SPRAY-DRIED FRESH MILK POWDERS FOR ORAL DRUG DELIVERY IN PEDIATRICS

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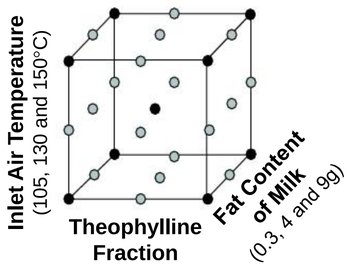
BACKGROUND

Nowadays, the need to formulate **medicines specifically designed for children** is imperative[1] and **solid dosage forms** are the first choice for providing the required drug stability and dose accuracy. **Milk,** as a worldwide accepted food, is proposed in this study as a **platform to deliver drugs orally in pediatrics**.

The main goals of this work were **(a)** the assessment of the properties of spray-dried fresh milk powders, **(b)** the evaluation of drug-milk interactions and **(c)** to ascertain the stability of the spray-dried milk powders.

MATERIALS AND METHODS

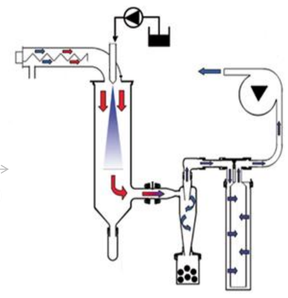
1. Preparation of theophylline : milk systems



Solutions of API : Fresh Milk with different solids ratio

0:1, 0.08:1, 0.16:1, 0.31:1, 0,62:1 and 1:1 (w/w)

2. Spray-drying process



3. Powder Analysis

Yield Moisture Content	⟷	**Spray-drying Properties**
Particle Shape and Size Density Wettability Theophylline content (HPLC)	⟷	**Properties of Spray-dried powders**
FT – IR DSC	⟷	**Drug-Milk Interaction**
Chemical Microbiological	⟷	**Stability (in-use and shelf-life)**

4. Data Analysis

One-way ANOVA with Bonferroni post-hoc test; $p<0.05$

RESULTS AND DISCUSSION

1. Yield and Moisture content

An increase in production yield was expected as the inlet air temperature (T_{inlet}) over spray-drying increased. However, the highest yields (ranging from **31.0-76.0%**) were obtained for the T_{inlet} of 130°C, showing a statistically significant variability from the yields obtained at the remaining temperatures. The high fat content milk (HFM), dried at 150°C, has led to the **melting of fat in the surface of the particles** promoting the accumulation of dried particles in the cyclone[2], thus decreasing the yields of the powders produced.

As the T_{inlet} increased, the moisture content of the powders decreased as anticipated.

2. Properties of spray-dried powders

Regarding particle size (**mean: 3.6µm; span: 0.19; range: 3.0-4.3µm**) and shape (**high sphericity**), no significant differences were found between the powders obtained at the three different T_{inlet} ($p>0.05$) (Figure 1). Results from density (**range: 1.244 – 1.552g.cm^{-3}**) have shown that there was a statistical significant variability between the three different fat contents, regardless of T_{inlet} or theophylline fraction in the formulation. The higher and the lowest density values were obtained for low and high fat contents milks (LFM and HFM), respectively.

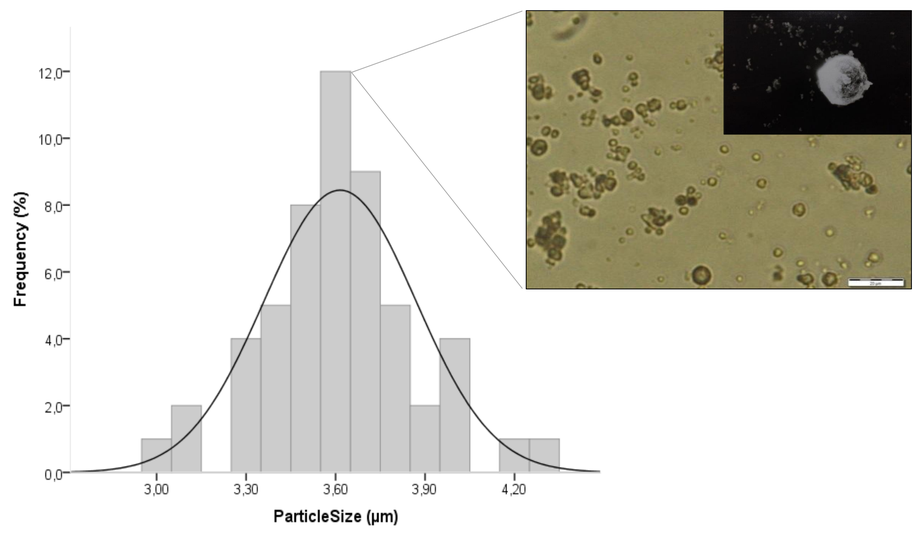


Figure 1: Particle size distribution and shape (optical and SEM microscopy) of spray-dried milk powders

The contact angles in water, for **LFM samples** exhibited the lower values **(84.72±0.53°)**, when compared to **MFM (86.32±0.34°)** and **HFM samples (86.40±0.62°)**. During particle formation it was possible that proteins molecules, either free or in micelles, became **located at the particle's surface**, lowering their surface energy[3].

Quantification of theophylline in the spray-dried milk powders revealed that samples **above 0.31 of theophylline fraction failed to have all drug present in the initial theophylline : milk solutions**. During the spray-drying process, **considerable losses of theophylline** were observed for samples above 0.31 of theophylline fraction, which was in line with the results from the assays (HPLC).

3. Drug-milk interaction

Data from the calorimetric studies has shown that above 0.62 of theophylline content, regardless the fat content, revealed that the drug **was not completely solubilized by milk components** and, therefore, endotherms due to melting of theophylline started to appear in the thermograms. This finding was also corroborated by the microscopic analysis where **theophylline crystals were predominantly observed in the samples mentioned earlier**, indicating a limited capacity of milk to incorporate the drug.

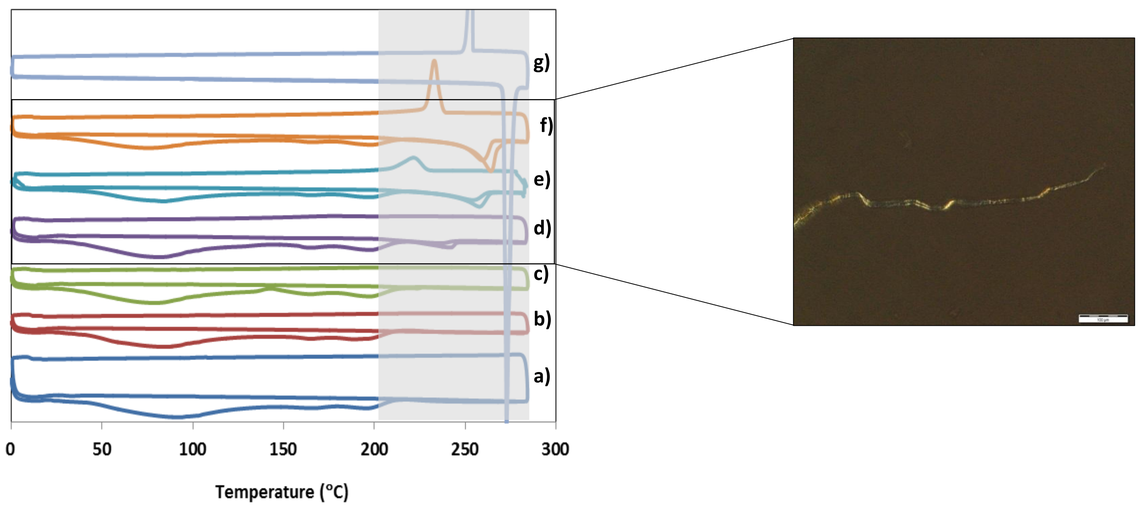


Figure 2: DSC thermogram of MFM powders atomized at 150 °C and theophylline crystal observed by polarized light

a) Spray-dried milk; b)Theophylline-milk 0.08:1; c) Theophylline-milk 0.16:1; d) Theophylline-milk 0.31:1; e) Theophylline-milk 0.62:1; f) Theophylline-milk 1:1; g) Theophylline raw material

Due to an existing peak overlap of theophylline and spray-dried powdered milk components, the FT-IR results have shown that, when the milk components were present in higher fractions, the peaks in the amine region of the spectra due to theophylline were less intense (e.g. **3125-3120cm^{-1}** region). No peak due to the resulting **imine group from the Maillard's reaction (1647-1630cm^{-1})** was observed. Furthermore, no new bond formation was observed in any spectra (data not shown).

4. Stability

Shelf-life stability testing of powders has proven that the **amount of drug in the spray-dried powders remained constant for 6 months**. Regarding in-use stability of reconstituted powders in water, at room temperature, microbial content criteria[4] were met by all samples at 24h, regardless of their fat content. At 4ºC, criteria were met by all samples at 48h, but only LFM samples met the criteria, 7 days after reconstitution (Figure 3).

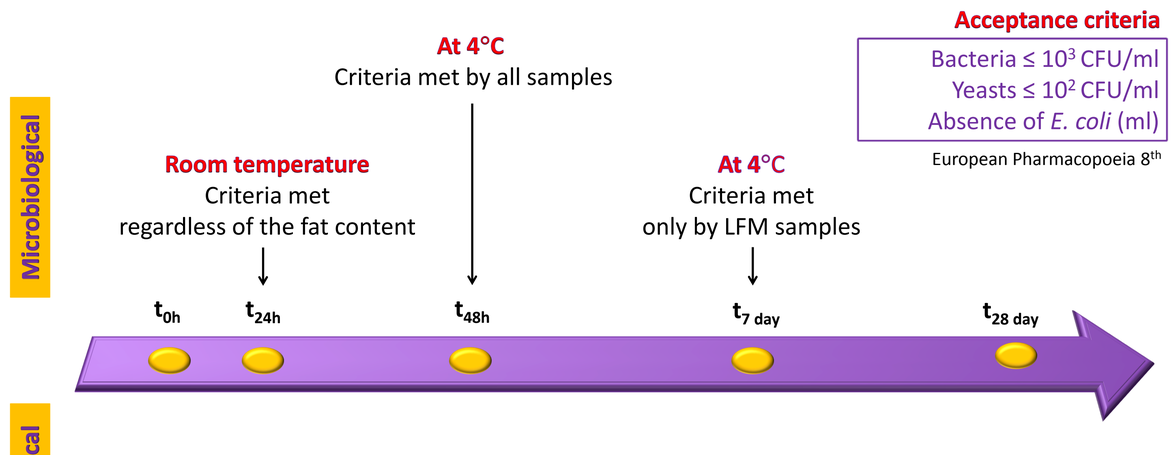


Figure 3: Stability in-use of drug-containing milk powders, after reconstitution in water.

Arrows indicate the last time point at which the compendial limits were met.

CONCLUSIONS

- This study suggests that a spray-dried milk drug loaded powder is a promising platform to deliver drugs orally in pediatrics.
- The powders obtained were stable after an easy extemporaneous reconstitution.

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