INTRODUCTION

In recent years, it has got to be clear that the advancement of novel medications is decisive for ensuring the advancement in medical treatment. The data obtained in the in vitro studies are often trailed by disappointing results in the in vivo or clinical circumstance. Predominant reasons for this failure are the insufficient drug levels in the body due to its rapid metabolism, the high medication poisonous quality in view of broad distribution, and a high fluctuation of plasma medication levels [1].

A few methodologies have recently been explored to create nanosized drug delivery systems. These systems can be partitioned into two gatherings: polymeric and lipid systems [2]. The quantity of items in view of polymeric nanoparticles in the business sector is restricted in light of the poisonous qualities of polymers, what’s more, the absence of suitable expansive scale generation strategies. All together to conquer these issues, a lot of hope has been centred on lipid-based carriers, for example, nanoemulsions (NEs) and nanostructured lipid carriers (NLCs). NEs are medication conveyance systems comprising of emulsified oil and water systems with mean droplet diameters ranging from 50 to 1000 nm. Generally, the normal droplet size is somewhere around 100 and 500 nm and can exist as oil-in-water (o/w) or water-in-oil (w/o) form, where the internal phase is either oil or water, separately [3, 4]. These systems have points of interest for medication conveyance, for example, the utilization of physiologically tolerated lipids, large-scale production, prevent the medications from destruction, enhanced bioavailability, and controlled-release qualities [5]. The flaws of NEs are poor drug loading capacities, medication deterioration during storage and they have physical instability that can be increased by the joined drug [6, 7]. NLCs made out of a strong lipid matrix with a certain content of a fluid lipid are another era of lipid nanoparticles. NLCs are viewed as a more advanced era of nanoparticles, which have enhanced properties for drug loading, adjustment of the delivery profile, and stable medication during storage [8-11]. Because of the lipophilic content of the NLCs, they are considered especially helpful in the administration of lipophilic medications.

Broadly speaking, energy is normally required in emulsion formulation in light of the fact that the procedure may be non-spontaneous. The creation of nanoemulsions expenses more energy than that required to deliver macroemulsions [12].

High-energy emulsification routines make utilization of instruments that use high mechanical energy to make nanoemulsions with high kinetic energy. The mechanical instruments make serious disruptive forces which separate the oil and water stages to make Nano-sized droplets. This can be accomplished with ultrasonicators, micro fluidizer and high shear Homogenizers [13-15]. Molecule size here will rely on the type of instruments utilized and their working conditions like time and temperature alongside sample properties and compositions [16].

The objective of the present work was to study the effect of certain formulation factors on the size of NLCs and NEs in order to realize the optimum formulation factors that give the optimum particle size. 

MATERIALS AND METHODS

Materials

Naterol GMS® (Glyceryl stearate) as solid lipid, Dermarol DCO® is an ester of decyl alcohol and oleic acid (Decyl Oleate), Dermarol CCT® is a mixed triester of glycerin and Caprylic and Capric acids (Caprylic/Capric triglyceride) as liquid lipids and Tween 80® (Polysorbate80) as-surfactant were obtained from CISME Italy s. n. c. via Marcora, Milano-Italy. Span 20® (Sorbitan monolaurate) as-surfactant, and Lechthin® (cosurfactant). All other chemicals are of HPLC grade.

Preparation of NLCs and NEs

NLCs and NEs were prepared by high shear homogenization method [17, 18]. Briefly, the lipid phase consisted of Naterol GMS, as solid lipid in case of NLC was melted at 80 °C and then mixed with the liquid lipid Dermarol DCO® for Dermarol CCT® and added to the Oily surfactants (Span 20 and Lechthin), or the liquid lipids Dermarol

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DCO® or CCT® Dermarol CCT® in case of NE was added to the Oily surfactants (Span 20 and Lechitin). An aqueous surfactant phase consists of Tween 80 was heated up to the same temperature of the molten lipid phase. The hot surfactant solution was poured onto the hot lipid phase and homogenization was carried out at 12,000 or 18,000 rpm for 4 cycles (2 min with 30 s off) using high shear homogenizer (IKA T25 digital Ultra-Turrax Germany). Then leave to cool to room temperature.

| NLC formula code prepared at 12 000 rpm | NLC formula code prepared at 18 000 rpm | Naterol GMS (w/w%) | Dermarol DCO® (w/w%) | Tween/Span |
|----------------------------------------|-----------------------------------------|--------------------|-----------------------|-------------|
| NLC1*                                  | NLC13*                                  | 90%                | 10%                   | 2.5/1       |
| NLC2*                                  | NLC22*                                  | 80%                | 20%                   | 2.5/1       |
| NLC3*                                  | NLC32*                                  | 70%                | 30%                   | 2.5/1       |
| NLC4*                                  | NLC42*                                  | 60%                | 40%                   | 2.5/1       |
| NLC5*                                  | NLC52*                                  | 50%                | 50%                   | 2.5/1       |
| NLC6*                                  | NLC62*                                  | 40%                | 60%                   | 2.5/1       |
| NLC7*                                  | NLC72*                                  | 30%                | 70%                   | 2.5/1       |
| NLC8*                                  | NLC82*                                  | 20%                | 80%                   | 2.5/1       |
| NLC9*                                  | NLC92*                                  | 10%                | 90%                   | 2.5/1       |
| NLC1*                                  | NLC13*                                  | 90%                | 10%                   | 10/1        |
| NLC2*                                  | NLC23*                                  | 80%                | 20%                   | 10/1        |
| NLC3*                                  | NLC33*                                  | 70%                | 30%                   | 10/1        |
| NLC4*                                  | NLC43*                                  | 60%                | 40%                   | 10/1        |
| NLC5*                                  | NLC53*                                  | 50%                | 50%                   | 10/1        |
| NLC6*                                  | NLC63*                                  | 40%                | 60%                   | 10/1        |
| NLC7*                                  | NLC73*                                  | 30%                | 70%                   | 10/1        |
| NLC8*                                  | NLC83*                                  | 20%                | 80%                   | 10/1        |
| NLC9*                                  | NLC93*                                  | 10%                | 90%                   | 10/1        |

| NLC formula code prepared at 12 000 rpm | NLC formula code prepared at 18 000 rpm | Naterol GMS (w/w%) | Dermarol CCT® (w/w%) | Tween/Span |
|----------------------------------------|-----------------------------------------|--------------------|----------------------|-------------|
| NLC10*                                 | NLC10*                                  | 90%                | 10%                  | 2.5/1       |
| NLC11*                                 | NLC11*                                  | 80%                | 20%                  | 2.5/1       |
| NLC12*                                 | NLC12*                                  | 70%                | 30%                  | 2.5/1       |
| NLC13*                                 | NLC13*                                  | 60%                | 40%                  | 2.5/1       |
| NLC14*                                 | NLC14*                                  | 50%                | 50%                  | 2.5/1       |
| NLC15*                                 | NLC15*                                  | 40%                | 60%                  | 2.5/1       |
| NLC16*                                 | NLC16*                                  | 30%                | 70%                  | 2.5/1       |
| NLC17*                                 | NLC17*                                  | 20%                | 80%                  | 2.5/1       |
| NLC18*                                 | NLC18*                                  | 10%                | 90%                  | 2.5/1       |
| NLC10*                                 | NLC10*                                  | 90%                | 10%                  | 10/1        |
| NLC11*                                 | NLC11*                                  | 80%                | 20%                  | 10/1        |
| NLC12*                                 | NLC12*                                  | 70%                | 30%                  | 10/1        |
| NLC13*                                 | NLC13*                                  | 60%                | 40%                  | 10/1        |
| NLC14*                                 | NLC14*                                  | 50%                | 50%                  | 10/1        |
| NLC15*                                 | NLC15*                                  | 40%                | 60%                  | 10/1        |
| NLC16*                                 | NLC16*                                  | 30%                | 70%                  | 10/1        |
| NLC17*                                 | NLC17*                                  | 20%                | 80%                  | 10/1        |
| NLC18*                                 | NLC18*                                  | 10%                | 90%                  | 10/1        |

Table 1: NLC prepared at 12 000 and 18 000 rpm using liquid lipid dermarol DCO® and different surfactant ratio

Table 2: NLC formulae prepared at 12 000 and 18 000 rpm using liquid lipid Dermarol CCT® and different surfactant ratio
Table 3: NE formulae prepared at 12 000 and 18 000 rpm using different concentrations of liquid lipids Dermarol DCO®, Dermarol CCT® and different surfactant ratio

| NE Formula code prepared at 12 000 rpm | NE Formula code prepared at 18 000 rpm | Dermarol DCO® (w/w%) | Dermarol CCT® (w/w%) | Tween/Span |
|----------------------------------------|----------------------------------------|-----------------------|-----------------------|------------|
| NLC14                                  | NLC14*                                 | 50%                   | 50%                   |            |
| NLC15                                  | NLC15*                                 | 40%                   | 60%                   |            |
| NLC16                                  | NLC16*                                 | 30%                   | 70%                   |            |
| NLC17                                  | NLC17*                                 | 20%                   | 80%                   |            |
| NLC18                                  | NLC18*                                 | 10%                   | 90%                   |            |

Particle size analysis

Particle size analysis of NLC and NE were carried out using Laser diffraction particle size analyzer (LD, Master size Malvern Instruments Ltd. Worcestershire, UK) at 25 °C. Before the analysis carried out, samples were diluted using distilled water.

RESULTS AND DISCUSSION

Preparation of NLCs and NEs

Different methods are used for the preparation of NLCs and NEs [19, 20]. In the present study, we had adopted a cost-effective, simple and reproducible method for the preparation of nanoemulsions, i.e. High shear homogenization method [17, 18].

NLCs were composed of 5(w/w %) Natrol GMS and Dermarol DCO® or Dermarol CCT® used in different concentrations and stabilized by 1(w/w %) Lecithin as co-surfactant and different ratios of surfactant concentrations Tween 80 and Span 20 (2.5/1, 5/1, 10/1, 15/1) w/w %, while NEs were composed of 5(w/w %) Dermarol DCO® and Dermarol CCT® used in different concentrations and stabilized by 1(w/w %) Lecithin as co-surfactant and different ratios of surfactant concentrations Tween 80 and Span 20 (2.5/1, 5/1, 10/1, 15/1) w/w %.

Effect of surfactants ratios on particle size

Fig. [1-12] presents the obtained results for the effect of surfactant ratio on the particle size of NEs and NLCs. Firstly, Fig. 1, 2 demonstrate that the best NEs obtained using the surfactant concentration ratio 2.5/1 (w/w%). While Fig. 3, 4 demonstrate that the best NLC obtained using the surfactant concentration ratio 5/1, (2.5/1) w/w %. A similar results were reported by Wulff-Perez et al. [21] who found that at high surfactant concentrations, some surfactant molecules may
increase the local osmotic pressure, which causes moving of continuous phase between some droplets to them, and this cause depletion of the continuous phase between the drops and the aggregation happened and so the particle size increase. While different results were reported by Chanana et al. [22] Who found that increasing surfactant concentration leads to decrease in particle size of nanoparticles. Fig. [5-12] presents the effect of each surfactant concentration ratio on the particle size of NEs and NLCs.

Fig. 1: Effect of surfactant ratio on the particle size of nanoemulsions (NEs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)

Fig. 2: Effect of surfactant ratio on the particle size of nanoemulsions (NEs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)

Fig. 3: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)
Fig. 4: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)

Fig. 5: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)

Fig. 6: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)
Fig. 7: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)

Fig. 8: Effect of certain surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 12 000 rpm (mean±SD, N=3)

Fig. 9: Effect of certain surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)
Fig. 10: Effect of certain surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)

Fig. 11: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)

Fig. 12: Effect of surfactant ratio on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared using homogenization speed at 18 000 rpm (mean±SD, N=3)
Effect of lipid type and concentration

Normally NEs formulate by using two liquid lipids only without solid lipid. While NLCs formulate by using solid lipid and liquid lipid, so we studied the effect of lipid concentrations on NEs particle size and the effect of lipid type and concentration on NLCs particle size. In our study, we used two liquid lipids Dermarol DCO® and Dermarol CCT® in different concentration to prepare NEs and the same liquid lipids each one separately with Natemol GMS as solid lipid to prepare NLCs.

Fig. [13–28] presents the obtained results of the effect of lipid type and concentration on the size of particles. Fig. [13,14,16–17,19 and 20] demonstrate that NLCs prepared by using liquid lipid Dermarol CCT® gave the smallest NLCs particle size, but only figs. 15 and 18 demonstrate that the best NLCs particle size resulted with Dermarol DCO® as liquid lipid, the study presents that by increasing the concentration of liquid lipid the particle size of NLCs decrease. A similar results were reported by Puglia, et al. and (Mu and Feng, 2003) who suggested that the addition of liquid lipid to solid lipid tends to promote the formation of small particle population, which may be due to increasing in molecular mobility of the matrix after liquid oil addition [23, 24]. Different results were reported by Soleimanian et al. [25] who suggested that particle size increase by increasing the liquid oil concentrations due to the more disordered crystalline structure inside the nanoparticles. Fig. [21-28] comparisons between NEs and NLCs prepared at different homogenization speed. It was found that the best NEs resulted when we increase Dermarol CCT® concentration and decrease Dermarol DCO® concentration, while the best NLCs obtained when we use Dermarol CCT® as liquid lipid.
Fig. 16: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) prepared with a surfactant ratio (15/1) (mean±SD, N=3)

Fig. 17: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) prepared with a surfactant ratio (2.5/1) (mean±SD, N=3)

Fig. 18: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) prepared with a surfactant ratio (5/1) (mean±SD, N=3)

Fig. 19: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) prepared with a surfactant ratio (10/1) (mean±SD, N=3)
Fig. 20: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) prepared with a surfactant ratio (15/1) (mean±SD, N=3)

Fig. 21: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (2.5/1) (mean±SD, N=3)

Fig. 22: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (5/1) (mean±SD, N=3)
Fig. 23: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (10/1) (mean±SD, N=3)

Fig. 24: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (15/1) (mean±SD, N=3)

Fig. 25: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (2.5/1) (mean±SD, N=3)
Fig. 26: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (5/1) (mean±SD, N=3)

Fig. 27: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (10/1) (mean±SD, N=3)

Fig. 28: Effect of lipid type and concentration on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (15/1) (mean±SD, N=3)
Fig. 29: Effect of homogenization speed on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (2.5/1) (mean±SD, N=3)

| Lipid ratio | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|-------------|----|----|----|----|----|----|----|----|----|----|
| NE at 12000 rpm | 220 | 200 | 170 | 170 | 170 | 170 | 169 | 160 | 150 |
| NE at 18000 rpm | 100 | 170 | 170 | 165 | 160 | 159 | 165 | 160 | 155 |
| NLC (DCO) at 12000 rpm | 1624 | 1401 | 506 | 454 | 459 | 458 | 218 | 216 | 209 | 179 |
| NLC (DCO) at 18000 rpm | 1795 | 1002 | 555 | 364 | 200 | 190 | 169 | 165 | 165 | 159 |
| NLC (CCT) at 12000 rpm | 1449 | 624 | 189 | 180 | 178 | 166 | 165 | 162 | 160 |
| NLC (CCT) at 18000 rpm | 578 | 394 | 330 | 174 | 173 | 168 | 165 | 164 | 163 |

Fig. 30: Effect of homogenization speed on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (5/1) (mean±SD, N=3)

| Lipid ratio | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|-------------|----|----|----|----|----|----|----|----|----|----|
| NE at 12000 rpm | 324 | 317 | 238 | 222 | 177 | 167 | 161 | 160 | 157 |
| NE at 18000 rpm | 958 | 794 | 788 | 441 | 388 | 317 | 167 | 157 | 156 |
| NLC (DCO) at 12000 rpm | 1162 | 466 | 453 | 413 | 391 | 340 | 284 | 239 | 182 |
| NLC (DCO) at 18000 rpm | 964 | 929 | 653 | 490 | 432 | 175 | 173 | 169 | 161 |
| NLC (CCT) at 12000 rpm | 541 | 531 | 474 | 469 | 181 | 171 | 178 | 168 | 158 |
| NLC (CCT) at 18000 rpm | 996 | 925 | 740 | 685 | 632 | 597 | 535 | 212 | 158 |

Fig. 31: Effect of homogenization speed on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions (NEs) prepared with a surfactant ratio (10/1) (mean±SD, N=3)

| Lipid ratio | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |
|-------------|----|----|----|----|----|----|----|----|----|----|
| NE at 12000 rpm | 497 | 448 | 467 | 339 | 333 | 277 | 252 | 234 | 208 |
| NE at 18000 rpm | 439 | 435 | 218 | 215 | 193 | 191 | 189 | 187 | 181 |
| NLC (DCO) at 12000 rpm | 637 | 547 | 480 | 443 | 314 | 309 | 268 | 255 | 233 |
| NLC (DCO) at 18000 rpm | 1748 | 1101 | 220 | 223 | 269 | 192 | 187 | 173 | 166 |
| NLC (CCT) at 12000 rpm | 696 | 216 | 210 | 190 | 189 | 187 | 186 | 184 | 183 |
| NLC (CCT) at 18000 rpm | 1225 | 1104 | 998 | 790 | 596 | 400 | 180 | 178 | 165 |
Effect of homogenization speed

Results of the effect of homogenization speed on the particle size of NEs and NLCs are illustrated in fig. [29–32]. This fig. reveal that increasing the homogenization speed from 12 000 to 18 000 rpm. Led to decrease the particle size of NEs and NLCs.

A similar result was obtained by Kovacevic et al. [26] who found that smaller particle size are obtained by increasing the homogenization speed which may be attributable to the increased force of deforming droplets at higher speed results in a decrease of particles. A different result was obtained by Lander et al. [27] who found that smaller particle sizes are acquired by increasing the processing temperatures because of the lowered viscosity of the lipid phase, the increase of the homogenization speed resulted in an increase of the particle size due to particle coalescence, this occurred because of the high kinetic energy of the particles. It was found that the best NEs and NLCs particle size obtained at homogenization speed 18 000 rpm.

NLCs formulated at surfactant concentration ratio 2.5/1 (w/v %) present that the mean particle size of the resulted formulations when using homogenization speed 12 000rpm ranging from 162 nm to 179 nm while the mean particle size of the resulted formulations when using homogenization speed 18 000 rpm ranging from 1795 nm to 158 nm.

**Fig. 32: Effect of homogenization speed on the particle size of nanostructured lipid carriers (NLCs) and nanoemulsions(NEs) prepared with a surfactant ratio (15/1) (mean±SD, N=3)**

**CONCLUSION**

Different formulative of factors which influenced the size of particles of NEs and NLCs prepared by high shear homogenization method were successfully studied. The results suggested the importance of controlling the critical formulation and process parameters during formulation such as (type of liquid lipids, homogenization speed, and surfactant concentration ratio) as they greatly affected the particle size of the final prepared nanoparticles. The optimum NEs resulted when we use Dermarol CCT® as liquid lipid and surfactant ratio 2.5/1(w/v %) with homogenization speed 18 000 rpm. While the optimum NLCs obtained when we increase Dermarol CCT® concentration and use surfactant ratio 2.5/1(w/v %) with homogenization speed 18 000 rpm.

**AUTHORS CONTRIBUTIONS**

Author Ahmed R. Gardouh designed the study, responsible of correspondence with journal and aided author Samar H. Faheim in laboratory work. All authors co-operated in writing paper, writing results, data interpretation, and reference management.

**CONFLICT OF INTERESTS**

Declared none

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