Medicinal powders made of fresh milk for pediatric use

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Introduction

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. Therefore, the main goals of this project are: (a) to assess the properties of spray-dried milk powders, (b) to evaluate drug-milk interactions and (c) to ascertain the stability of the spray-dried milk powders.

Methods

Theophylline-milk solutions were prepared using fresh commercial milks with different fat contents (Low Fat Milk – LFM, 0.3g; Middle Fat Milk – MFM, 4g; and High Fat Milk – HFM, 9g) and different theophylline:milk solids ratios (0:1; 0.08:1; 0.16:1; 0.31:1; 0.62:1; 1:1). Samples containing only milk were used as controls. These solutions were spray-dried using three different inlet air temperatures (T_{inlet} – 105, 130 and 150°C). At the end of the process, yield, moisture content (loss on drying), particle size and shape (microscopy), density (gas pycnometry) and wettability (contact angles in water and surface free energy) of the drug-containing milk powders produced were assessed. Quantification of theophylline in the spray-dried milk powders was performed by HPLC-UV. Theophylline-milk interactions were evaluated by Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FT-IR). Shelf stability of powders and in-use stability, after reconstitution in water, (chemical and microbiological) was assessed according the European Pharmacopeia [2]. Results were analyzed using one-way ANOVA, followed by a post-hoc Bonferroni test, and statistical significance considered at $p<0.05$ (IBM SPSS v.22.0).

Results and Discussion

Upon spray-drying an increase in production yield was expected as the T_{inlet} 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 ($p<0.05$). As anticipated, as the T_{inlet} increased the moisture content of powders decreased. Regarding particle size and shape, no differences between the powders generated at the three different T_{inlet} were found. Spherical particles with a mean particle size ranging from 3.0-4.3µm were obtained. Results from density show that there is a statistical significant variability between the three different fat content milks, regardless of T_{inlet} or theophylline fraction ($p<0.05$). Lower contact angles in water were obtained for LFM samples and, interestingly, higher ones were obtained for MFM samples. Quantification of theophylline in the spray-dried milk powders revealed that samples above 0.31 of theophylline fraction did not include the total

amount of the drug present in the initial theophylline:milk solutions. With DSC, regardless of the milk fat content, above 0.31 of theophylline content (inclusive), the drug was not completely solubilized by milk components and, therefore, melting peaks 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. FTIR results showed that, due to an existing peak overlap between theophylline and spray-dried powdered milk, when the latter was present in higher quantity, the amide region peaks of the spectra tend not to be as intense, especially in the 3120-3125cm^{-1} region. Shelf-life stability testing of powders has proven that the amount of drug remained constant for at least 6 months. Regarding in-use stability of reconstituted powders in water, at room temperature microbial criteria were met by all samples at 24h, regardless of the fat content considered. At 4ºC, criteria were met by all samples at 48h, but only LFM samples met the criteria, 7 days after reconstitution. Drug content remained stable throughout the assay (Figure 1).

Conclusion

Variables such as T_{inlet} and fat content of fresh milk proved to affect some properties of the spray-dried milk powders (e.g. wettability and density). Results also suggest that no drug-milk interaction occurs and LFM samples proved to be stable at 4ºC, for at least, one week after reconstitution in water. This study suggests that spray-dried milk powders are promising in promoting drug shelf-life stability, allowing for extemporaneous, easy reconstitution by the caregiver, for oral drug delivery in pediatrics.

References

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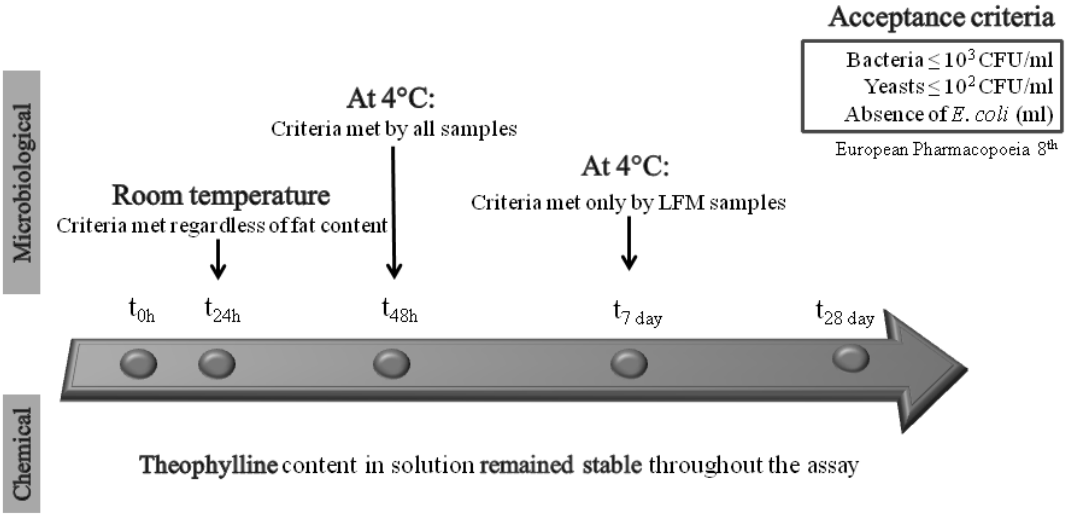

Figure 1: Stability in-use of drug-containing milk powders, after reconstitution in water. Arrows indicate the last time point at which the compendial limits were met.