EVALUATION OF THE ABILITY OF POWDERED MILK TO PRODUCE MINI-TABLETS TO DELIVER PARACETAMOL IN PEDIATRICS

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ABSTRACT

This work aims to evaluate the usefulness of powdered milk as a vehicle of drugs for direct compression into mini-tablets specifically designed for the pediatric population.

A $2^3$ full factorial design was carried out to identify the effect of selected variables and their interactions (paracetamol to milk ratio, fraction of disintegrant and compression force), on selected responses (weight variation, thickness and tensile strength of minitablets and dissolution time of paracetamol) of the mini-tablets. Tablets were manufactured according to a matrix design resulting in eight combinations of four different tableting formulations compacted at two distinct forces. Each batch of tablets was evaluated for thickness ($n=6$), uniformity of weight ($n=20$), diametric crushing strength and tensile strength ($\sigma$) ($n=6$) and dissolution testing ($n=12$). 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 to identify the significant variables and variable interactions responsible for the effects observed.

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 also 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, lubricants and taste masking agents), which individually or in combination contribute to easier the production of tablets. A marked decrease on the dissolution time was observed as sodium croscarmellose was added to the milk rich formulations, as anticipated. The increase of the compression force was reflected by the production of thinner compacts with slightly higher tensile strengths but little effect on the dissolution median time. At high forces it was often observed a higher crushing strength and an increase of the importance of particle deformation in disintegration time.

The study has proved the viability of using powdered milk on the production of minitablets to the delivery of drugs. 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 product.
KEYWORDS

DOE (Design of experiments); Milk; Mini-tablets; Paracetamol; Pediatrics.

1. INTRODUCTION

In recent years the publication of numerous guidelines in the area of pharmaceutical development of medicines for pediatric use [1-3] has increased awareness and promoted research in the field. These guidelines also point out that solid dosages forms are preferable when developing new medicines for children. The later may pose a challenge considering that pediatrics represent a very heterogeneous group in need of individualized dosing and ease of administration palatable medicine, reason why small flexible solid dosage forms as mini-tablets are an attractive choice when developing new solid dosage forms for children [4, 5]. Lennartz and Mielck [6] described mini-tablets as tablets with a diameter equal or smaller than 2-3 mm, however the age of the child able to swell this tablets remains inconclusive. Recent evidence showed that round uncoated tablets are well accepted by 1 to 4 year old children [7], while other studies deemed safe their usage in children as young as 2 years old [4]. Furthermore, is important to keep in one’s mind that when developing new solid dosage forms for children a careful consideration of the to be used excipients must be done. Excipients that are innocuous, when used in adults may pose a threat to the different age groups within pediatrics [8] 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 mentioned population.

The primary function of milk is to meet the complete nutritional requirements of the child making it a nutrient dense food. The recognition of milk’s richness in nutrients that play a key-role in human physiology has in recent years led to a wide variety of novel application in dairy technology [9]. In this work paracetamol, a worldwide well-known analgesic drug, was chosen as a model drug because of its essential role in the relieve of pain and palliative care of children [10].

Often times when developing new dosage forms an experimental design approach is used, in order to efficiently extract the most useful information possible from experimental results using a small number of trials, minimizing costs, saving time and improving the properties of the resulting products [11]. As so, it is crucial to identify the variables that affect the most the quality of the product obtained. In this study a full factorial design [12] was employed to identify the variables (both formulation and manufacturing) and their interactions with significant impact on selected properties of mini-tablets made of paracetamol and powder milk produced by direct compression.

2. MATERIALS AND METHODS

2.1 Materials

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

2.2 Experimental design and statistical analysis

To investigate the properties of the mini-tablets, a design of experiments approach was considered. The design was constructed based on previous experiments (results not shown) which have shown that the milk/drug ratio and disintegrant fraction and the compression force were critical to the manufacture of the mini-tablets. The influence of the independent variables (milk/paracetamol ratio, disintegrant fraction and compression force) and their interactions on mini-tablets’ weight 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.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variables</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (-)</td>
</tr>
<tr>
<td>Milk / Paracetamol ratio</td>
<td>m/M</td>
<td>20/80</td>
</tr>
<tr>
<td>Disintegrant (%)</td>
<td>d/D</td>
<td>1</td>
</tr>
<tr>
<td>Compression pressure (GPa)</td>
<td>f/F</td>
<td>73</td>
</tr>
</tbody>
</table>

Statistical analysis was performed using an IBM SPSS Statistics version 22.0 for windows (IBM Corporation, Endicott, NY, USA). Results were analyzed by ANOVA to identify the significant ($p<0.05$) variables and variables’ interactions and their impact on the properties of the mini-tablets. The analysis proceeded by application of multiple linear regression to identify the relationships between each response and the studied variables and their respective interactions [13, 14]. The inclusion or exclusion of variables in the equations was based on the significance ($p<0.05$) of each variable. Furthermore, the best models were chosen after careful 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 [15].

2.3 Formulation and production of the mini-tablets

Tablets were manufactured according to the design matrix (Table 2) resulting in eight combinations of four different tableting formulations compacted, using two distinct forces. Powder milk, paracetamol, mannitol and sodium croscarmellose were weighted and blended in a cube mixer (Erweka, Heusenstamm, Germany) for 10 min, prior to the addition and mixing of magnesium stearate for another 5 min. All formulations were subject to a compression rate of 5 mm/min in a mechanical press (LR 50K, Lloyds Instruments, Leicester, UK) equipped with flat faced punches and dies (2.5 mm diameter).
Different compression forces of 3, 5 and 7 kN correspondent to 76, 127 and 178 GPa, were applied. Each experiment was carried out twice.

Table 2. Complete matrix for the full factorial design

<table>
<thead>
<tr>
<th>Factors&lt;sup&gt;a)&lt;/sup&gt;</th>
<th>Variables' Levels</th>
<th>Variables' Interactions&lt;sup&gt;b)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>D</td>
</tr>
<tr>
<td>mdf</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mdf</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>mDf</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MDf</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>mDF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MdF</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>mDF</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MDF</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>a)</sup> m/M, d/D and f/F represent milk content, sodium croscarmellose content and compression pressure at low and high levels, respectively.

<sup>b)</sup> To obtain signs for interaction terms in combination, multiply signs of factors.

### 2.4 Characterization of the mini-tablets

**Uniformity of weight:** The uniformity of weight of the mini-tablets (n=20) was carried out according to British Pharmacopoeia [16] using an analytical balance (Mettler-Toledo AG204DR, Columbus, OH, USA);

**Tensile strength and thickness:** All mini-tablets were stored at least two weeks at room temperature (21°C) and relative humidity (RH=65%) prior to evaluation. Tablets (n=6) of each batch were evaluated for thickness (calipers) and diametric crushing strength (Texture Analyzer, TA-XT Plus, Stable Micro Systems, Godalming, UK, at a constant rate of 0.5 mm/s). Results from the crushing test were also analyzed for tensile strength (σ) [17];

**Dissolution test:** The evaluation of the release of paracetamol from the mini-tablets was carried out by dissolution tests (n=12) in conformity with the British Pharmacopoeia [16] (paddle apparatus, at 50 rpm in phosphate buffer solution, pH=5.8,Sotax AT7, Sotax AG, Allschwil, 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, Darmstadt, Germany) once the method was validated (results not shown).

3. RESULTS

Table 3. Results for different properties of mini-tablets according to the $2^3$ factorial design

<table>
<thead>
<tr>
<th>Factors</th>
<th>Uniformity of weight (mg)</th>
<th>Thickness (mm)</th>
<th>Tensile Strength (N/mm²)</th>
<th>Mean dissolution time ($t_{50}$/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mdf</td>
<td>11.68 ±0.65</td>
<td>2.14 ± 0.07</td>
<td>0.35 ± 0.18</td>
<td>2.1 ± 0.08</td>
</tr>
<tr>
<td>Mdf</td>
<td>12.10 ± 0.39</td>
<td>1.99 ± 0.06</td>
<td>0.89 ± 0.37</td>
<td>15.48 ± 2.11</td>
</tr>
<tr>
<td>mDf</td>
<td>11.81 ± 0.54</td>
<td>2.14 ± 0.07</td>
<td>0.13 ± 0.10</td>
<td>1.94 ± 0.24</td>
</tr>
<tr>
<td>MDf</td>
<td>11.95 ± 0.60</td>
<td>2.01 ± 0.06</td>
<td>0.91 ± 0.31</td>
<td>5.12 ± 1.22</td>
</tr>
<tr>
<td>mdF</td>
<td>11.76 ± 0.57</td>
<td>2.04 ± 0.05</td>
<td>0.37 ± 0.21</td>
<td>1.88 ± 0.26</td>
</tr>
<tr>
<td>MdF</td>
<td>11.99 ± 0.48</td>
<td>1.96 ± 0.05</td>
<td>0.97 ± 0.26</td>
<td>15.58 ± 0.71</td>
</tr>
<tr>
<td>mDF</td>
<td>11.90 ± 0.64</td>
<td>2.05 ± 0.07</td>
<td>0.22 ± 0.18</td>
<td>2.05 ± 0.06</td>
</tr>
<tr>
<td>MDF</td>
<td>11.89 ± 0.45</td>
<td>1.96 ± 0.06</td>
<td>0.96 ± 0.24</td>
<td>5.40 ± 0.94</td>
</tr>
</tbody>
</table>

a) Uniformity of weight $n=20$, thickness and tensile strength $n= 6$, Mean dissolution time $n=3$

3.1 Experimental Design

The variables and levels of variables were selected based on previous experiments (results not shown) for the production of mini-tablets for pediatric delivery of paracetamol. In order to understand the potential use of milk as vehicle for the delivery of drugs a stepwise procedure was considered to understand the performance of the mini-tablets maximizing the significance of the selected variables.

3.1.1 Uniformity of weight

Table 3 shows that all batches complied with the British Pharmacopoeia specifications for uniformity of mass for single dose preparations [16]. Statistical results (Table 4) show a positive correlation between increasing quantities of powdered milk, $M'$, in the formulation and mini-tablets weight, as for the increase in disintegrant percentage ($D'$) and compression load ($F'$) both showed to have a minimum negligible or no effect on the studied response. It was also possible to discern that the addition of higher fractions of
sodium croscarmellose to milk rich formulations, 'MD', lead to an adverse effect on batches' weight. A similar effect is found, when higher compression forces were applied to milk rich formulations, 'MF'. Finally, the interaction of both the 'D' and 'F' variables and interaction of the former with the milk/paracetamol ratio, 'M' produced a minimum imperceptible effect on mini-tablets' weight.

Statistical approach showed that for the relationship between the above described effects and the studied response the only significant effects are milk/paracetamol ratio, 'M' and the interaction between the former and the disintegrant fraction, 'MD'. Therefore, mini-tablets' weight can be described by the reduced equation Eq (1) (RMSE = 0.523, R²_adj =0.039, MSE= 0.273, F=8.222).

\[ Weight(mg) = 11.888 + 0.111M - 0.064MD \] 

**3.1.2. Thickness**

Analyzing Tables 3 and 4 it’s possible to see that the increase of powdered milk, 'M', on the formulations and the use of higher compression loads, 'F', clearly produced thinner compacts. Contrastingly, the increase of 'D' showed a very small almost imperceptible incrementing effect on compacts’ thickness. As for the formulations containing higher powdered milk loads it was possible to determine that the addition of increasing disintegrant percentages produced no effect whatsoever ('MD'), but that increasing compression forces caused a distinguishable antagonistic positive effect on compacts' thickness, 'MF'. When increasing compression loads are applied to sodium croscarmellose rich formulations no discernable effect is found. Finally, a small negative effect was observed, when the levels of all three variables were increased ('MDF').

Results show that the only statistically significant variables are milk/paracetamol ratio, 'M', the compression force 'F' and the interaction between the two 'MF'. Consequently, the correlation between thickness and the studied variables can be described by the reduced equation Eq(2) (RMSE = 0.063, R²_adj =0.498, MSE= 0.004, F=36.325).

\[ Thickness(mm) = 2.029 - 0.056M - 0.034F + 0.014MF \] 

**3.1.3 Tensile Strength**

The crushing resistance test and, consequently, tensile strength results (Table 3 and 4) demonstrated that the addition of increasing powdered milk quantities, 'M', to the to be compressed formulations produced a huge raise in mini-tablet's mechanical strength. A similar however, much smaller positive effect on compacts strength was discernable, when increasing compression loads ('F') were applied. On the other hand, weaker compacts were produced when higher fractions of sodium croscarmellose, 'D', were used it lead to the production of weaker compacts. When higher fractions of disintegrant were added to powdered milk rich formulations ('MD'), the former had a favourable impact in compacts' mechanical strength, when high loads were applied to this same formulations ('MF') a similar, however very small positive effect was also produced. A slightly more pronounced positive effect is detected when increasing forces are applied to compress formulations containing greater sodium croscarmellose percentages, 'DF'. Finally and surprisingly, the
simultaneously increase of all three variables, ‘MDF’ caused a small antagonistic negative
effect on the produced compacts.

Statistical analysis of the results indicates that the only significant effect is the
milk/paracetamol ratio ‘M’ one, as so mini-tablets tensile strength can be modeled by the
reduced following equation Eq. (5) (RMSE = 0.233, R²Adj = 0.646, MSE= 0.055,
F=196.486):

\[ Tensile \text{ Strength}(\frac{N}{mm^2}) = 0.599 + 0.334M \]  \hspace{1cm} \text{Eq(3)}

Statistical analysis also shows that milk/paracetamol ratio coefficient is tremendously
significant, so it’s no surprise to have observed such a striking difference between tensile
strengths of mini-tablets with more paracetamol and the ones with a higher percentage of
milk (Table 3).

3.1.4. Mean dissolution time

Results (Table 3) from the performed dissolution tests show that when comparing milk
rich tablets with the ones with higher fraction of paracetamol, the former disintegrate at a
much slower rate, furthermore a significant difference is observed when 1% or 5% of
disintegrant was used. When a higher fraction of croscarmellose sodium is used a \( t_{50} \) of 5-8
is obtained whereas smaller fractions of disintegrant result in \( t_{50} \) of 14-16 min. Mini-tablets
containing more paracetamol disintegrated almost instantly resulting in more than 90%
drug release within the first 2 minutes of test. Notwithstanding, even the batches with the
slowest dissolution profiles showed 80% drug release after 40 minutes, complying with the
British pharmacopeia monograph for paracetamol tablets [16].

Analysis of coefficient statistics (Table 4) supports the findings described above. Greater fractions of powdered milk, ‘M’, in the formulations increased the \( t_{50} \), delaying the
mini-tablets' dissolution. Contrastingly, the presence of higher fractions of sodium
croscarmellose, ‘D’, decrease \( t_{50} \), promoting a quicker desintegration of the tablets. As for
the manufacture variable, ‘F’ a very small increase in the dissolution rate is observed when
higher compression forces were used. Equally, to the sole increase of ‘D’ a marked decrease
in the mean dissolution time was detected, when higher percentages of disintegrant are
present in the formulation of milk rich mini-tablets. The interaction between ‘F’ and ‘M’ and
‘F’ and ‘D’, shows an increasing small in \( t_{50} \). Finally, the interaction between the three
variables (‘MDF’) causes a minimum decrease in mini-tablets’ dissolution time.

The linear regression rendered statistically significant the influence of milk/paracetamol
ratio, percentage of disintegrant and the interaction between the two. Accordingly, the \( t_{50} \)
can be traduced by the following reduced equation \text{Eq(4)} (RMSE = 1.120, R²Adj = 0.952,
MSE = 1.252, F= 241.756).

\[ t_{50}(min) = 6.139 + 4.199M - 2.572D - 2.566MD \]  \hspace{1cm} \text{Eq(4)}
Eq(4) significantly describes mini-tablets disintegration behaviour, seeing as the main effects in it account for the almost totality of the different phenomenon occurring during dissolution test ($R^2_{adj}=0.967$).

Table 4. Evaluation of the results for different properties of the mini-tablets made by ANOVA.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Uniformity of weight (mg)</th>
<th>Thickness (mm)</th>
<th>Tensile Strength (N/mm$^2$)</th>
<th>Mean dissolution time ($t_{50}$/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Effect$^a$</td>
<td>Mean</td>
<td>Effect</td>
</tr>
<tr>
<td>$m/M$</td>
<td>11.8/12.0</td>
<td>0.20***</td>
<td>2.09/1.98</td>
<td>-0.11***</td>
</tr>
<tr>
<td>$d/D$</td>
<td>11.9/11.9</td>
<td>0.01</td>
<td>2.03/2.04</td>
<td>0.01</td>
</tr>
<tr>
<td>$md/MD$</td>
<td>11.9/11.8</td>
<td>-0.13*</td>
<td>2.04/2.04</td>
<td>0.00</td>
</tr>
<tr>
<td>$f/F$</td>
<td>11.9/11.9</td>
<td>0.00</td>
<td>2.07/2.00</td>
<td>-0.07***</td>
</tr>
<tr>
<td>$mf/MF$</td>
<td>11.9/11.9</td>
<td>-0.08</td>
<td>2.02/2.05</td>
<td>0.03*</td>
</tr>
<tr>
<td>$df/DF$</td>
<td>11.9/11.9</td>
<td>0.01</td>
<td>2.04/2.04</td>
<td>0.00</td>
</tr>
<tr>
<td>$mdf/ MDF$</td>
<td>11.9/11.9</td>
<td>0.01</td>
<td>2.04/2.03</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

$^a$ Effect p of significance: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

4. DISCUSSION

The increase of powdered milk fraction in the formulation causes an increase in batches weight, thinner harder compacts are produced and a slower dissolution profile is obtained. Taking into account paracetamol's well-known poor compressibility behaviour [18], it is no surprise that when a raw material such as powdered milk (rich in proteins, lactose and lipids) is used in the formulation it shows the ability to improve the API compressibility behaviour. Measurements of compressive strength of powder compacts are sometimes used to study the cohesion and caking of dairy powders [19], cylindrical powder plugs are produced using low pressures, demonstrating powdered milk good compressibility behaviour. Furthermore, results show that increasing fat contents in milk powder's
composition promote cohesion and caking, facilitating the obtention compacts [20]. Additionally, the melting of fat milk (~40°C) can promote the formation of fatty bridges that when the temperature drops crystallize and increase cohesiveness and caking [21]. At high pressures it's possible that due to the increasing temperatures during compression and its decrease after tablet's injection fatty bridges crystallization may take place, further improving tablets interparticle bonding. Finally, studies also show that increasing moistures content due to absorption of water by lactose and milk proteins result in higher cohesiveness, possibly due to plasticization of the powder material or liquid bridging occurring due to moisture condensation between particle [20, 22]. However, the last phenomenon is more critical for samples with higher contents of lactose and proteins as skimmed powdered milk. As so, powdered milk seems to comprise a series of characteristics that could possibly potentiate its use as binder in direct compression. Macroscopically it was possible to verify powdered milk utility as a binder, as formulations with a higher percentage of paracetamol, contrastingly with the ones with a higher fraction of powdered milk, delivered more fragile powdery tablets, raising doubt to their ability to withstand further handling.

Super disintegrants are excipients used to promote rapid breakdown of oral solid dosage forms and because they can be present at lower concentrations in the overall formulation any possible adverse effect on fluidity or compactibility is minimized [23]. So it is not surprising that one's work revealed similar results, where in one hand the increase of croscarmellose in the formulations showed to be crucial in promoting the rapid desegregation of the mini-tablets and in the other seem to adversely affect powdered milk good flowability behaviour [22], producing lighter batches. In dissolution the addition of higher fractions of disintegrants seem to be particularly important when powdered milk was the main component in the formulation, in fact a marked decrease of nearly 50% in the mean dissolution time, was detected when testing it. This may be explained by concentration-dependent croscarmellose action [24] and by its effect in disintegration time being dependent on the plastic deformation capacity of the powder mixture [25].

It is known that compression forces influence tablets proprieties as thickness, porosity, crushing strength, friability and disintegration time [26, 27]. However, in this study it was only possible to discern a significant influence of the compression force on tablets’ thickness. At high pressures crushing strength shows a tendency to level off, contrary to its increase by a power function with increasing pressure, when lower pressures are applied [28]. It is also worth to mentioned that at high pressure particle deformation becomes paramount in disintegration due to hindrance of fluid penetration by further reduction of porosity [23]. The former may pose an explanation as to why only minor insignificant effects for compression force increase and its respective interactions were detected when analyzing mini-tablet’s tensile strength and dissolution profile.

Uniformity of weight and thickness models show a weaker correlation with the studied variables. One possible reason for this is the fact that both responses are highly dependent on proper powder rheology and uncountable environmental aspects, such as humidity, temperature may have influenced powder characteristics [29], explaining why no better adjustment was found. Better, stronger models were found for the mean dissolution time and the tensile strength responses. Dissolution rate is highly sensitive test that can be
influenced by numerous factors related to: the physicochemical properties of the drug substance, product formulation, manufacturing processes and factors related to dissolution testing conditions [30]. As for the mechanical strength of a tablet it depends on both formulation and processing parameter [31]. So, in one hand, it’s no surprise that formulation variables correlate so strongly with the mean dissolution time and tensile strength and on the other it’s curious to note, as mentioned before, that no quantifiable effect was found for the manufacture one.

5. CONCLUSION

Globally the regression equations seem to explain the studied responses with an acceptable significance, indicating that formulation variables display a more distinguishable influence in the chosen responses than the manufacture, in particular milk/paracetamol ratio, which proved to be crucial in the proprieties of the final product. An excipient intended for direct compression when added to the formulation should produce tablets with enough tensile strength to withstand handling, with low friability and weight variation, a short disintegration time and a high drug dissolution rate. Considering the results, it seems that powdered milk may prove to be a promising new excipient for the mini-tabletting of poor compressible drugs. The predictive mathematical models originated will, hopefully, in the future facilitate the pick and choose of the most preferable characteristics when producing powdered milk based mini-tablets for a population as heterogeneous as pediatrics.

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