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Modelling of dynamic behaviour for total parenteral nutrition

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Summary

This work is concerned with the stability of all-in-one mixtures of lipid emulsion with amino acid and carbohydrate solutions used in total parenteral nutrition, through the measurements of pH and size distribution of fat droplets. These responses have been studied in one standard mixture with the most common electrolytes added: potassium, sodium or calcium ions. They have been described by additive models ($Y = A_0 + A_1.X_1 + A_2.X_2 + A_3.X_3 + A_4.X_4$) as functions of the following influent parameters X_1:

period from the preparation of the nutritive mixture
storage temperature
electrolyte concentration
period from electrolyte addition into the mixture.

Such a modelling allows analysis and quantification of the influences of each parameter.

Introduction

Total parenteral nutrition (TPN) has been used for many years with much success in patients who cannot be fed orally or enterally. It is a process now commonly utilized in hospitals and well-controlled both by physicians and pharmacists.

In the Grenoble hospital most of the patients receive the necessary nutrients from a single source, such as a 2-litre bag containing lipids mixed with aminoacid and dextrose, plus essential electrolytes. This TPN mixture allows simplification of the regimen and prevention from local infections or metabolic disorders which may happen with separate infusion of nutrients. On the other hand, it implies perfect mastering of the behaviour of this complex emulsion (Bourin, 1981; Saubion et al., 1984).

Our study consisted of investigating the stability of these parenteral mixtures: we measured the pH and the particle size of fat globules (the emulsion must not be infused if the droplets have a size different from physiological chylomicra) (Whateley et al., 1984).

We have studied the variation of those two responses, depending on the storage period and the addition of common electrolytes, Na^+, K^+ and Ca^{2+} to the ternary mixtures containing lipids, amino acids and dextrose.

Materials and Methods

Materials

Ternary mixtures. Two mixtures have been pre-

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TABLE 1

Composition and properties of mixtures

	Mixture A	Mixture B
Lipids *	500 ml	500 ml
Dextrose 30% **	750 ml	750 ml
Dextrose 50% **	250 ml	250 ml
Amino acids A ***	500 ml	-
Amino acids B ****	-	500 ml
Volume	2000 ml	2000 ml
Calories	2300 ml	2300 ml
Nitrogen	12,5 g	10 g
Calories/gN	184	230
Osmolality	1400 mOsm	1400 mOsm

Provided by:
* Kabivitrum: 93160 Noisy le Grand - France
** Delmas: 37170 Chambray les Tours - France
*** Roger Bellon: 92201 Neuilly S/Seine - France
**** Egic: 45203 Montargis - France

pared (mixture A and mixture B) (Table 1).

Electrolytes. Three electrolytes have been added to the mixture: Na^+, K^+ (chloride solutions) and Ca^{2+} (gluconate solution) at 3 different concentrations.

Containers. The mixtures have been stored in single-use bags made of copolymers of ethylene and vinyl acetate (EVA) (U.S.P. XIX).

Preparation of the mixtures. The EAV bags were filled in an aseptic room under a laminar air flow, by qualified operators wearing appropriate sterile uniforms. The 3 essential components were put into each bag with nitrogen normally used for medical purposes and sterilized by filtration (0.22 μm). The bags were stamped and stored in a cold room (+4°C). The electrolytes were added just before the infusion, according to the metabolic needs of each patient.

Methodology used to investigate the stability of TPN mixtures

Two ternary mixtures have been prepared: mixture A (containing amino acid A) and mixture B (containing amino acid B) (see Table 1); the stability has been studied by the measurement of pH (pH meter Tacussel TS 4N) and the number of globules (per 10^{-3} mm^3) having a diameter greater than 2 μm (Coulter counter SII), and the following parameters P_i have been considered:

(a) Storage period of ternary mixtures: P_4. The mixtures have been kept at +4°C for 1, 2, 3 or 4 weeks before addition of electrolytes into the bag.

(b) Concentration of added electrolyte: P_1. Three concentrations have been studied for each cation: 13.4 mM, 26.8 mM and 80.4 mM. Parameter P_1 has been defined as a reduced concentration with levels 1, 2 and 6.

(c) Storage period after addition of electrolyte: P_2. Three different conditions of storage period have been chosen: 24 h, 48 h and 72 h.

(d) Storage temperature after addition of electrolyte: P_3. Two temperatures have been tested: +4°C and +20°C.

Modelling

For each ternary mixture supplemented with a given electrolyte, 90 experiments were performed on each bag among the 4 chosen as a sample. These experiments correspond to all the possible combinations of the levels for the four parameters. For any ternary mixture with any electrolyte studied here, we assumed initially a second-degree model for describing the pH and the logarithm of the droplet size characteristic:

$$Y = a_0 + a_1.P_1 + a_2.P_2 + a_3.P_3 + a_4.P_4 + a_{11}.P_1^2 + a_{22}.P_2^2 + a_{33}.P_3^2 + a_{44}.P_4^2 + a_{12}.P_1.P_2 + a_{13}.P_1.P_3 + a_{14}.P_1.P_4 + a_{23}.P_2.P_3 + a_{24}.P_2.P_4 + a_{34}.P_3.P_4 + \text{residues}$$

in which the residues have to be normally distributed with mean zero.

In fact, the determination of the significant effects and interactions by using a t-test (Box, 1978) showed that both the responses may be described by a linear response model:

$$Y = b_0 + b_1.P_1 + b_2.P_2 + b_3.P_3 + b_4.P_4 + \text{residues}$$

with differences between the model and experiments which do not exceed 10% for pH and 20% for logarithm of droplet size characteristics.

The significance of coefficient b_i is as follows:

TABLE 2

Reproducibility check

Sample	1	2	3	4
b_0	1.74	1.95	1.90	1.96
b_1	0.16	0.12	0.13	0.12
1000 b_2	14.6	9.94	9.62	8.82
1000 b_3	8.93	6.62	6.63	7.42
b_4	0.32	0.34	0.35	0.32

b_1 is the response variation corresponding to the addition of 13.4 mmol electrolyte in 1 liter of ternary mixture,

b_2 is the response variation for 1°C rise in temperature,

b_3 is the response variation for an increase of 1 h in the storage period before electrolyte addition,

b_4 is the response variation per week of storage period after electrolyte addition.

TABLE 3

Model coefficients

	pH			Coalescence		
	K^+	Na^+	Ca^{2+}	K^+	Na^+	Ca^{2+}
Mixture A						
b_0	7.29	7.31	7.06	1.71	1.95	1.77
1000 b_1	−42.2	−53.1	−73.5	62.3	47.0	126
1000 b_2	−4.88	−7.53	−5.80	12.4	8.45	9.80
1000 b_3	−0.20	−0.31	−0.12	7.48	7.44	6.30
b_4				0.29	0.28	0.30
Mixture B						
b_0	7.42	7.36	7.45	2.16	2.14	1.94
1000 b_1	−57.1	−70.5	−79.4	43.7	48.8	124
1000 b_2	−6.72	−12.7	−7.00	5.51	7.55	9.48
1000 b_3	−8.52	−8.06	−11.6	3.88	6.56	6.89
b_4	−0.29	−0.24	−0.33	0.36	0.35	0.34

Results

The values of coefficient b_i have been calculated by using a multilinear regression analysis. For each response, the agreement between the b_i

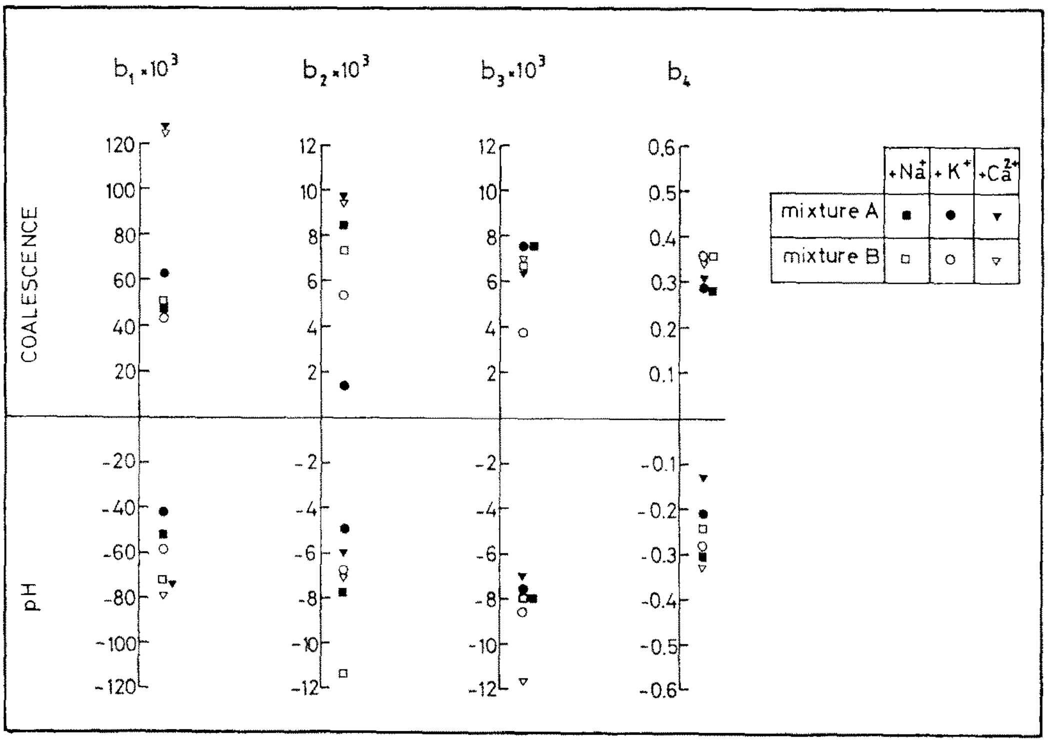

Fig. 1. Comparison of electrolyte behaviour from model coefficients.

values deduced from each bag of a same nutrition mixture is quite satisfactory. It has been shown elsewhere for the pH of mixture A with KCl, NaCl or calcium gluconate (Antonelli et al., 1986). It is illustrated here by Table 2 for the parameter related to coalescence in mixture B added with calcium.

We shall list here only the mean values of each coefficient for all the studied cases (Table 3). Another report of these results is given by Fig. 1 in order to point out more easily the analogies and the differences between the studied mixtures.

Discussion

For the different sorts of mixtures all the coefficients corresponding to principal effects are negative in the case of pH and positive for the coalescence. Physically it means that pH decreases linearly every time one of the parameters enhances; on the contrary the studied number of fat globules increases under the influence of each parameter. A decrease in pH values can be explained by partial hydrolysis of lecithines into isolecithines. Considering the degradation of the tensioactive agent, the emulsion is less stable and a coalescence phenomenon develops more and more when pH decreases (Hakansson, 1986).

The evolution of pH and size droplet characteristics is about the same for both amino acid solutions A and B (although solution B contains 3 organic acids which are not included in A): amino acids have a positive influence on stability, due to their buffer capacity (Black and Popovich, 1981).

Concerning the nature of electrolyte added to the mixture: it is shown that Na^+ and K^+ induce less variation than Ca^{2+} on pH values and fraction of fat globules studied, which confirms Schulze and Hardy's theory about valency of elements, (Dawes and Gloves, 1978).

K^+ is the least destabilizing monovalent ion: storage period after addition of ion, temperature, and even concentration have the least effect on T.P.N. mixture containing K^+.

This can be explained by ionic radius lengths: 13.3 nm for K^+ and 9.5 nm for Na^+. Since this value is smaller for Na^+ than for K^+, attractive forces (Van der Waals) between fat droplets may be greater.

Conclusion

The stability of T.P.N. mixtures containing the essential nutrients (amino acids, dextrose, lipids) to which the most common electrolytes were added, can be investigated by different methods (Scherbel, 1986); we have used the measurements of pH and size of fat globules. Our study shows the influence of all parameters which have been considered in these experiments:

-nature of electrolyte
-concentration of electrolyte
-storage period (before and after addition of ionic solutions)
-storage temperature.

This modelling allows to quantify precisely the influence of each parameter and to determine the best conditions of conservation of T.P.N. mixtures used in hospitals, in order to provide a better quality and efficiency to the patients.

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