Milk as a drug delivery platform in paediatrics

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PURPOSE

To assess the physical properties of spray dried milk powders and evaluate drug-milk interactions.

MATERIALS AND METHODS

Materials

Fresh milk with different fat content (Mimosa, LACTOGAL Produtos Alimentares S.A., Porto, Portugal), anhydrous theophylline (Sigma Life Science, Switzerland) and deionized water (W, Merck Millipore, Massachusetts, USA).

Methods

Samples were prepared with three types of commercial fresh milks: Low Fat Milk (LFM; 0.3g), Middle Fat Milk (MFM; 4.0g) and High Fat Milk (HFM; 9.0g). Mixtures of each milk type and theophylline at different concentrations (8, 16, 31, 62 and 100%) were prepared. Samples containing only milk were used as controls.

Spray-drying was performed in the Mini Spray-Dryer B-191 (Büchi Labortechik GmbH, Flawil, Switzerland) using three different inlet air temperatures (T_{inlet}; 105, 130 and 150°C). The remaining parameters were kept constant. Yield, moisture content (loss on drying) and physical properties (particle size and shape, and density by gas pycnometry) were assessed. Powders were stored at room temperature with a relatively humidity of 65%. Theophylline-milk interactions were evaluated by Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR).

Results were analysed using bivariate ANOVA, followed by a post-hoc Bonferroni test, and statistical significance considered at $p<0.05$ (IBM SPSS v.22.0).

RESULTS AND DISCUSSION

Results from yield, moisture content and physical properties are shown in Table 1. An increase in 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, and showing a statistically significant variability from the yields obtained for the remaining temperatures ($p<0.01$). This can be explained by the order of spray-drying of the samples: 130°C (LFM, MFM and HFM), 150°C (HFM, MFM and LFM) and 105°C (MFM, HFM and LFM). Starting with the HFM, at 150°C, has led to the melting of fat, which started to accumulate in the cyclone, therefore making the film of the piece sticky (1). As expected, 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 temperatures were found. Spherical particles with a mean particle size ranging from 3.0-4.3µm were obtained regardless of the T_{inlet} considered.

Table 1: Yield, moisture content and physical properties of powders generated at different inlet air temperatures

T_{inlet} (°C)	Milk Fat Content (g)	Assay	Theophylline concentration (%)					
			0	8	16	31	62	100
105	0.3	Yield	42.0	33.7	45.8	52.7	49.9	53.6
		MC	4.9	6.4	4.7	5.7	5.5	6.4
		PS	3.3	3.1	3.5	3.5	3.6	3.7
		ρ	1.50	1.51	1.52	1.50	1.50	1.51
	4	Yield	39.2	56.6	54.2	36.6	38.5	54.1
		MC	6.1	6.5	8.5	4.5	5.3	4.1
		PS	3.3	3.3	3.0	3.6	3.7	3.5
		ρ	1.43	1.40	1.41	1.45	1.45	1.45
	9	Yield	28.4	38.9	36.6	46.6	33.8	37.4
		MC	7.1	4.8	10.3	5.9	9.4	4.2
		PS	3.4	3.4	3.7	3.6	3.4	3.8
		ρ	1.38	1.38	1.38	1.36	1.41	1.44
130	0.3	Yield	76.0	73.3	68.5	65.3	43.0	70.0
		MC	1.6	1.1	1.0	1.0	2.5	1.1
		PS	3.3	3.6	3.8	4.2	4.0	4.0
		ρ	1.49	1.49	1.50	1.50	1.50	1.50
	4	Yield	59.6	31.0	57.0	58.3	71.0	56.3
		MC	5.1	6.3	4.8	4.1	3.6	3.0
		PS	3.7	3.5	3.7	3.6	3.5	3.4
		ρ	1.40	1.43	1.41	1.40	1.42	1.43
	9	Yield	47.2	72.1	72.6	45.7	64.6	68.9
		MC	6.1	2.6	1.0	2.8	8.2	4.1
		PS	3.5	3.6	3.7	3.6	3.8	3.3
		ρ	1.40	1.24	1.29	1.34	1.36	1.39
150	0.3	Yield	13.6	25.2	32.5	36.0	44.9	61.9
		MC	0.7	5.9	2.1	2.7	1.7	0.6
		PS	3.9	3.6	3.4	3.6	3.8	3.1
		ρ	1.43	1.55	1.52	1.50	1.50	1.48
	4	Yield	28.4	44.1	38.3	68.3	47.4	50.0
		MC	2.8	1.9	0.3	1.9	1.8	0.4
		PS	3.6	3.6	3.8	3.6	4.0	4.3
		ρ	1.41	1.38	1.39	1.40	1.42	1.42
	9	Yield	31.2	34.0	50.4	52.5	53.3	51.6
		MC	0	1.2	0	1.2	2.8	0.4
		PS	3.7	3.9	3.5	3.7	3.5	4.0
		ρ	1.30	1.30	1.31	1.33	1.37	1.38

Yield (%), MC - Moisture Content (%), PS - Particle Size (μm), ρ - Density ($g.cm^{-3}$).

It was also possible to ascertain that increasing drug concentration does not necessarily means that particle size will increase as well. Density of powders was assessed using gas pycnometry and the results show that there is a statistical significant variability between the three different fat content milks, regardless the inlet air temperature ($p<0.01$). Moreover, in the majority of samples, when the drug concentration increases, the density also increases, but values are similar to those obtained for the control samples containing only milk.

The evaluation of theophylline-milk interaction was assessed using two different methodologies: DSC and FTIR. With the first one, for all the different fat contents considered, it was found that above 31% theophylline content (inclusive), the drug was not completely solubilized by milk components and, therefore, peaks started to appear in the thermograms. Milk thus seems to have a limited capacity to incorporate theophylline. With FTIR it was possible to assess new bonding formation between milk components and theophylline. Analysis of the 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 3120-3125 cm^{-1} region. Thus, it is difficult to assess any interaction in this region.

CONCLUSIONS

It is possible to conclude that the physical properties of spray-dried powders are not affected by the inlet air temperatures, provided that the other parameters are kept constant. Results also suggest that no interaction between theophylline and the milk components occurs.

CHALLENGES AND FUTURE WORK

The use of other model drugs with different water solubility, the assessment of the organoleptic properties and the evaluation of long term stability of spray dried powders and of the stability in use, after extemporaneous reconstitution, are warranted.

REFERENCES

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