1 INTRODUCTION

The topical and dermatological therapy is responsible for the fact that during day-life, the patients apply many physicochemically different preparations to the skin, ranging from powders to liquids, passing through semi-solid formulations. Stability, compatibility, and patient acceptability of the vehicle were the main concerns of the pharmaceutical technologists in the past. Nowadays, an additional parameter – the bioavailability of the drug – needs to be considered when developing such formulations. In fact, only relatively recently scientists have shown that the type of the vehicle can affect the absorption of a drug through the skin [1].

The purpose of topical and dermatological dosage forms is to conveniently deliver drug molecules across a localized area of the skin. To develop an ideal dosage form one must take into account the flux of the drug across skin, the retention of the dosage form on the skin's surface, the reservoir capacity of the dosage form, and the patients' acceptability of the formulation.

The development of a new delivery system for a particular drug is complex due to the wide diversity of the drug solubility in the vehicle components and the vast range in cutaneous fluxes. In the majority of the pharmaceutical formulations intended for topical and dermatological therapy the drug molecules are totally dissolved in a liquid phase of oil-in-water (o/w) or water-in-oil (w/o) emulsions. However, due to the low viscosity of the inner phase of the afore-mentioned systems it is difficult to achieve a prolonged or controlled release of a model drug [2].

The main purpose of this thesis has been the investigation of the latest developments of innovative solid lipid carriers, particularly solid lipid nanoparticles (SLN®) and nanostructured lipid carriers (NLC®), for topical delivery of model drugs. The phase behaviour of multi-component, pharmaceutically interesting systems containing lipid, polymer and water and the possibilities to use lipid particles for sustained or controlled release applications have also been discussed.

In the scientific literature the use of lipid matrices for pharmaceutical technological purposes is reported to be very old. Nevertheless, only at the beginning of the eighties, the first lipid microparticles were described by Speiser *et al*. [3]. These systems were prepared by high speed stirring of a melted lipid phase in a hot surfactant solution obtaining an emulsion, which was cooled at room temperature, and after crystallization of the inner lipid phase, solid

microparticles were formed. The obtained products were called "lipid nanopellets" and they have been developed for oral administration [4]. Similar systems have been described by Domb as "lipospheres", which were produced in the same way however by a sonication procedure [5-7].

In order to overcome the drawbacks associated to the traditional colloidal systems [8], such as emulsions, liposomes and polymeric nanoparticles, solid lipid nanoparticles (SLN®) were developed at the beginning of the nineties [9]. SLN consist of a matrix composed of a lipid being solid at both room and body temperatures, having a mean particle size between 50 nm and 1000 nm. The first patents for SLN were filed in 1991, one by Müller and Lucks [10] describing the production of SLN by high pressure homogenization (HPH), and another by Gasco [11] describing it via microemulsions.

A clear advantage of the use of lipid particles as drug carrier systems is the fact that the matrix is composed of physiological components, i.e. excipients with generally recognized as safe (GRAS) status for oral and topical administration, which decreases the danger of acute and chronic toxicity. SLN were realized by exchanging the liquid lipid (oil) of the emulsions by a solid lipid [12], which can bring many advantages in comparison to a liquid core [2]. A major disadvantage of emulsions and liposomes is the lack of protection for chemically labile drugs, in addition drug release takes place as a burst (emulsions) or at least relatively fast (from liposomes). In contrast, SLN possess a solid lipid matrix identical to polymeric nanoparticles. It can also be pointed out that SLN are low cost products [13]. In fact, the excipients and production lines are relatively cheap and the production costs are not much higher than those established for the production of parenteral emulsions [14, 15].

The second generation of lipid nanoparticles was achieved with the so-called "nanostructured lipid carriers" (NLC®) [16-19]. The main difference between SLN and NLC is the fact that the concept of these latter is performed by nanostructuring the lipid matrix, in order to increase the drug loading and to prevent its leakage, giving more flexibility for modulation of drug release. This approach is achieved by mixing solid lipids with liquid lipids in NLC, instead of highly purified lipids with relatively similar molecules in SLN. This mixture has to be solid at least at 40ºC. The result is a less ordered lipid matrix with many imperfections, which can accommodate a higher amount of drug [14, 16, 17, 20].

During the last ten years different substances have been entrapped into lipid nanoparticles (SLN and NLC), ranging from lipophilic and hydrophilic molecules, including labile compounds, such as peptides and proteins. For the present chapter, an intensive review of

scientific literature has been made concerning lipid nano- and microparticles and it is summarised in Table I.

Table I: Examples of drugs, active ingredients and macrocyclic skeletons incorporated into lipid particles.

Incorporated drug or substance	References
Aciclovir	[21-23]
Albumin	[24, 25]
Alpha lipoic acid	[26]
Amphotericin B	[27, 28]
Ascorbyl palmitate	[29]
3'-Azido-3'-deoxythymidine palmitate	[30, 31]
Azidothymidine palmitate	[32]
Betamethasone valerate	[33, 34]
Benzocain	[35]
Benzyl nicotinate	[36]
Bupivacaine	[37]
Calcitonin	[38-40]
Calixarenes	[41-44]
Camptothecin	[45-47]
Carbamazepine	[48]
Chloramphenicol	[35]
Cholesteryl acetate	[49-51]
Cholesteryl butyrate	[52, 53]
Clobetasol proprionate	[54, 55]
Cloricromene	[56]
Clotrimazole	[57-62]
Clozapine	[63, 64]
Cortisone	[33]
Cyclodextrins	[65, 66]
Cyclosporin A	[19, 67-75]
Deoxycorticosterone acetate	[76]
Dexamethasone	[77, 78]
Diazepam	[33, 79, 80]
3'-5'-dioctanoyl-5-fluoro-2'-deoxyuridine	[81]
Desoxy ribonucleic acid	[24, 82-86]
Doxorubicin	[53, 87-92]
17β-o-estradiol derivatives	[3, 93]
Etomidate	[94-97]
Etoposide	[98-100]
Felodipine	[101]
Fenbufen	[102]
Fenotiazin	[103]
Ferrulic acid	[104]
5-Fluorouracil	[105-107]
Ftorafur	[106]

Table I: Examples of drugs, active ingredients and macrocyclic skeletons incorporated into lipid particles (cont.).

Incorporated drug or substance	References
Gadolinium (III) complexes	[108]
Gonadorelin	[109]
Gonadotropin release hormone	[110]
Halofantrine	[111]
^{99m}Tc-HMPAO [a]	[112, 113]
Hydrocortisone	[114, 115]
Ibuprofen	[97, 115]
Idarubicin	[87, 116]
Indometacin	[115, 117]
Insect repellents	[118-122]
Insulin	[38, 123-126]
Iotrolan	[24]
Ketoconazole	[127]
Ketoprofen	[115]
[D-Trp-6]LHRH [b]	[128, 129]
Lysozyme	[130]
Macrolides	[131]
Magnetite	[132]
Menadione	[33, 133]
Miconazole	[97]
Mifepristone	[134]
Mitomycin C derivatives	[135]
Nifedipine	[103]
Nile red	[136]
Nimesulide	[137]
Ovalbumin	[138]
Oxazepam	[33]
Oxytetracycline	[5]
Paclitaxel	[53, 89, 139-141]
Pancreatin	[124]
Pepsin A	[124]
Perfumes	[118, 142]
Phenylpropanolamine hydrochloride	[143]
Pilocarpine	[93, 144]
Piribedil	[145]
Polycyclic aromatic hydrocarbons	[146]
Prednicarbate	[34, 147, 148]
Prednisolone	[33, 94, 143, 149-152]
Progesterone	[3, 97, 114, 153]
Propranolol	[92]
Pseudoephedrine hydrochloride	[154]

[a] D,L-hexamethylpropileneamine oxime; [b] Luteinizing hormone-releasing hormone.

Table I: Examples of drugs, active ingredients and macrocyclic skeletons incorporated into lipid particles (cont.).

Incorporated drug or substance	References
Quinidine sulfate	[92]
Retinoids	[33, 153, 155-169]
Rhodamine B	[38, 39, 170]
Salbutamol sulphate	[171]
Somatostatin acetate	[172]
Spin-labelled compounds	[129, 173-182]
Spironolactone	[183]
Sunscreens	[118, 166, 184-193]
Tashinone	[194]
Tetracaine	[94-96]
Theophylline	[102, 115, 143, 195, 196]
Thymocartine	[126]
Thymopentin	[197]
Timolol	[198, 199]
Tobramycin	[200-202]
Tocopherol	[118, 185, 203-205]
Tributyrin	[206]
Triptolide	[207, 208]
Ubidecarenone	[33, 203, 209-214]
Verapamil	[92, 215, 216]
Vitamin K	[217]