EVALUATION OF THE ABILITY OF POWDERED MILK TO PRODUCE MINI-TABLETS CONTAINING PARACETAMOL

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INTRODUCTION

Pediatric patients represent a very heterogeneous group in need of individualized dosing and ease of administration palatable medicines. Small flexible drug dosing forms as mini-tablets, might be a preferred alternative when formulating new dosage forms for children [1].

Excipients are crucial for the properties of the final dosage. Excipients that are innocuous, when used in adults may pose a risk to the different age groups within the pediatric population [2], therefore a complete, universally accepted food component used in children's diet since birth, would be an innovative and attractive excipient in formulating dosage forms for the pediatric population. Due to its rich composition, milk has been proposed as a vehicle for physiologically active entities [3].

Paracetamol is accepted as a very effective treatment for the relief of pain and fever in adults and children.

The study aims at the assessment of the feasibility of using powdered milk to delivery drugs orally to children based on a methodology to optimize both the process and formulation parameters to lessen costs, save time and improve the properties of the resulting products. Consequently, it is critical to identify the variables that affect the most the quality of the product obtained. In this study full factorial designs [4] were employed to identify the variables (both formulation and processing) and their interactions with significant impact on selected properties of powders, compacts and minitablets made of paracetamol and powder milk produced by direct compression.

MATERIALS AND METHODS

A 2^3 full factorial design was carried out to identify the effect of selected variables and their interactions (see, Table 1), on selected responses (weight variation, thickness, tensile strength and dissolution time) of the mini-tablets manufactured.

Tablets were manufactured according to a matrix design resulting in eight combinations of four different tableting formulations compacted at two distinct pressures. Each experiment was carried out twice, resulting in a total of 16 different mini-tablets batches, randomly produced.

Each tablet batch was evaluated for thickness (n=6), uniformity of weight (n=20), diametric crushing strength and tensile strength (σ) (n=6) and dissolution testing (n=12), were carried out accord-ing to Eur. Pharm., when appropriate.

A stepwise multiple linear regression was used to identify and quantify the relationships between each response and the variables studied and their interactions. Results were analyzed by ANOVA in order to identify the significant variables and variable interactions responsible for the effects observed; the criteria considered to accept or reject a variable was based on its significance, reflected by the F-value ($p< 0.05$).

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

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

RESULTS AND DISCUSSION

The increase on milk fraction in the formulation improved the compressibility of paracetamol with a decrease on weight variation. Thinner and harder compacts with slower paracetamol releases were obtained. These observations were not surprising if powdered milk composition is taken into consideration: milk proteins, lactose (widely used as diluent) and lipids (often used as binders and taste masking agents), which individually or in combination contribute to easier the production of tablets.

A marked decrease on the dissolution time (approx. 50%) was observed as sodium croscarmellose was added to the milk rich formulations. These findings are in good agreement with the expected use of sodium croscarmellose.

The increase of the compaction force was reflected by the production of thinner compacts with slightly higher tensile strengths but random effect on the dissolution median time. Mechanical strength increases by a power function with increasing pressure, but at high pressures it is often observed and expected that the crushing strength levels off. Another phenomenon occurring at high pressure is the increase importance of particle deformation in disintegration due to hindrance of fluid penetration by further reduction of porosity. The former may explain why no significant effect was detected when analyzing tensile strength and dissolution profile.

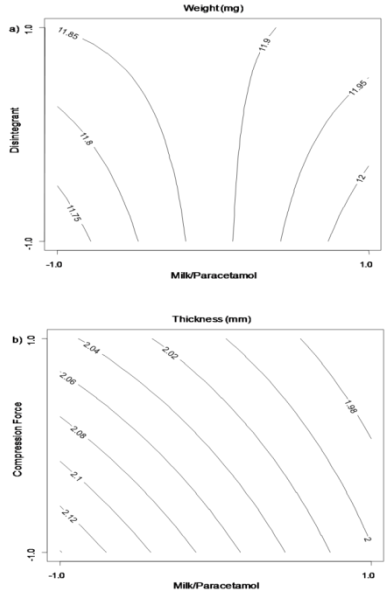

Figure 1. Graphical representation of the equations for weight variation (a), thickness (b).

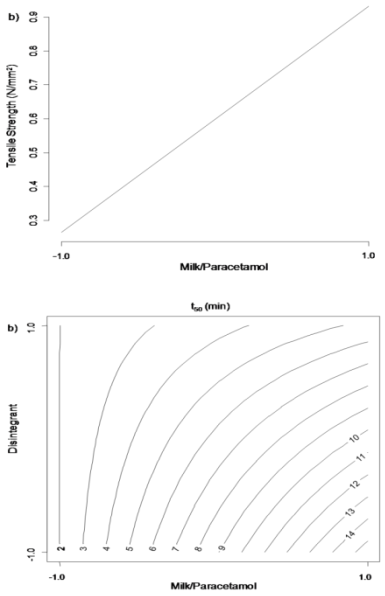

Figure 2. Graphical representation of the equations for tensile strength (a), dissolution test (b).

CONCLUSION

The experimental design and statistical analysis enabled the identification of the most significant variables and their interactions affecting the properties of the mini-tablets, particularly the milk/paracetamol ratio which proved to be critical for the proprieties of the final An excipient intended for direct compression when added to the formulation should produce tablets with enough tensile strength to withstand handling, a low friability, a low weight variation, a short disintegration time and a high drug dissolution rate, considering the showed results it seems that powder milk may be a promising new main excipient for the minitablettng of poor compressible drugs

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