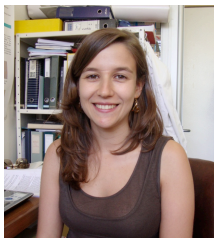
P-051 **Transcutol-containing NLCs as potential carriers for Mometasone Furoate**



Raposo S.*, Salgado A.*, Urbano M. **, Ribeiro H.*, Almeida A.*
*iMed.UL (Research Institute for Medicines and Pharmaceutical Sciences) - Faculdade de Farmácia da Universidade de Lisboa. Av. Prof. Gama Pinto 1649-003 Lisboa - Portugal
**Laboratórios Edol, Produtos Farmacêuticos, S.A.Lisboa, Portugal
aalmeida@ff.ul.pt

INTRODUCTION AND OBJECTIVES

Topical therapy of skin diseases by means of glucocorticoids requires assuring not only the administration of adequate dose of the drug on the desired area of the skin, but also preventing the possibility of undesired effects of these potent drugs, such as atrophy, skin-irritation, and photosensitivity.
Advanced formulations which would help eliminating these effects are still on demand. Nanostructured lipid carriers (NLC) have been tested as effective carriers of a variety of drugs for topical therapy of skin diseases (Doktorovová 2010). These systems combine good local tolerability, a high inclusion rate for lipophilic substances and small particle size providing close contact to the *stratum corneum* (Maia 2000).
The inner structure of NLC is composed of mixtures of solid and liquid lipids (oils). The solubility of active ingredients in oils is generally much higher than in solid lipids, resulting in a higher loading capacity.
A mixture of liquid with solid lipids leads to the creation of a less ordered inner structure. Thus, the drug molecules can be accommodated in between lipid layers and/or fatty acid chains. With this approach, drug expulsion during storage time is also minimized (Teeranachaideekul 2007).
Mometasone Furoate (MF), a synthetic 16 α-methyl analogue of beclomethasone, is classified as a class 3 glucocorticoid for dermatological use as an anti-inflammatory and anti-pruritic drug.
The present work reports the first nanoencapsulation studies of MF in NLC formulations intended for dermatological use, including the influence of the amount of surfactant and preservatives on nanoparticle characteristics.

MATERIALS AND METHODS

Solubility studies
1. MF (Cristal Pharma, Spain) was added to different excipients until saturation. Saturation was achieved when an excess solid persisted for more than 12 h with constant shaking at 22ºC.
2. The mixtures of tripalmitine (Sigma) and Transcutol® CG (TC) (Gattefossé) were melted above the melting point of the tripalmitine then small quantities of MF were added until visible saturation.

Preparation of NLC
NLC were prepared by the emulsification-solvent evaporation method (with or without parabens) under ultrasonication (Branson, Sonifier 250). The pre-dispersion obtained was then high-shear homogenized, (Silverson, UK).

Particle size analysis and zeta potential (ζ) measurements
Particle size analysis was performed by Photon Correlation Spectroscopy (Zetasizer Nano S, Malvern Instruments, UK) at a detection angle of 173º, at 25ºC. The analysis yielded the mean diameter of the particles (*Z*-average) and the polydispersity index (PI).
The surface charge was determined by measurements of the ζ potencial carried out with a Zetasizer 2000 in water (Malvern Instruments, UK) at 25ºC.

Drug entrapment
Drug entrapment efficiency was determined indirectly in the NLC supernatants after ultrafiltration (Amicon® Ultra, Millipore), using a HPLC technique.

RESULTS AND DISCUSSION

The choice of TC as a liquid lipid was based on solubility values of MF in different glycols (Table 1).

Table 1. Solubility of MF in excipients (mean ± SD; n=3)

Excipient	Solubility (mg/g)
Hexyleneglycol	8.5 ± 0.2
Labrasol®	21.7 ± 0.9
Transcutol® CG	34.8 ± 0.6
PEG 400	19 ± 3.5
Ter-butanol	3.2 ± 0.1
Pentandiol	7 ± 0.8
Propileneglycol	2 ± 0.3
Butanediol	3.2 ± 0.2
1,5 Pentanediol	1.9 ± 0.4

Concerning MF solubility in different tripalmitine/TC ratios (Table 2), it was found that it decreases in the same proportion of an increase in tripalmitine content.

Table 2. Solubility ranges of MF in different Tripalmitine/TC mixtures

Ratio (Tripalmitine/TC)	Solubility (mg/g)
1:1	[19.9-20.7]
2:1	[7.7-9.1]
3:1	[3.8-5.4]

As the 1:1 and 2:1 ratios allowed the incorporation of higher MF amounts, blank NLC formulations were prepared using these ratios, containing either 1% or 2% of PVA (Table 3).

Table 3. Particle size and PI of NLC formulations differing on the lipid ratio and % of surfactant

Ratio of lipid mixture	PVA (%)	Particle size (nm)	PI
1:1	1	213.4	0.129
1:1	2	247.2	0.164
2:1	1	209.5	0.137
2:1	2	241.7	0.154

An increase of PVA from 1% to 2% causes a higher mean particle size and PI. Moreover only slight differences in particle size were observed between the two lipid ratios. Therefore, further studies were performed using the 1:1 lipid ratio with 1% PVA.

The influence of preservatives on NLC characteristics was investigated upon paraben addition (0,18% of methylparaben and 0,02% of propylparaben) to the selected formulation. As shown in Table 4, the inclusion of parabens has a minimal influence on particle size and reduces ζ potencial, which do not affect NLC physical stability (Fig. 2).

Table 4: Influence of parabens on particle size and ζ potencial

Sample	Particle size (nm)	PI	ζ
F1*	230,5	0,158	-26,3
F2**	241,4	0,140	-18,4

*formulation without parabens; **formulation with parabens.

The entrapment efficiency of MF reaches 90% for an initial amount of 7 mg and decreases for higher initial theoretical loadings (Fig.1).

Mean particle size was determined throughout time as a measure of physical stability of NLC formulations: F1 (7mg of MF); F2 (7mg of MF and 0,2% of parabens) and a F3 (blank NLC suspension).

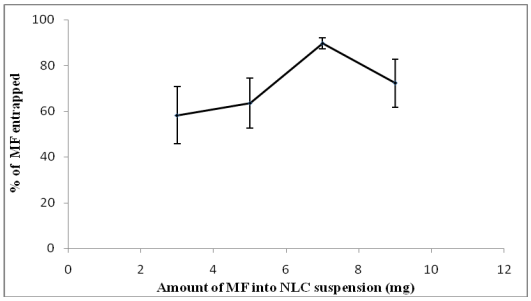


Figure 1. % of MF entrapped into NLC (mean ± SD; n=3)

All the formulations seem to be stable during 1 month storage at 5ºC, concerning the particle size (Fig. 2).

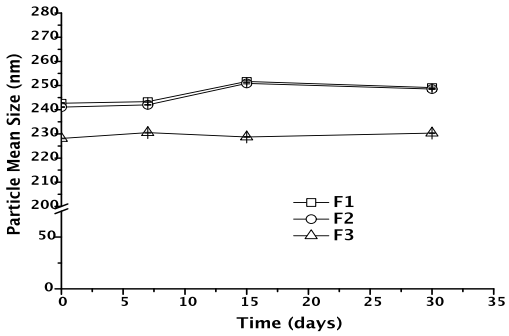


Figure 2: Particle size diameter variations during 30 days at 4 ºC. (n=3 ± SD)

CONCLUSION

The results suggest Transcutol® CG is a suitable excipient to be included in NLC intended for topical delivery of MF. Finally, full stability testing and *in vitro* permeation studies are currently being performed.

ACKNOWLEDGEMENTS

This study was supported by ADI/FCT, Portugal (SFRH/BDE/33550/2009) and Laboratórios Edol, Portugal.

REFERENCES

- Doktorovová et al. (2010) *Formulating fluticasone propionate in novel PEG-containing nanostructured lipid carriers (PEG-NLC)*. Colloids and Surfaces: Biointerfaces (75) 538–542.
- Maia et al. (2000) *Solid lipid nanoparticles as drug carriers for topical glucocorticoids*. International Journal of Pharmaceutics (196) 165-167.
- Teeranachaideekul et al (2007) *Cetyl palmitate-based NLC for topical delivery of Coenzyme Q_{10} – Development, physicochemical characterization and in vitro release studies*. Eur. Journal of Pharmaceutics and Biopharmaceutics (67) 141-148.