Pediatrics, 123:235-238.
[2] S. Salunke, G. Giacoia, C. Tuleu (2012) Int. J. Pharm., 435:101-111.
[3] N. Özkan, N. Walisinghe, X.D. Chen (2002). J. Food Eng. 55:293-303.

ACKNOWLEDGEMENT

This work was supported by Fundação para a Ciência e a Tecnologia (PTDC/DTP-FTO/1057/2012).