The Milky Way: Paediatric milk-based dispersible tablets prepared by direct compression – a proof-of-concept study.

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Abstract

Objectives: Dispersible tabletsare proposed by the World Health Organisation as the preferred paediatric formulation. It was hypothesised that tablets made from a powdered milk-base that disperse in water to form suspensions resembling milk might be a useful platform to improve acceptability in children.

Methods: Milk-based dispersible tablets containing various types of powdered milk and infant formulae were formulated. The influence of milk type and content on placebo tablet properties was investigated using a design-of-experiments approach. Responses measured included friability, crushing strength, and disintegration time. Additionally, the influence of compression force on the tablet properties of a model formulation was studied by compaction simulation.

Key findings: Disintegration times increased as milk content increased. Compaction simulation studies showed that compression force influenced disintegration time. These results suggest that the milk content, rather than type, and compression force were the most important determinants of disintegration.

Conclusion: Up to 30% milk could be incorporated to produce 200 mg 10 mm flat-faced placebo tablets by direct compression disintegrating within 3 minutes in 5-10 ml of water, which is a realistic administration volume in children. The platform could accommodate 30% of a model API (caffeine citrate).

Keywords: Paediatric, milk-based, dispersible tablets, direct compression, design-of-experiments.

Introduction

Medicines for children are not always age-appropriate leading to problems with dosing, acceptability and adherence which can affect safety and efficacy of administered medicines (1, 2). With young children under 5 years old, the main issues are swallowability of intact conventional solid dosage forms, and palatability (3, 4). The World Health Organisation (WHO) proposes flexible solid oral dosage (FSOD) forms as the preferred formulations for children. FSOD forms are medicines made as solids but administrable as other forms; for example dispersible tablets, which are intended to be administered in a small volume of water, or other liquid, to young children (5).

Milk is a highly nutritive product that is known and liked by children. They usually come to know milk through breast milk which has a predominately sweet or umami taste (6-8). Breast milk and liquid milk are composed of about 88% water, with about 12% made up of fat, carbohydrates, proteins, minerals and vitamins (9). Commercially, milk obtained from different animalsources is processed by pasteurisation to obtain liquid milk. Removing water from processed liquid milk by spray-drying or other methods produces powdered milk (10).

The Food and Agricultural Organisationand the WHO classify powdered milk into three types differing mainly in their content of milk-fat. These are: (i) whole/full-cream (full-fat) milk with ≥26% weight-in-weight (w/w) milk-fat; (ii) partly-/semi-skimmed milk with milk-fat > 1.5% but <26% w/w; and (iii) skimmed milk with < 1.5% w/w milk-fat (11). Powdered milk, on reconstitution, yields a dispersion containing 8-12% w/v of milk, simulating the composition of liquid milk (9). While breast milk is recommended for children up to the age of 6 months, for children unable to be exclusively breast-fed, infant formulae are used. From 6 months to 1 year, these formulae can also be used in complementary feeding (12). There are also specialist infant formulae, for example formula with reduced lactose for infants with lactose intolerance (13).

The use of milk in pharmaceutical formulations to improve biopharmaceutical properties is reported in the literature. For instance, full-fat liquid milk has been used to provide gastro-protective effects with non-steroidal anti-inflammatory drugs (NSAIDs), andto improve solubility and bioavailability (14, 15). Powdered skimmed milk has also been similarly used to produce a prednisolone formulation with reduced gastric irritation and improved aqueous solubility (16). Liquid semi-skimmed milk has been shown to reduce the irritancy, but not bitterness, of ibuprofen (17).Powdered skimmed milk was combined with unpleasant-tasting active pharmaceutical ingredients (APIs), such as nitrazepam,in ratios ranging from 1:1 to 1 000 000:1 w/w (skimmed milk: API) to obtain taste masking, however, in association with sweeteners such as sorbitol and mannitol(18). Fewer studies have examined the material properties of powdered milk or infant formula(19-22). The compaction behaviour of the different milk typesand infant formulae, and hence, suitability as potential excipients in dispersible tablets manufactured by direct compression is thus not well understood.

Presently, it was hypothesised that a milk-based dispersible tablet that could be reconstituted in 5-10 ml of water, a typical administration volume, to produce a suspension with similar organoleptic properties as milk would improve acceptability and,subsequently, adherence in young children already familiar with milk. Further, that the ability to produce such tablets by the relatively

inexpensive direct compression technology would make these tablets accessible in resource-limited settings.

To explore this concept, several powdered milk and infant formulae were assessed for suitability for the DC production of a dispersible tablet using a design-of-experiments (DoE) approach. To be suitable for processing by DC, a powder blend must flow sufficiently well to ensure the production of tablets with uniform weights and undergo densification on the application of a compression force to form a compact. In addition, the tablets produced must meet quality/pharmacopoeial requirements. For a dispersible tablet, these include a disintegration time within 3 minutes in water at room temperature to produce a homogenous dispersion that passes through a 710 µm sieve.Blend processability and tablet characteristics are determined by a combination of blend properties (particle size and shape, size distribution, and deformation behaviour), processing (press type, compression force, and tableting speed), and environmental conditions (23, 24). DoE is a systematic and efficient approach to experimentation that involves performing experiments in a randomised manner in which several factors are simultaneously varied between certain limits and the response(s) measured. DoE is useful in mapping all possible factor combinations that maximise or minimise a response using response surface modelling in an optimisation objective (25).

The processability and tablet characteristics of a "basic" formulation consisting of powdered milk or infant formula, mannitol as a polyol filler, crospovidone as the superdisintegrant and sodium stearylfumarate as the lubricant was investigated. The influence of milk or formula type on the maximum amount of milk that can be incorporated in a placebo tablet was assessed. Caffeine citrate, used for the treatment of neonatal apnoea (26), was then included as a first model API to determine the feasibility of producing medicated milk-based dispersible tablets by direct compression. This is the first work to evaluate the flowability and compressibility of several different types of powdered milk and infant formula for the DC production of milk-based dispersible tablets as potential delivery platform for young children.

Materials and methods

Materials

Powdered milk used were: skimmed milk powder(Marvel®, Premier International Foods, UK), and full-cream milk (Nido®, Nestle, Switzerland). Powdered infant formulae were: one suitable for use from 0-6 months (Aptamil®1, Danone, UK), and a specialist milk for infants with lactose-intolerance (SMA® Lactose-Free (LF), Wyeth, UK) (Table 1). Mannitol, DC grades (Pearlitol® 300DC, and Pearlitol® 200SD; Roquette, UK); crospovidone (Polyplasdone® XL; ISP, UK); sodium stearylfumarate (Lubripharm®; SPI Pharma, USA); caffeine citrate (Fagron, UK).

Methods

Design-of-experiments

Experiment design, randomisation, regression analysis, model evaluation and optimisation were performed using a DoE software (MODDE 9.1.1, MKS Umetrics AB, Umea, Sweden). This software allows the user to input factors, and to specify their limits and experiment objective; specify responses and input results after experimentation. Based on factor limits and objective, the software suggests suitable experiments designs or models. After experimentation, the software conducts a statistical analysis of results, and allows for prediction and optimisation depending on experiment objectives.

Experiment objective and design

Experiment objective was formulation "optimisation" using a determinant optimum (D-optimum) mixture design. The optimum formulation was defined as the one with the maximum amount of milk producing a placebo tablet with a friability <1%, and a disintegration time within 3 minutes. Experiment design was the D-optimum mixture design, considered suitable as factors were proportions of a mixture which formed an irregular design region best analysed using the D-optimum design (30).

Factors and responses

Four factors (Table 2) and ten responses were specified. The responses were: angle-of-repose (α), Carr's Index (CI), and Hausner ratio (HR) for the powder blends; and disintegration time, fineness of dispersion, tensile strength, uniformity of weight, thickness, diameter, and friability for the tablets. Disintegration time was the only response used in the optimisation studies.

A total of 14 experiments with 11 formulations (N1-N11) and 3 repeats of N11 (N12-N14) were conducted in a randomised order. The formulations were of three distinct types: (i) "high-milk", (ii) "high-mannitol", and (iii) 1:1 milk and mannitol combinations. "High-milk" and "high-mannitol" corresponded to the high level setting for these factors; at the 1:1 combinations (N11-N14) – the design centre point – all factors were at their average levels. The experiments, randomisation or run order, blend properties and mean tablet weights are shown in Table 3.

Modelevaluation and optimisation

Experimental data was modelled using partial least squares regression analysis. A quadratic model was selected to facilitate the analysis of any interaction between factors. The regression equation, or model, used for data analysis was of the general form:

$$y= \beta_0+ \beta_1x_1+ \beta_2x_2+ \beta_3x_3+ \beta_{11}x_1^2 + \beta_{22}x_2^2+ \beta_{33}x_3^2 + \beta_{12}x_1x_2+ \beta_{13}x_1x_3+ \beta_{23}x_2x_3+ \varepsilon \quad (1)$$

where y = disintegration time, β_0 is the disintegration time at the design centre point, β_1 - β_3 are coefficients, $x_1 – x_3$ are the variable factors, x_i and x_j are interaction terms, x_i^2 are square terms,and ε is the residual response variable.

All models were optimised for validity and predictability. Optimisation was performed by the removal of non-significant interaction terms in the regression equation, runs with disintegration times that were outliers (standard deviation > 1.5), or one of the repeats (31). Model validity and predictive power were evaluated using two in-built statistical "diagnostic tools". The first tool was based on analysis of variance (ANOVA). Acceptance criterion with this tool was a model validity ≥ 0.25 (corresponding to a p value ≥ 0.05) which indicates no "lack-of-fit" or validity of the model used to analyse the data. The second tool used a set of four parameters to assess model suitability and predictive power (Table 4). Of these four parameters, Q^2, the goodness-of-prediction, is the most

important, and its value should be maximised. In a good (very predictive) model, R^2 and Q^2 would be as close to 1 as possible. With very good reproducibility (value > 0.9), that is very high agreement among the repeats, model validity in the first tool can be lower than 0.25. In this case, the second tool becomes very useful (31).

Formulation development and characterisation

Formulation development and characterisation

Powder particle fractions between 125 and 710 µm were used.

Pre-compression characterisation

α

This was determined using the fixed-height cone method with funnel tip maintained at 8 cm from a stainless steel base 5 cm in diameter. α was determined (n=3) using the equation:

$$\tan \alpha = 2h/d \quad (2)$$

where*h* is the height of powder cone (cm), and *d* is the diameter of the steel base (cm).

HR and CI

Tapped density measurement (n=1) was conducted according to the BP (32). HR and CI were calculated respectively as shown:

$$\mathrm{HR} = (\mathrm{Vi})/(\mathrm{Vf}) \quad (3)$$

$$\mathrm{CI}\ (\%) = [1 - (\mathrm{Vf}/\mathrm{Vi})]\ \mathrm{X}\ 100 \quad (4)$$

The calculated α, HR, and CI were then compared against reference values to provide indications of flowability, using α and HR values, and compressibility using CI values.

Blending

All ingredients except sodium stearylfumaratewere blended in a Turbula® mixer (T2F, WAB AG, Switzerland) at 32 rpm for 10 minutes. Sodium stearylfumaratewas then added followed by mixing for 5 minutes at 80 rpm in a roller mixer(PascallEngineering Ltd., UK). After pre-compression characterisation, blends for the placebo formulation werere-aerated by mixing in the Turbula® mixer at 32 rpm for 5 minutes before tabletting. The blend for the caffeine citrate formulation was not characterised and was tabletted directly.

Tabletting

Tablets were manufactured by direct compression on a single-punch press (Manesty F3, UK) equipped with round 10 mm flat-face punches. Target weight was 200 mg. Compression force was 25 kN.Tabletting speed was 70-80 tablets/minute. Batch size for the placebo tablets was 110 g; and 40 g for the caffeine citrate tablets.

Tablet evaluation

Uniformity of weight was determined as detailed in the BP (33). Acceptable tablet weight was 200 ± 15 mg. Thickness and diameter were measured using a micrometer (PK0515, Mitutoyo, Japan).

Friability was measured as described in the BP (34) using a friabilator (Erweka FR1000, Copley, UK). About 6.5 g of tablets (initial weight, W_o) were loaded and the friabilator operated at 25 rpm for 4 minutes. Tablets were de-dusted by shaking over a 1 mm sieve, and weighed (final weight, W_f). Friability was calculated as:

$$\text{Friability}\ (\%) = [(\text{Wo} - \text{Wf})/\text{Wo}]\ \text{X}\ 100 \quad (5)$$

Crushing strength was determined (n=10) using a hardness tester (Erweka TBH 200, Copley, UK) (35). Tablet tensile strength, σ_t, was then calculated using the equation proposed by Fell and Newton (36):

$$\sigma_t\ (\text{MPa}) = 2F/\pi DT \quad (6)$$

where F = crushing strength (N), D is tablet diameter (mm), and T is tablet thickness (mm).

Porosity was calculated as:

$$\text{Tablet porosity}\ (\%) = [(1 - \text{tablet solid fraction})\ \text{X}\ 100] \quad (7)$$

Solid fraction was calculated as apparent tablet density (tablet mass/volume) divided by the true density. True density was measured by helium pycnometer.

Disintegration testing was conducted using a disintegration apparatus (ErwekaZT-34, Copley,UK*).* The disintegration time was the time taken for 6 tablets to break into particles small enough to pass through the screen of the disintegration chamber. The apparatus was operated at room temperature (19-25°C). Disintegration medium was distilled water (37). Disintegration time was determined 24 hours after production following storage at controlled conditions (50% RH; 20°C).

Fineness of dispersion was determined using a modification of the BP's test for dispersible tablets (36) where the dispersion produced on disintegration was passed through a 710 µm sieve (Pascall, UK). The dispersion passed the test if there were no tablet residues left on the sieve.

The reconstitution behaviour of an optimised placebo formulation in 5 and 10 ml of water at room temperature, simulating likely use conditions, was studied. The time taken for tablets to disintegrate without stirring and the appearance of the final dispersion were noted.

Compaction simulation

The tableting behaviour of the placebo milk-based tablets was studied by compaction simulation on a rotary tablet press using a Servo-Hydraulic simulator (ESH, UK) equipped with 10-mm flat-faced tooling with tablet target weight set to 200 mg. The model formulation used in the compaction studies contained 31.5% infant formula (SMA® LF), 63% mannitol, 5% crospovidone, and 0.05% sodium stearylfumarate. Mannitol was used as a positive control and SMA® LF as a negative control.

Compatibility determinations

The solid-state stability of ingredients in the medicated formulation containing caffeine citrate was studied by differential scanning calorimetry (DSC) and Attenuated Total Reflectance Fourier-Transform Infra-Red (ATR FT-IR). A 1:1 w/w binary mixture of ingredients was prepared by vortexing (HatiRotamixer, UK) for 2 minutes before analyses.

DSC

Samples (3-8mg) were placed in non-hermetically-sealed aluminium pans (Tzero, TA, USA) and heated from 30–300 °C at a rate of 10 °C/minute under nitrogen gas purge at a flow rate of 50 ml/min (Q2000, TA, USA). Calibration for temperature and heat capacity was carried out using Indium.

FT-IR

Samples were scanned over the range 4000–650 cm^{-1} with an accumulation of 4 scans per sample at a resolution of 1 cm^{-1} (Perkin-Elmer, S100, UK).

Where the DSC thermogram or FT-IR spectrogram of the 1:1 w/w mixture was a superimposition of the individual ingredients with no new peaks or absorbance, solid state compatibility was inferred.

Results

Blend characteristics and tablet properties of the placebo formulations

The formulations had differing blend characteristics (Table 3). In terms of flow, the "high-milk" blends(≥ 94.5% milk) had α values > 40, indicative of poor flow, apart from Marvel®'swith values ≤ 34 suggesting good flow. Similarly, Marvel® was the most compressible (Carr's Index of 12-14); Aptamil® 1, Nido®, and SMA® LF had higher values of 16-25.

All tablets had acceptable mean weights (185 to 215 mg), except for one Nido® formulation (Table 3b, N13) which was slightly outside the desired range.

Disintegration time increased as the milk or formula content increased (Figures1a-d).

Marvel® produced formulations had the highest tensile strengths, with friabilities< 1% (Figure 1d), confirming Marvel® as the most compressible of the products assessed.

Most of the tablets on disintegration produced dispersions that had a few particles about 710 µm; possibly from swollen milk, or aggregated crospovidone, particles.

Placebo optimum formulations

The models used for optimisation had acceptable validity or predictive values (Table 4).

The maximum amount of milk that could be incorporated into the tablets was similar for all products, ranging from 24% for SMA® LF to 28% with Nido® (Table 5). Predicted and actual disintegration times did not exactly match, but all optimised formulations disintegrated in <3 minutes. For Aptamil® 1 and Nido®, the formulations presented in the table contained the next higher amount of milk in the simplex matrix used for optimisation. With Aptamil® 1, this was because the formulation with the highest amount of milk (27%) had a friability of 2.7%: tabletting

the formulation with the next highest amount of milk gave tablets with an acceptable friability <1%. For Nido®, the tablet with the highest amount (29% milk) disintegrated in >3 minutes (198 seconds); thus the formulation with the next higher amount of milk was tabletted.

Tablet tensile strengths differed with Marvel® produced tablets having the highest value (2.45 MPa), and Nido® produced tablets the least (0.87 MPa).

Compaction simulation

Compression force and press type affect tablet properties and disintegration time. The influence of compression force on tablet tensile strength, solid fraction, and disintegration time of a model placebo formulation under actual high-speed tableting conditions was studied by compaction simulation. The studies showed that crushing strength peaked at a compression force of about 10 kN for SMA® LF; and did not change much between 10 and 30 kN for the 1:2 mixture of SMA® LF and mannitol. The maximum tensile strength achieved for each of the formulations differed, illustrating a difference in tabletability between the infant formula and the SMA® LF: mannitol composition.Mannitol alone exhibited tensile strength increasing linearly across the range of compression forces (Figure 2a). Tablet solid fractions also increased with compression force, peaking at about 15 kN for both SMA® LF and the SMA® LF: mannitol composition. For instance, with the SMA® LF: mannitol composition, tablet solid fraction increased from 0.87 at 6.5 kNto a maximum of 0.94 at 13 kN, with a consequent decrease in porosity from 13% to 5% (Figure 2b). With the 1:2 mixture of SMA® LF:mannitol, disintegration time, and tensile strength, increased with compression force; with disintegration time increasing from about 70 seconds (1.2 minutes) at 6.5 kN to 160 seconds (2.7 minutes) at about 25 kN (Figure 2c). These studies thus indicated a positive relationship between compression force, tensile strength, solid fraction, and disintegration time.

Reconstitution behaviour

A sample of the optimisedplacebo formulation containing 28%Nido® disintegrated in about 2 minutes in 5 ml and 10 ml of water at room temperature to produce milky suspensions (Figure 3).

Formulation with an API

Having the milk-based dispersible tablet platform challenged with a BCS I API did not change disintegration time. The inclusion of a caffeine citrate (30%) did not alter the disintegration time of the platform. When compressed at 20 kNto give tablets with a friability <1%, disintegration time was < 3 minutes (Table 6).

Compatibility

The ingredients in the medicated formulation with Aptamil® 1 showed compatibility.DSC results are presented in Figure 4a-d. With Aptamil® 1, (Figure 4a), protein denaturation from Aptamil® 1 at ≈150 °C and the melting point (mp) of caffeine (164.45 °C) are visible. With sodium stearylfumarate(Figure 4b), peak shifts and the absence of its exothermic peak suggest some interactions or incompatibility. With mannitol (Figure 4c), the emergence of a new endothermic peak at 153.9 °C; different from the mp of caffeine citrate (164.45 °C) and mannitol (166.22 °C) suggest the formation of a euthetic mixture. DSC thermograms showed no interactions with crospovidone (Figure 4d), with water loss from crospovidone at ≈95 °C and the mannitolmpat ≈165 °C visible in the composite thermogram.

FT-IR results are presented in Figure 5a-d. All spectra showed no incompatibility in the solid state. For each binary mixture, the spectrum was a superimposition of the two components, and there were no changes in characteristic FT-IR absorbances.

While the results from the DSC seemed to suggest interactions between caffeine citrate and sodium stearyl fumarate, these were not detected with FT-IR. The clinical significance of the formation of a possible euthetic mixture between caffeine citrate and mannitol is not known.

Discussion

Excipients were selected based on function such as solubility and known use and lack of safety issues in children. Mannitol was used as filler-binder with sweetening action and the direct-compression grade with an average particle size of 250 µm was selected to ensure good flow (37, 38). Crospovidone was selected as the superdisintegrant of choice and was used in the recommended range (38). Sodium stearylfumaratewas selected as its relatively hydrophilic nature helps it serve as a lubricant without adversely affecting disintegration time (39). It was used here at the minimum amount of 0.5% (38). All excipients are precedented in children's medicines (41), and, in the amounts used, are generally recognised as safe (GRAS).

Powder blend flowability and compressibility are essential for tabletting by direct compression. Two simple indicators of how a powder would flow during tablettingare provided by Hausner Ratio and angle-of-repose values. A blend with a Hausner Ratio value < 1.25, or angle-of-repose < 40°, can be considered to have a flow sufficient as to be tabletted. Blends withangle-of-repose> 50° are considered not suitable for manufacturing (32). Thus, of all the "high-milk" formulations, only those of Marvel®, with angle-of-repose ≤ 34°, had suitable flowability for manufacturing by direct compression. The other "high-milk" formulations were not suitably flowable for direct compression purposes, and may need reformulation to include flow aids.

Compressibility is often predicted using Carr's Index; the lower this is, the greater the ability of the material to undergo volume reduction on the application of a load. In turn, the capacity to form tablets with tensile strengths considered acceptable – ≥ 0.8-1 MPa – is influenced by the composition of the material and compression force (42-45). A material must deform or undergo bond breakage or molecular rearrangement on application of a load and form relatively stable new bonds on load removal in order to form mechanically strong compacts. It is known that hydrophobic/oily substances oppose particle-particle bonding and can lead to low-strength compacts (46). This is thought to be the reason why the "high-milk" and 1:1 combinations of the high milk-fat containing powder blends of Nido®, Aptamil® 1, and SMA® LF produced tablets with tensile strengths < 1 MPa while the low milk-fat containing Marvel® produced tablets with tensile strengths > 1 MPa. Thus, overall, Marvel® was the most processable and tablettable milk powder. The other high milk-fat containing powder blends might benefit from the inclusion of a binder.

All optimised placebo formulations contained approximately the same amount of milk, regardless of the type. However, at a mean of 25%, one 200 mg tablet dispersed in5-10 ml of water would produce a suspension 12-16 times less concentration than reconstituted powdered milk.

One quality requirement for compressed tablets is a friability <1%. This ensures that the tablets are sufficiently robust to withstand further processing and handling during transportation and storage (34). This limit was adopted for the optimum placebo formulation and caffeine citrate tablets.

The influence of compression force on tablet properties of a reference formulation with 31.5% SMA® LF was studied using compaction simulation. This amount of milk was based on experimental data which showed that a formulation with 31.5% Aptamil®1, 63% mannitol, 5% crospovidone, and 0.5% SSF had the lowest disintegration times of all the milk-containing formulations. It was decided to substitute Aptamil® 1 with the more poorly-compressible SMA® LF to obtain information that may be applicable to the other milk and formula powders. The results suggested a positive relationship between compression force, tensile strength, and disintegration time, in agreement with other studies with tablets produced by direct compression (47-49).

Preformulation studies with caffeine citrate indicated no solid-state instability. The inclusion of this hydrophilic API (50) in the milk-based formulation still produced dispersible tablets. This was despite the fact that the spray-dried grade of mannitol with better compressibility which gave rise to tablets with a higher tensile strength was used (51). It is thought that the inclusion of the same amount of a hydrophobic API, on the other hand, if it leads to the tablet being less wettable, may prolong disintegration time. More studies are warranted.

While this work used direct compression as a low-cost production technique for the dispersible tablet, advances in tablet manufacturing mean that other relatively low-cost production techniques such as 3D printing may also be applicable for the rapid production of individualised doses of medicines using this platform in the future (52,53).

This work did not aim at a complete organoleptic evaluation of the milk-based platform. However, It is possible to include intense sweeteners such as neotame and flavours such as vanilla to improve the organoleptic properties of these milk-based tablets, and hence paediatric acceptability.

Conclusions

A milk-based dispersible tablet formulation that redisperses in water to form a suspension with similar organoleptic properties with milk might be a useful drug delivery platform to improve adherence in young children. This work demonstrated that the low-cost production of such a platform by direct compression is technically feasible. This platform can be used in the formulation of low-dose APIs, OTC products, or multivitamin preparations.

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Table 1 Differences in macronutrient composition of the four powdered milk and infant formulae assessed [Sources: 27-29]

Nutrient (typical values g/100 g powder)	MARVEL®	NIDO®	APTAMIL® 1	SMA ® LF
Protein	36.1	25.7	10	12
Carbohydrate	52.9	36.5	55	55
of which lactose	52.9	36.5	52	< 0.052
Fat	0.6	28.2	25	28

Table 2 Factors and levels in the design-of-experiment

Factor (% tage composition)	Low level (%)	High level (%)
Milk/Infant formula	0.0	97.5
Mannitol	0.0	97.5
Crospovidone	2.0	5.0
Sodium stearylfumarate	0.5	0.5

Table 3 Experimental worksheet with randomisation (run) order, composition, blend characteristics, and tablet weight for: (a) skimmed-milk powder, Marvel®, (b) full-fat milk powder, Nido® , (c) full-fat infant formula, Aptamil® 1, and (d) specialist lactose-free infant formula, SMA® LF

(a)	Run order	**Formulation composition, %**				**Blend characteristics**			**Tablet**
Exp.		Marvel®	Mannitol	Crosp	SSF	C.I	H.R	α	Weight (mg)
N1	4	0	97.5	2	0.5	12	1.1	24	208.6
N2	5	97.5	0	2	0.5	12	1.1	29	205.4
N3	10	0	94.5	5	0.5	12	1.1	23	200.6
N4*	6	94.5	0	5	0.5	14	1.2	30	202.5

N5	13	96.5	0	3	0.5	12	1.1	32	196.6
N6	9	95.5	0	4	0.5	13	1.2	34	207.2
N7	12	0	96.5	3	0.5	10	1.1	24	203.4
N8	11	0	95.5	4	0.5	13	1.2	23	203.1
N9	14	65	32.5	2	0.5	14	1.2	30	206
N10	8	31.5	63	5	0.5	13	1.1	29	204.4
N11*	3	48	48	3.5	0.5	18	1.2	27	205.8
N12	1	48	48	3.5	0.5	14	1.2	26	204.5
N13	2	48	48	3.5	0.5	14	1.2	21	206
N14	7	48	48	3.5	0.5	11	1.1	28	204.5

(b)

Exp.	Run order	**Formulation composition, %**				**Blend characteristics**			**Tablet**
		Nido®	Mannitol	Crosp	SSF	C.I	H.R	α	Weight (mg)
N1	1	97.5	0	2	0.5	25	1.3	50	205.3
N2	6	0	97.5	2	0.5	17	1.2	23	208.4
N3	11	94.5	0	5	0.5	16	1.2	54	206.2
N4*	3	0	94.5	5	0.5	13	1.2	22	211.5
N5	9	0	96.5	3	0.5	12	1.1	22	207.6
N6	12	0	95.5	4	0.5	8	1.1	23	205.4
N7	8	96.5	0	3	0.5	19	1.2	55	210.2
N8	14	95.5	0	4	0.5	16	1.2	54	202.9
N9	13	32.5	65	2	0.5	15	1.2	31	201.2
N10	4	63	31.5	5	0.5	16	1.2	63	204.3
N11	5	48	48	3.5	0.5	13	1.2	35	204.1
N12	2	48	48	3.5	0.5	14	1.2	33	210.3
N13*[1]	10	48	48	3.5	0.5	15	1.2	35	217.5
N14	7	48	48	3.5	0.5	12	1.1	39	207.5

(c)

Exp.	Run order	**Formulation composition, %**				**Blend characteristics**			**Tablet**
		Aptamil® 1	Mannitol	Crosp	SSF	C.I	H.R	α	Weight (mg)
N1	11	0	97.5	2	0.5	10	1.1	17	204.1
N2	8	97.5	0	2	0.5	17	1.2	49	199.3
N3	10	0	94.5	5	0.5	10	1.1	17	200.8
N4*	2	94.5	0	5	0.5	17	1.2	44	202.6
N5	5	96.5	0	3	0.5	17	1.2	49	205.5

N6	14	95.5	0	4	0.5	16	1.2	52	201.5
N7	13	0	96.5	3	0.5	10	1.1	18	204.2
N8	12	0	95.5	4	0.5	11	1.1	17	203.4
N9	9	65	32.5	2	0.5	10	1.1	17	208.9
N10	6	31.5	63	5	0.5	15	1.2	28	208.3
N11	1	48	48	3.5	0.5	18	1.2	25	206.6
N12	7	48	48	3.5	0.5	14	1.2	30	209
N13*	4	48	48	3.5	0.5	17	1.2	30	207.7
N14	3	48	48	3.5	0.5	15	1.2	25	209.3

(d)

Exp.	Run order	**Formulation composition, %**				**Blend characteristics**			**Tablet**
		SMA® LF	Mannitol	Crosp	SSF	C.I	H.R	α	Weight (mg)
N1	4	97.5	0	2	0.5	24	1.3	60	206.8
N2	5	0	97.5	2	0.5	7	1.1	22	207.7
N3*	9	94.5	0	5	0.5	18	1.2	56	209.2
N4	14	0	94.5	5	0.5	11	1.1	22	205.5
N5	13	0	96.5	3	0.5	9	1.1	20	207.2
N6	2	0	95.5	4	0.5	8	1.1	20	203.1
N7*	8	96.5	0	3	0.5	21	1.3	58	213.9
N8	10	95.5	0	4	0.5	24	1.3	59	205.9
N9	1	32.5	65	2	0.5	14	1.2	30	203.5
N10	11	63	31.5	5	0.5	27	1.4	48	200.8
N11	12	48	48	3.5	0.5	19	1.2	43	203.5
N12	3	48	48	3.5	0.5	13	1.2	32	197.9
N13*	7	48	48	3.5	0.5	18	1.2	40	206.1
N14	6	48	48	3.5	0.5	13	1.2	43	203.3

Notes:

∗ Experiments excluded from the regression analysis. Crosp = crospovidone, SSF = sodium stearylfumarate; C.I = Carr's Index; H.R = Hausner Ratio; α=angle of repose. 1. The variation in tablet weight could be attributable to operational error in manually adjusting the powder compression volume in the tablet press. However, as this result was excluded in the analysis, there is no influence in the interpretation of the results.

Table 4 Diagnostic values of validity and predictability for adjusted regression models used for formulation optimisation.

	R^2	**Q^2**	**R^2- Q^2**	**Model validity**	**Residual standard deviation (RSD)**
Aptamil® 1	0.975	0.92	0.055	0.95	66.84
Marvel®	0.992	0.98	0.012	0.40	97.98
Nido®	0.989	0.96	0.029	0.27	73.15
SMA® LF	0.77	0.67	0.1	<0.25	215.2

Notes: (I). Acceptable (target) values are: R^2 (Goodness-of-fit) and Q^2 (Goodness of prediction)> 0.5; R^2 - Q^2< 0.3; model validity > 0.25. (II) While SMA® LF had model validity less than the target; Q^2 was good enough for the model to be accepted.

Table 5 Composition of the optimum formulations and properties of corresponding tablets compressed at 25kN.

Formulation composition (%)				**Blend properties**			**Tablet properties**						
Milk/ Infant formula	Man	Cro	SSF	α	HR	CI	Weight (mg) (mean ± s.d)	Thickness (mm)	Diameter (mm)	Tensile strength (MPa)	Friability (%)	Disintegration time (sec)	
												Predicted	Actual
Aptamil® 1	22.58	73.12	3.8	0.5	30	1.18	15	198.6 ± 1	1.81	10.08	1.17	0.8	153	128
Marvel®	26.98	67.87	4.65	0.5	28	1.16	14	200.3 ± 3	1.81	10.05	2.45	0.7	153	127
Nido®	27.73	68.25	4.67	0.5	31	1.17	15	201.1 ± 1	1.88	10.08	0.87	0.7	128	157
SMA® LF	23.45	71.1	4.93	0.5	29	1.21	17	200.2 ± 3	1.86	10.08	1.15	0.6	170	123

Notes: Man = mannitol; Cro = crospovidone; SSF = sodium stearylfumarate; α = angle of repose; HR = Hausner Ratio; CI = Carr's Index

Table 6 Tablet properties of a milk-based formulation containing caffeine citrate as a model API

Formulation composition	**(%)**	**Amount weighed (g)**
Aptamil® 1	23	9.2
Caffeine citrate	30	12
Mannitol(Pearlitol®200 SD)	41.77	16.71
Crospovidone	4.73	1.89
Sodium stearylfumarate	0.5	0.2
	100	40
Tablet properties		
Weight uniformity (mg)		201 ± 1*
Tensile strength (MPa)		1.93 ± 0.15*
Friability (%)		0.8
Disintegration time (sec)		167

* Values are mean±s.d; n=10