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Research Article

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Stability evaluation of lipid nanocapsules in parenteral nutritional mixture

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ABSTRACT

Olive and soybean oils are commonly used in parenteral nutrition. Lipid NanoCapsules based on vegetal oils (vo-LNC) can be used to allow both an easy dispersion of the oily phases in water and an improvement of parenteral mixture stability. To evaluate the stability of vo-LNC by size measurement, we chose to inspire us from the storage conditions and measurement intervals of the guideline of international conference on harmonization (ICH); stability testing of new drug substances and products Q1A(R2). Results showed that the size of vo-LNC was stable which allows safe administration by parenteral use.

Keywords: Lipid NanoCapsules, Parenteral nutrition, vegetal oils, Stability, Ripening.

INTRODUCTION

Lipid NanoCapsules based on vegetal oils (vo-LNC) are very stable nanometric devices for lipidic encapsulated components [1-7]. Their structure is an hybrid between polymeric nanocapsules and liposomes because of their oily core which is surrounded by a tensioactive rigid membrane, they have a lipoprotein-like structure. These properties confer great stability to the structure [1, 6-9].

In parenteral nutrition the lipid emulsions are usually presented separately from other nutrients [10-13]. The mixture of lipid emulsion with electrolytes, amino acids and glucose is made just before or during the administration since the stability of this mixture does not exceed 24 hours [14, 15].

Two oils are commonly used in parenteral nutrition: olive and soybean oils. vo-LNC can be used to allow both an easy dispersion of the oily phases in water and an improvement of parenteral mixture stability [5, 6].

The size evaluation of vo-LNC based on the olive and soybean oils showed evidence of a ripening process. More precisely, it is the variation of size control coefficients of each components of parenteral nutrition after mixture which showed evidence of a ripening process [5].The ripening process exploration of vo-LNC suggest a long time stability [6].

In this work, we chose to evaluate the stability of vo-LNC in water and in parenteral nutritional mixture. The selected storage conditions and measurement intervals are inspired from the guideline of international conference on harmonization (ICH); stability testing of new drug substances and products Q1A(R2) [16, 17]. The purpose is to show that the size of vo-LNC is stable which allow safe administration by parenteral use.

EXPERIMENTAL SECTION

Instruments and Reagents

Lipoïd® S75-3 (soybean lecithin at 69% of phosphatidylcholine) with an average molecular weight of 800 was a gift from Lipoïd GmbH (Ludwigshafen, Germany). The lipophilic Labrafac® WL 1349 (capric and caprylic acid

triglycerides) with an average molecular weight of 512g.mol^{-1} and the Solutol® HS 15 (mixture of free polyethylene glycol 660 and 12-hydroxystearate of polyethylene glycol 660) with an average molecular weight of 911g.mol^{-1} were kindly provided by Gattefosse S.A. (Saint-Priest, France) and BASF (Ludwigshafen, Germany), respectively. The water used was ultrapure grade from a Milli-Q plus system (Millipore, Paris, France). Olive oil was provided by European Pharmacopoeia. Soybean oil was provided by Sigma-Aldrich. Amino acids 10 % Baxter®. Glucose 50 % B Braun®. Sodium chloride 20 % Aguettant®. Potassium chloride 15 % Biosedra®. Calcium 10 % Aguettant®.Magnesium 15 % Aguettant®. Phosphate monopotassique 13,6 % Renaudin®.

For the preparation of LNC, the material used was: a stirring and heating plate (Ikamag® RCT basic), a sensor for precise control of temperature (Ikatron® ETS-D4 fuzzy). For25°C and 40°C storage conditions, a stove (Memmert UM100, Germany) was used. For 5°C storage condition, a refrigerator (Frank, Switzerland), was used .For the size control of LNC Zetasizer 3000HS (Malvern Instruments, France) was used.

Preparation of vo-LNC

LNC was prepared by a phase-inversion temperature method (PIT) [1, 4, 8, 18]. The PIT method was first introduced by Shinoda and Saito (1969) and is now widely used in industry [1, 18].

This low energy and solvent-free method use the particular ability of emulsions stabilized by polyethoxylated nonionic surfactants to undergo a phase inversion following a variation of temperature. The transitional phase inversion occurs, when, at a fixed composition, the relative affinity of the surfactant for the different phases is changed and controlled by the temperature. As a result, oil-in-water (o/w) macro-emulsion undergoes a phase inversion to a water-in-oil (w/o) one during a temperature increasing, and vice versa [18].

Hence, the PIT method consists in suddenly break-up such a microemulsion network by performing, at the PIT, a rapid cooling and/or a sudden water dilution. This stage is considered as an irreversible process since it leads to the generation of the kinetically stable LNC. This great stability is due to the fact that the steric stabilization prevents the droplets fiocculation and therefore coalescence [1, 4, 18].

For the preparation of the vo-LNC the formula was Olive oil 11,2%, soybean oil 2,8%, Labrafac® 6%, Solutol® 25%, Lipoïd® 1,5% and water 53,5% [5].

The first step to form the particles consisted of magnetic stirring of all the components while heating from ambient temperature to 85 °C at a rate of 4 °C/min. Three cycles of progressive heating and cooling in between 85 and 60 °C at a rate of 4 °C/min were realised. The second step was a fast cooling-dilution process by cold water (0±1°C) in order to divide the hot initial structure. Then, a slight magnetic stirring was applied to the nanocapsule suspension during 5 min [2].

Parenteral nutritional mixture

The chosen parenteral nutritional mixture was the one revealing the highest increase in average size of vo-LNC during 28 days[6]. This parenteral nutritional mixture contains : 2 % of amino acids, 11,9% of glucose, 5,5% of vo-LNC, 0,5% of electrolytes and 80,1% of water [6].

Storing conditions and size determination of vo-LNC

The size determination of vo-LNC in water or inparenteral nutritional mixturewas determined by the Zetasizer 3000HS. The size is an obvious criterion of control of dispersions, which can be used to show the great stability of vo-LNC [1, 19]. In both cases, in water dispersion and in parenteral nutritional mixture, vo-LNC are stored at 5°C, 25°C and 40°C.The size measurement of vo-LNC is made at day 0, 1, 2, 3, 4, 7, 15, 30, 60, 120, 180 and 360.

RESULTS AND DISCUSSION

Values of mesured size are done as good result quality by Malvern Dispersion Technologie Software 5.10. The size evolution of vo-LNC in water stored at 5°C, 25°C and 40°C showeda fluctuation of the size between day 0 and day 7 (Fig. 1). Table I showed that at worst, this size fluctuation is between 44,22nm (at 5°C) to 49,18nm (at 40 °C), under 4%. After the day 7, the average size of vo-LNC was stabilized (Fig. 1). Table I shows that, in average, vo-LNC size was stabilized at 44,42 nm when stored at 5°C, at 44,77 nm when stored at 25°C and at 46,12 nm when stored at 40°C, under 0,05%.

In the same way, the size evolution of vo-LNC in parenteral nutritional mixture stored at 5°C, 25°C and 40°C showed a fluctuation of the size between day 0 and day 15 (Fig. 2). Table II shows that at worst, this size fluctuation is between 49,19 nm (at 5°C) to 54,73 nm (at 40 °C), under 5%. After the day 15, the average size of vo-LNC

stabilizes (Fig. 2). Table II shows that, in average, vo-LNC size was stabilized at 49,85 nm when stored at 5°C, at 50,73 nm when stored at 25°C and at 51,81 nm when stored at 40°C, under 0,19%.

As we can see, the general profile of the evolution of the size is similar in both cases, in water and in parenteral nutritional mixture (Fig. 1 and 2).The difference is that the stabilization of the size of vo-LNC in water appears from day 7 and for vo-LNC in parenteral nutritional mixture appears from day 15.

In both cases, the ripening process affected the vo-LNC in a very limited way as it can be demonstrated by the small fluctuations of the size before the day 30, under 5%. This small size fluctuation of vo-LNC can't be interpreted as classical Ostwald ripening or the coalescence [6, 20, 21]. This is related to the tensioactive rigid membrane with lipoprotein-like structure [1]. After the day 30 the stability of vo-LNC in water or in parenteral nutritional mixture is clearly demonstreted by considering the low variation of the size, under 0,19%.

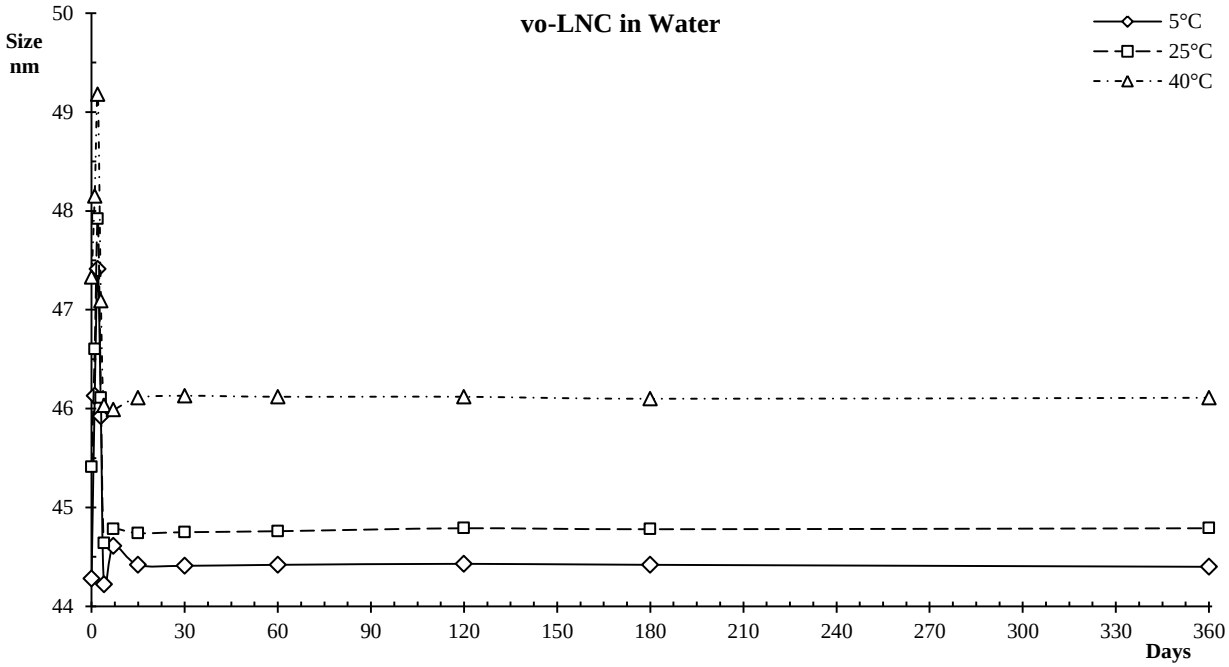

Figure 1: Size evolution of vo-LNC in water stored at 5°C, 25°C and 40°C

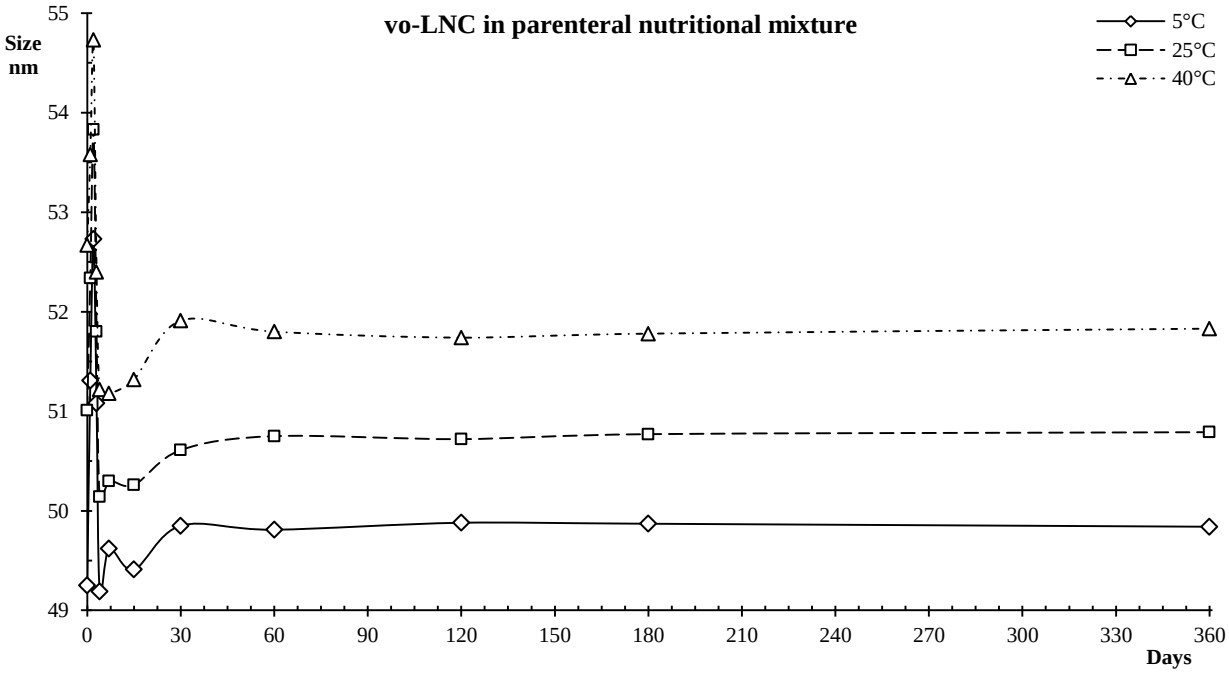

Figure 2: Size evolution of vo-LNC in parenteral nutritional mixture stored at 5°C, 25°C and 40°C

Table I. Size values of vo-LNC dispersed in water

Days	Storedat5°C ± 3°C/			Storedat 25°C± 2°C/			Storedat 40°C ± 2°C		
	Size nm	Average size nm	Highest variation %	Size nm	Average size nm	Highest variation %	Size nm	Average size nm	Highest variation %
0	44,28	45,43	4%	45,41	45,91	4%	47,33	47,30	4%
1	46,13			46,60			48,15		
2	**47,41**			**47,92**			**49,18**		
3	45,92			46,11			47,09		
4	44,22			44,64			46,03		
7	44,61			44,78			45,99		
15	44,42	44,42	0,03%	44,74	44,77	0,05%	46,11	46,12	0,03%
30	44,41			44,75			**46,13**		
60	44,42			44,76			46,12		
120	**44,43**			**44,79**			46,12		
180	44,42			44,78			46,10		
360	44,40			**44,79**			46,11		

Table II. Size values of vo-LNC dispersed in parenteral nutritional mixture

Days	Storedat 5°C ± 3°C/			Storedat 25°C± 2°C/			Storedat 40°C ± 2°C		
	Size nm	Average size nm	Highest variation %	Size nm	Average size nm	Highest variation %	Size nm	Average size nm	Highest variation %
0	49,25	50,37	5%	51,01	51,38	5%	52,67	52,44	4%
1	51,31			52,34			53,58		
2	**52,73**			**53,83**			**54,73**		
3	51,08			51,80			52,40		
4	49,19			50,14			51,22		
7	49,62			50,30			51,18		
15	49,41			50,26			51,32		
30	49,85	49,85	0,06%	50,61	50,73	0,12%	**51,91**	51,81	0,19%
60	49,81			50,75			51,80		
120	**49,88**			50,72			51,74		
180	49,87			50,77			51,78		
360	49,84			**50,79**			51,83		

CONCLUSION

As expected, the evaluation of the stability of vo-LNC showed a very low fluctuation of size in all storage conditions (5°C, 25°C and 40°C) confirming the great stability in water and in parenteral nutrition mixture.

The components of parenteral nutritional mixture don't lead to the destabilization of the vo-LNC because it competes with the steric effect which prevents the droplets flocculation and therefore coalescence.

The small impact of ripening process associated to the stability of the size after day 30, even stored at 40°Cbeyond 6 months (Accelerated ICH conditions) at 25°Cduring 12 months (Long term ICH conditions), suggests that it can be administered safely by parenteral use.

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