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# Formulation of parenteral nutrition based on argan oil nanocapsule system using d-optimal mixture design

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ABSTRACT

In parenteral nutrition, the lipid emulsions are usually presented separately from other components. The admixture is made just before or during administration because of limited stability. The purpose of the present study is the formulation of lipid nanocapsules (LNC) based on Argan-oil and their introduction into preparations for parenteral nutrition, then the evaluation of their stability. The lipid nanocapsules have been prepared according to the phase inversion temperature method. The experimental design was used to determine the feasibility of LNC with Argan oil (A.O.-LNC), the evaluation of their size and the stability in the final mixing parenteral nutrition. The average size of the LNC was chosen as a response. The LNC based on 14% Argan oil, 6% Labrafac ®, 55% water and 25% of Solutol ® with an average size of 44 nm was selected for the preparation of the parenteral nutrition. The particle size distribution with a value of 70 nm and a polydispersity index of 0.102 indicates the homogeneity of the populations of particles. The statistical analysis shows the excellent stability of parenteral nutrition for 14 days.

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## INTRODUCTION

Parenteral nutrition (P.N.) is a mixture of solutions that include amino acids, dextrose, vitamins, electrolytes, trace elements, minerals and lipid emulsion. The P.N. is induced in patients with the impossibility to assure adequate nutritional support through enteral way (Lappas *et al.*, 2017; Fell *et al.*, 2015). These patients are classified as having an intestinal failure. In the field of health care, a Total Nutrient Admixture (TNA), as known as 3-in-1 formulation, is the most used. Lipids are one of the components of P.N., which are incorporated separately to other compounds, and we talk about 2-in-1 formulation. The TNA formulation permitted to reduce cost, risk of microbial contamination and improve stability of the mixture (Lappas *et al.*, 2017; Rahali *et al.*, 2010).

Vegetable oils are known for their essential energy source, and they are used as a lipid component for P.N. formulation and incorporated separately to other compounds in the form of injectable emulsions (Bensouda, 2008). The lipid typically used is soybean oil which has been partly replaced with olive oil as a second approach (Raman *et al.*, 2017).

The substitution of soybean oil in the current P.N. is particularly essential. This is because of the reduced percentage of polyunsaturated fatty acids, the richness in alpha-tocopherol, the maintenance of the membrane status in fatty acids and finally the minimisation of hepatobiliary disorders associated with parenteral nutrition in animals (Garnier-Chevereau

**Table 1: Lower and upper limits of ao-LNC components used to made experimental design.**

| Nutritional constituent | Lower limit ( %) | Upper limit ( %) |
|---|---|---|
| Argan oil | 15 | 30 |
| Solutol® | 5 | 30 |
| Lipoïd® | 1.5 | 1.5 |
| NaCl | 1.78 | 1.78 |
| Water | 50 | 70 |

**Table 2: Lipid nanocapsules size with gradual inclusion of Labrafac®. Constant components for all formulations: Solutol ® 25 %, Lipoïd® 1.5 %, NaCl 1.78 % and water 55 %.**

| Formula | (a) | (b) | (c) | (d) | (e) | (f) |
|---|---|---|---|---|---|---|
| Labrafac ®% | 00 | 20 | 04 | 06 | 08 | 10 |
| Argan oil % | 20 | 00 | 16 | 14 | 12 | 10 |
| Average size of LNC (nm) | 352 | 47 | 331 | 44 | 49 | 49 |

**Table 3: Lower and upper limits of nutritional components used to make experimental design**

| Nutritional constituent | Lower limit ( %) | Upper limit ( %) |
|---|---|---|
| Lipids (prepared LNC) | 2.8 | 5.6 |
| Amino acids | 2 | 4 |
| Glucose | 8 | 12 |
| Electrolytes | 0.5 | 0.7 |
| Water | 78 | 87 |

**Table 4: Experimental fields for the evaluation of stability of vo-LNC in PN mixture**

| Run | Nutrients for parenteral nutrition % | | | | |
|---|---|---|---|---|---|
| | Lipid | Amino acids | Glucose | Electrolytes | Water |
| 1 | 2.8 | 2 | 8 | 0.5 | 86.7 |
| 2 | 5.5 | 3 | 9.9 | 0.6 | 81 |
| 3 | 5.5 | 3.9 | 11.9 | 0.5 | 78.2 |
| 4 | 5.5 | 2 | 11,9 | 0.5 | 80.1 |
| 5 | 4.8 | 2.5 | 9 | 0.6 | 83.1 |
| 6 | 4.2 | 3.9 | 9.9 | 0.6 | 81.4 |
| 7 | 4.2 | 3 | 11.9 | 0.6 | 80.4 |
| 8 | 4.8 | 3.5 | 9 | 0.6 | 82.1 |
| 9 | 4.8 | 3.5 | 10.9 | 0.6 | 80.2 |
| 10 | 3.5 | 2.5 | 10.9 | 0.6 | 82.5 |
| 11 | 3.5 | 3.5 | 9 | 0.6 | 83.5 |
| 12 | 5.5 | 2 | 8 | 0.5 | 84 |
| 13 | 5.5 | 2 | 8 | 0.5 | 84 |
| 14 | 2.8 | 3.9 | 8 | 0.5 | 84.8 |
| 15 | 4.2 | 3 | 9.9 | 0.6 | 82.3 |
| 16 | 2.8 | 3.9 | 11.9 | 0.5 | 80.9 |

 

**Table 5: Experimental fields with responses for the evaluation of stability vo-LNC in PN mixture.**

| Run | Average size of ao-LNC (nm) at | | | |
|---|---|---|---|---|
| | D0 (PdI*) | D1 (PdI) | D4 (PdI) | D14 (PdI) |
| 1 | 58(0.078) | 63 (0.085) | 63 (0.085) | 62 (0.099) |
| 2 | 70 (0.125) | 82 (0.130) | 73 (0.113) | 72 (0.149) |
| 3 | 70 (0.109) | 83 (0.119) | 78 (0.122) | 79 (0.132) |
| 4 | 70 (0.116) | 83 (0.130) | 75 (0.114) | 76 (0.142) |
| 5 | 63 (0.118) | 76 (0.120) | 72 (0.100) | 71 (0.118) |
| 6 | 67 (0.091) | 71 (0.133) | 69 (0.102) | 68 (0.142) |
| 7 | 68 (0.081) | 81 (0.098) | 74 (0.088) | 73 (0.118) |
| 8 | 67 (0.117) | 78 (0.120) | 72 (0.115) | 70 (0.118) |
| 9 | 70 (0.139) | 80 (0.116) | 75 (0.131) | 77 (0.137) |
| 10 | 65 (0.082) | 71 (0.060) | 67 (0.064) | 68 (0.096) |
| 11 | 62 (0.074) | 68 (0.077) | 66 (0.077) | 65 (0.090) |
| 12 | 63 (0.132) | 69 (0.120) | 65 (0.114) | 65 (0.125) |
| 13 | 62 (0.139) | 66 (0.130) | 66 (0.137) | 65 (0.123) |
| 14 | 61 (0.063) | 68 (0.091) | 65 (0.076) | 66 (0.104) |
| 15 | 64 (0.088) | 72 (0.112) | 69 (0.107) | 68 (0.120) |
| 16 | 69 (0.084) | 76 (0.100) | 72 (0.064) | 72 (0.097) |
| Average size of ao-LNC (nm) by day | 66 | 74 | 70 | 70 |
| Global Average size of ao-LNC (nm) | | | 70 | |

*PdI: Polydispersity Index.

**Table 6: Experimental fields with responses for the formulation of ao-LNC (Average size = 0 means that phase separation was occurred).**

| Run | Argan oil ( %) | Solutol® ( %) | Water ( %) | Average size (nm) |
|---|---|---|---|---|
| 1 | 25 | 5 | 70 | 0 |
| 2 | 30 | 15 | 55 | 0 |
| 3 | 30 | 5 | 65 | 0 |
| 4 | 20 | 10 | 70 | 0 |
| 5 | 30 | 10 | 60 | 0 |
| 6 | 25 | 10 | 65 | 0 |
| 7 | 15 | 20 | 65 | 0 |
| 8 | 20 | 25 | 55 | 353 |
| 9 | 25 | 20 | 55 | 432 |
| 10 | 15 | 25 | 60 | 0 |
| 11 | 25 | 15 | 60 | 0 |
| 12 | 20 | 20 | 60 | 387 |
| 13 | 20 | 15 | 65 | 0 |
| 14 | 15 | 30 | 55 | 0 |
| 15 | 20 | 30 | 50 | 0 |
| 16 | 25 | 25 | 50 | 0 |
| 17 | 30 | 20 | 50 | 0 |

**Table 7: Significance of the results and mathematical model used.**

| | Model | F0,05 | p Value | Significance for alpha at 5% | R-Squared (R2) | Precision |
|---|---|---|---|---|---|---|
| Day 0 | Linear | 24.57 | <0.0001 | Significant | 0.89 | 18.20 |
| Day 1 | Linear | 12.42 | 0.0005 | Significant | 0.81 | 12.51 |
| Day 4 | Linear | 17.69 | <0.0001 | Significant | 0.86 | 15.58 |
| Day 14 | Linear | 17.48 | <0.0001 | Significant | 0.86 | 15.41 |

F0.05: Fisher'sexact test for alpha at 10 %.

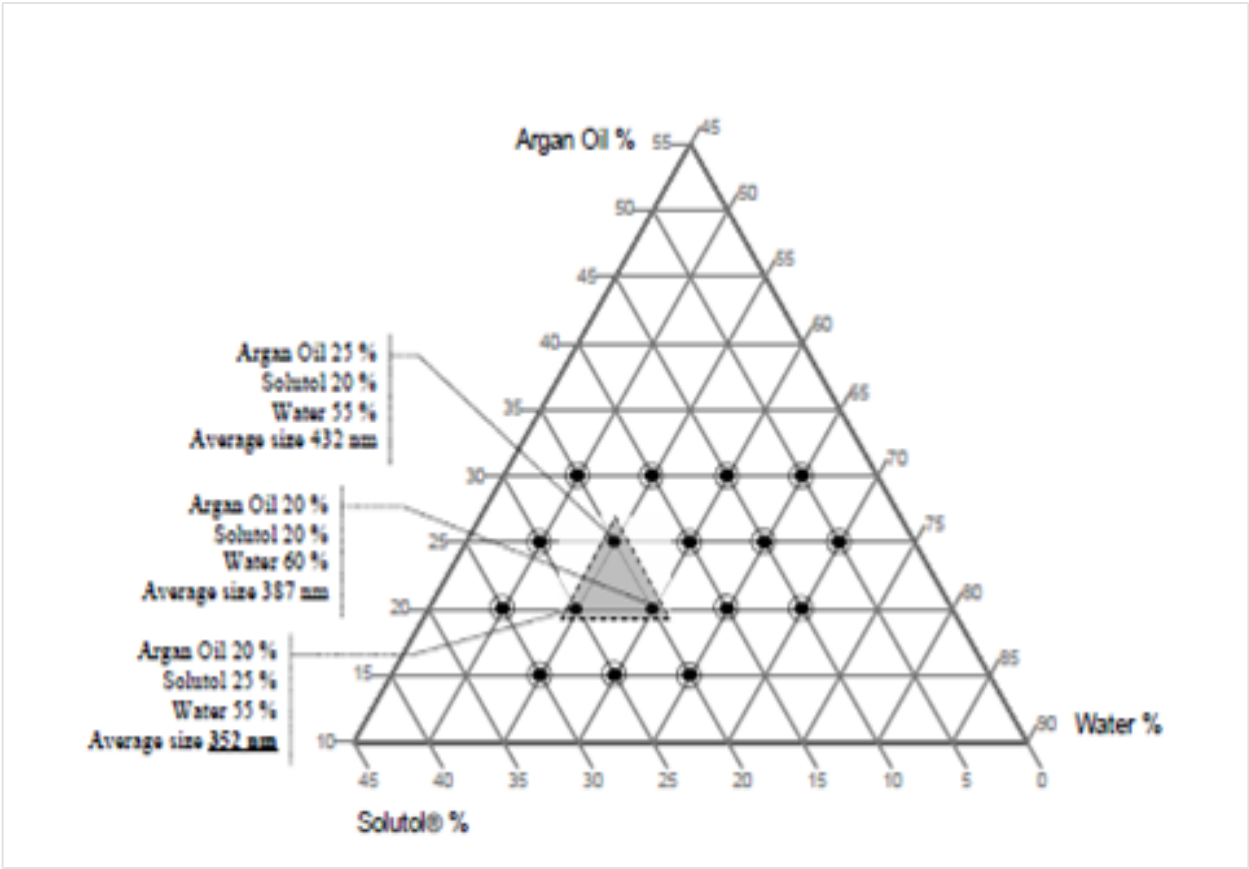


**Figure 1: Feasibility zone for the formation of ao-LNC**

*et al.*, 1991; Rössle *et al.*, 1992).

In 2008, an invention was patented; the objective of which was the introduction of Argan Oil (A.O.) for the first time into P.N. and enteral nutrition. The P.N. took the form of injectable lipid emulsion (Bensouda, 2008).

Argan oil is well known for its nutraceutical properties; it contains essential fatty acids, which play an indispensable role in human health promotion. The triacylglycerols are the main constituent of Argan oil, and the primary fatty acids are oleic, linoleic, stearic, and palmitic. All those considerations justified the use of Argan oil for P.N. preparations, which may provide a remarkable nutritional value (Abbassi *et al.*, 2014; Bensouda, 2008).

Nanotechnology has become one of the most promising technologies to revolutionise nanomedicine and pharmaceutical science fields. The encapsulation is a potential approach in the field of nanotechnology and a new process in which lipid droplets are recovered by a crust or enclosed in a matrix to create nanoparticles with size less than 1000 nm. According to the definition of NNI (National Nanotechnology Initiative), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix "nano" is commonly used for particles of several hundred nanometers. There are today different types of nanocarriers used in nanomedicine that differ according to their composition, form or structure (Ferreira and Nunes, 2019).

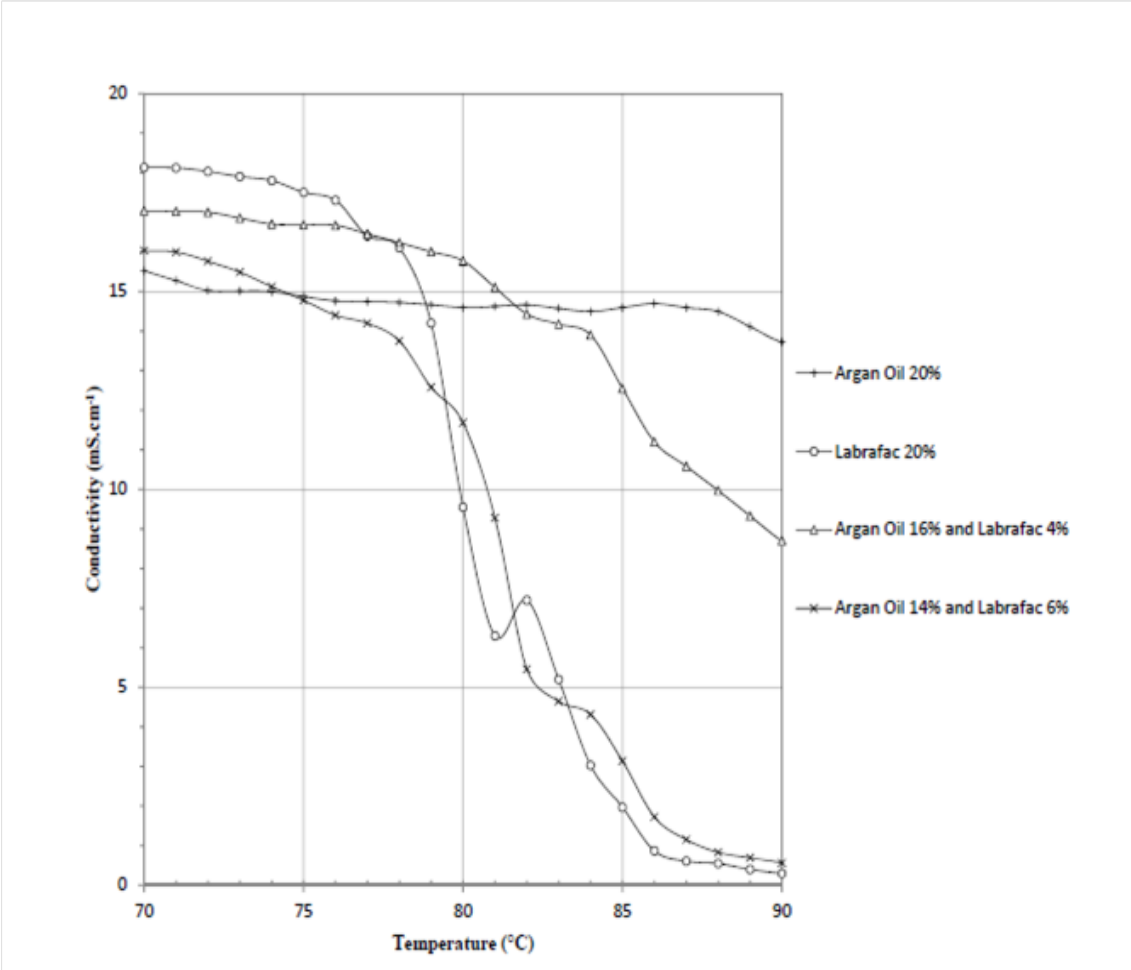


**Figure 2: Conductivity variations of the emulsions with different oil phase according to the temperature**

Among these carriers, the lipid nanocapsules (LNCs) which have been initially prepared according to phase inversion temperature method, their size ranges from 20 to 100 nm, and they are characterised by an oily core, corresponding to medium-chain triglycerides, surrounded by tensioactive rigid membrane (Huynh *et al.*, 2009; Rahali *et al.*, 2010). The LNCs present the advantages to be highly stable with a functional drug loading capacity and the possibility of scaling up their production quickly (Clavreul *et al.*, 2018).

The aim of the present study is the formulation of LNCs based on argan oil, which allows a good dispersion of the oily phase in water and the evaluation of their size using an experimental design. However, in this study, we are not targeting industrial production, but we are on a development scale.

## MATERIALS AND METHODS

### Reagents

The LNC is based on two phases and surfactant. The oily phase consists of Labrafac WL 1349 ® (capric and caprylic acid triglycerides), it was provided from Gattefossé S.A. (Saint-Priest, France) and the Argan oil (Pharmaceutical grade) which was purchased from TARGANTE with ECOCERT label. The aqueous phase mainly constituted of ultrapure water from a Milli-Q Plus system (Millipore, Paris, France). The Lipoïd S75-3 ® (soybean lecithin at 69 % of phosphatidylcholine) (purchased from Lipoïd GmbH (Ludwigshafen, Germany) was used as a surfactant. Another nonionic surfactant, Solutol HS 15 ® (a mixture of polyethene glycol 660 and 12-hydroxy stearate of polyethylene glycol 660) used for this study and provided from BASF (Ludwigshafen, Germany), it was a significant influence on LNC formation and stability (Heurtault *et al.*, 2002, 2003).

Furthermore, other components used were: Glucose 50 % (B Braun). Potassium chloride 15 % (Biosedra). Amino acids 10 % Baxter. Magnesium 15 % Aguettant. Sodium chloride 20 % (Aguettant). Phosphate monopotassique 13.6 % (Renaudin). Calcium

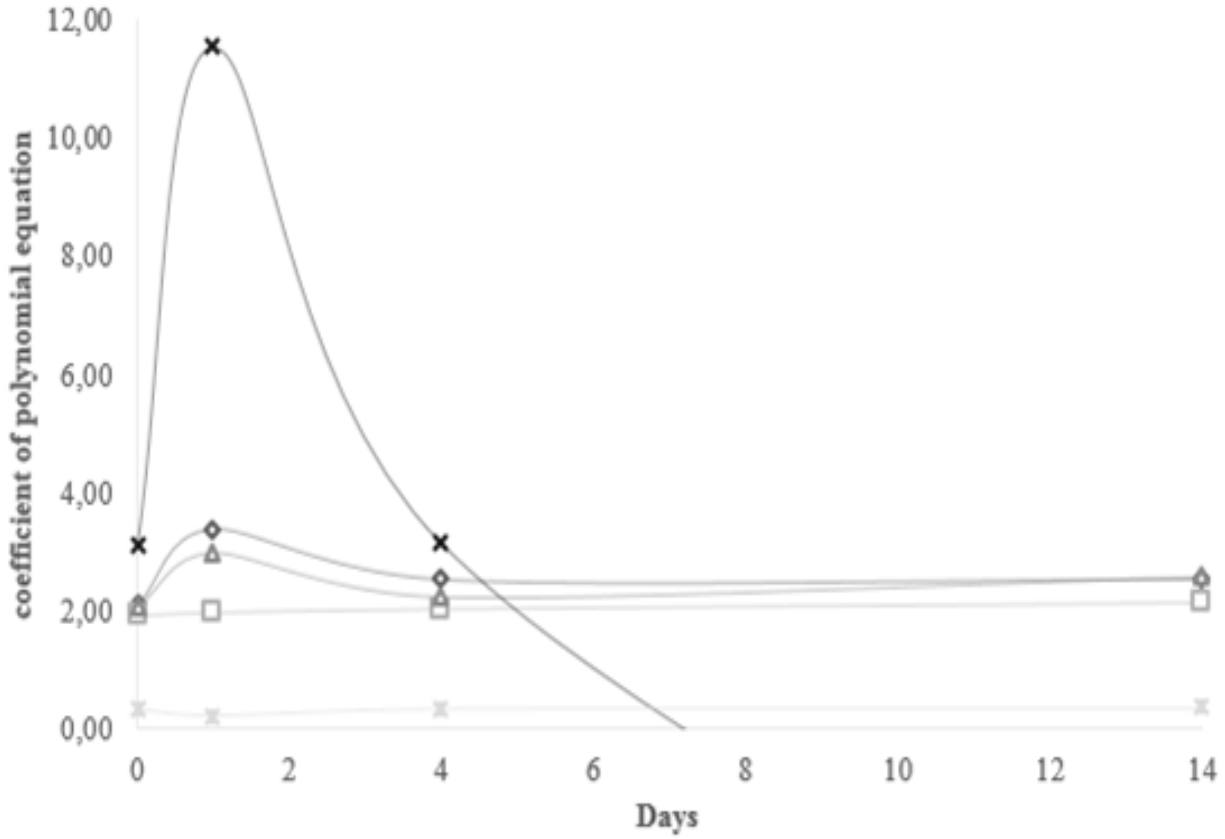


**Figure 3: Variationof size control coefficients of each parameters during 14 days after mixture. -Electrolytes - Lipid - Glucose - Amino acids - Water**

10 % (Aguettant).

**Materials**

The LNC was prepared using a stirring, heating plate (Ikamag RCT basic) and a sensor for precise control of temperature (Ikatron ETS-D4 fuzzy). The particle size was measured by Zetasizer 3000HS (Malvern Instruments, France). Cyber Scan PC510 measured the variation of conductivity with temperature.

**Preparation of LNC based on argan oil (A.O.-LNC)**

The preparation of Nanocapsules has been widely discussed and described in the literature (Huynh *et al.*, 2009). The LNC was prepared according to the Phase-Inversion Temperature (PIT) method, which is developed and described by K. (Shinoda and Saito, 1969) Shinoda. This technique provides stable fines emulsions, and an average size ranged from 100 to 4000 nm (Benoit *et al.*, 2012).

The above process generates lipid Nanocapsules constituted of an oily core, related to Labrafac®. The cohesive membrane is made up of the mixture of Lipoid® anchored in the oily phase formed by Argan Oil and Solutol®. The PIT technic is based on the changes in solubility of a nonionic surfactant according to the temperature (Huynh *et al.*, 2009; Rahali *et al.*, 2010). The molecule of surfactant has a large, positive, spontaneous curvature forming an oil in water emulsion at low temperature. In this case, the conductivity value is around 35 mS/cm at high temperature; the spontaneous curvature becomes negative. It forms a water/oil emulsion accompanied by a rapid decrease of conductivity value, lower than ten $\mu$S/cm and zero. However, a stable high steady-state reflects that the water continuous phase is reached (Morales *et al.*, 2003; Solans *et al.*, 2005).

The formulation feasibility of the A.O.-LNC was carried out according to an experimental design using software Design-Expert®. It permits calculation for factorial designs and drawing graphs for design evaluation. Furthermore, the design expert provides maximum information from a limited number for experiments (Lorentz *et al.*, 2014). The size of LNC was selected as an output parameter and measured after 48h. Table 1 shows the limits of LNC components selected as factors. The Labrafac®, which increases LNC size, was added gradually in a lipidic fraction at different amounts to optimise the size of A.O.-LNC, as shown in Table 2. The addition of NaCl decreases the PIT of LNC as described by Amir A. Mehrdad Sharif (Sharif *et al.*, 2012).

### Evaluation of A.O.-LNC stability in P.N. preparation

A D-optimal design (mixture design) was used to evaluate the effect of P.N. compounds on the size of LNC. The lower and upper limits of nutritional components were fixed, as presented in Table 3 to make this experimental design. The limits were chosen based on the general composition of nutritional admixtures and formulas for P.N. (Carpentier, 2009; Yailian *et al.*, 2019).

The studied factors were the amounts of lipids (prepared LNC), amino acids, glucose, electrolytes and water. The design expert allows the matrix of 16 formulations at different amount of all compounds as shown in Tables 4 and 5.

The soybean oil has been used in PN preparation since its adaptation in Europe with approval in 1961 (Raman *et al.*, 2017). In this paper and owing to reasons explained above, argan oil substituted the soybean oil at the same amount.

### Statistical analysis

The statistical analysis of variance, the R-Squared and precision was done. The mathematical modelling of response by polynomial equation at day 0, day 1, day 4 and day 14 was made by design expert.

## RESULTS AND DISCUSSION

### Formulation of LNC based on Argan oil (ao-LNC)

To optimize the formulation of ao-LNC and the proportions of the constituents, a ternary diagram was established using Design Expert ®. The software permitted the formulas of 17 mixtures as shown in Table 5.

The amount of NaCl in water was fixed at 1.78% because of its influence on the temperature of phase inversion during the formulation process. For Lipoïd® percentage, it was fixed at 1.5% as long as it does not influence on particle size (Heurtault *et al.*, 2003).

By fixing the amount of the two components, a feasibility zone of ao-LNC was determined as a triangle, which proportions were comprised from 20 to 25% of Argan oil, 20 to 25% of hydrophilic surfactant and 55 to 60% of water as described in Figure 1. In the domain of feasibility, an increase of Argan oil amount leads to an increase of particle size. However, the percentage of water has no effect on particle diameter. Conversely, a percentage of 25% of solutol® allows the formulation of ao-LNC with the smallest average size (352 nm) as described by Huynh et al. Furthermore, the properties at the triglyceride/water interface of the hydrophilic surfactant leads to a considerable decrease of average particle diameter, this phenomenon may justified the outcome (Huynh *et al.*, 2009; Heurtault *et al.*, 2003). On other hand, the amphiphilic properties of this compound reduce the effect of the oil as described by Heurtault et al. (Heurtault *et al.*, 2003).

The eighth preparation in Table 6 with an average size of 352 nm that contained 25% of Solutol®, 20 % and 55 % of water, was selected to determine the emulsion inversion zone. A gradual introduction of Labrafac® from 4 to 20% has permitted the preparation of ao-LNC. The Table 2 shows the average size after Labrafac ® inclusion.

The emulsion (a) with 20% of Argan oil shows a constant variation of conductivity that remains higher than 10 $\mu$S.cm-1. Such result indicates the absence of emulsion inversion. Where the 20% of oil were replaced by Labrafac ® in (b) formula, the emulsion presented a zone inversion as shown in the Figure 2. The (c) formula including 16% of Argan Oil and 4% of Labrafac ® show an intermediate status compared to previous formulas.

The last formulation (d) show a profile comparable to (b) formula, this preparation with an optimum amount of Labrafac ® (6%) which composed of capric and caprylic acid triglycerides, allows the TIP and an average size of LNC of 44 nm. Our outcome is comparable to the results published by Rahali who used Labrafac ® for the formulation of LNCs based on olive oil and soybean oil at the same proportion (Rahali *et al.*, 2010).

### Evaluation of stability of LNC in PN

### Mathematical modeling

The formulation including 6% of Labrafac ® and 14% of Argan oil, 25% of Solutol ®, 1.5% of Lipoïd®, 1.78% of NaCl and 55% of water, was selected to the preparation of PN. Experiments were carried out to determine the mathematical relationship between the studied factors influencing the PN based on ao-LNC. The response of average size of LNC in PN at Day 0, Day 1, Day 4 and Day 14 was expressed by a linear equation with X1(amino acid), X2(Glucose), X3 (Lipids), X4 (Electrolytes) and X5 (Water):

$$Y(\text{LNC Size}_{D0}) = 1.92X1 + 2.07X2 + 2.10X3 + 3.10X4 + 0.35X5$$

$$Y(\text{LNC Size}_{D1}) = 1.97X1 + 2.98X2 + 3.39X3 + 11.53X4 + 0.21X5$$

$$Y(\text{LNC Size}_{D4}) = 2.04X1 + 2.25X2 + 2.54X3 + 3.13X4 + 0.35X5$$

$$Y(\text{LNC Size}_{D14}) = 2.15X1 + 2.58X2 + 2.54X3 - 5.36X4 + 0.36X5$$

Considering the five studied factors given by our linear equation at day 1, it has been noticed that electrolytes are the coefficient that affects the most

LNC particle size after mixing all parenteral nutrition components, this factor has no effect on the last day ($14^{th}$) of the experiment as shown in Figure 3. According to this results, we can conclude that the stability of ao-LNC was not influenced by the component of PN.

**Polydispersity Index**

The particle size distribution and polydispersity index (PdI) of lipid-based nanocarriers are highly important physical parameters that affect product performance, stability and appearance of finished product. Also known as the heterogeneity index, Polydispersity index (PdI) is a parameter used to define the size range of the lipidic nanocarrier systems. The term polydispersity is used to describe the degree of non-uniformity of a size distribution of particles and can also indicate nanoparticle aggregation (Clayton *et al.*, 2016; Danaei *et al.*, 2018).

As shown in Table 5 the PdI is ranged from 0.060 to 0.146 after mixture for all points at Day 0, Day 1, Day 4 and Day 14. On other hand, the average size of LNC was 44 nm before mixture with a PdI of 0.112 which become 70 nm after mixture with PdI of 0.102 for all points at Day 0, Day 1, Day 4 and Day 14. As described in literature, the PdI numerical value ranged from 0.0 to 1.0. In drug delivery formulations using lipid-based carriers, a PdI of 0.3 and less is acceptable and indicates a homogenous population of particles (Danaei *et al.*, 2018). Such conclusion confirms that our results are good. As regards the particle size, there has been a global 50% increase of average size in all studied mixtures, this outcome may be justified by a steric effect as explained by Rahali (Rahali *et al.*, 2010).

**Statistical analysis**

To confirm the validity of the physical stability of the LNC mixed with PN, a statistical analysis of variance (ANOVA) at 5% was made by Design Expert® as shown in Table 7. A model was considered significant if the p-value was <0,05. The precision that measures the signal to noise should be more than 4. Our values are greater than 12.60. The model F-value of 24.57 implies that the model is significant. Moreover, a value greater than 0.81 of R-Squared (R2) is reasonable and acceptable.

For all this consideration, it can be concluded that our ao-LNC based PN is stable during the 14 days of the experiment.

## CONCLUSIONS

During recent years, Argan oil has found its place in medical use due to its nutritional properties. In PN, the formulations currently available are based on soybean and olive oils. The purpose of the present study was introducing Argan oil into PN using LNCs which are considered as an adequate system to vegetable oil encapsulation inside an aqueous core. The encapsulation allows the advanced introduction of lipids in PN, especially since these components do not influence the stability of the preparation. This stability may be optimized for a possible sterilization or storage in the hospital sector. Our study will continue in the sense to optimizing the levels of surfactants to avoid potential toxicity.

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**Conflict Of Interest Statement**

We declare that we have no conflict of interest.

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