EXPERIMENT 4

SOLID LIPID NANOPARTICLES

Safety information

The chemicals listed below will be used in this experiment. The likely hazards associated with each of the chemicals are noted and recommended procedures for handling are given. You must read this page and the experimental description carefully before starting the experiment and before coming into the laboratory. Note any potential hazards and adopt precautions as your safe lab practice. When you are satisfied that you understand any possible difficulties that might arise and the recommended procedures for dealing with them, sign the declaration and have it initialled by a demonstrator. This must be done prior commencing lab work. At the beginning of the lab session demonstrators will quiz you about the safety information and experimental procedure in order to identify your ability to work safely and efficiently. If you fail to prove ability for safe and efficient work you will not be allowed to start lab practical. Please note, that it is your own responsibility to complete the lab practical during time that is allocated to you. Be sure to request information or help if you are in doubt on any point.

Chemical	Hazard	Precautions
Poloxamers	Generally, they are not irritants to eyes, skin, and respiratory tract	Do not ingest, avoid skin/eye contact, wear gloves
Ibuprofen	Harmful if swallowed. Causes serious eye irritation. May cause respirator irritation. Suspected of damaging fertility or the unborn child.	Eye protection. Wear lab coat and gloves. Wash face, hands and any exposed skin thoroughly after handling. Don't eat, drink or smoke when using product. Avoid dust formation. (causes inhalation) – Avoid repeated or prolonged breathing of spray mist or dust.

Declaration - I have read and understood the contents of the safety information sheet and the script for the experiment

Signed (student): .....

Checked (demonstrator): ..... Date: .....

EXPERIMENT 4

SOLID LIPID NANOPARTICLES

LEARNING AIMS

- To gain familiarity with preparation and characterisation of Solid Liquid Nanoparticles

DIRECTED READING

Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. *Int J Pharm.* 312 (2006) 179-86.

Mehnert W, Mader K. Solid lipid nanoparticles Production, characterization and applications, *Adv Drug Deliv Rev.* 47 (2001) 165–196

Shah, R.; Eldridge, D.; Palombo, E.; Harding, I., Lipid Nanoparticles: Production, Characterization and Stability. 2015.

Müller R.H, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery: a review of the state of the art. *Eur J Pharm Biopharm.* 50 (2000) 161 – 177

Harms, M.; Müller-Goymann, C. C., Solid lipid nanoparticles for drug delivery. *Journal of Drug Delivery Science and Technology.* 21(1) (2011) 89-99.

Müller R.H, Mehnert W, Lucks J.S, Schwarz C, zur Mühlen A, Weyhers H, Freitas C, Rühl D. Solid lipid micronanoparticles (SLN) — An alternative colloidal carrier system for controlled drug delivery. *Eur J Pharm Biopharm.* 41 (1995) 62–69

Schwarz, C., Solid lipid nanoparticles (SLN) for controlled drug delivery II. drug incorporation and physicochemical characterization. *Journal of Microencapsulation.* 16(2) (1999) 205-213.

INTRODUCTION

Solid Lipid Nanoparticles (SLN) are particles made from solid lipids (i.e. lipids solid at room temperature and also at body temperature) and stabilised by surfactant(s). By definition, the lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes. Recently, SLN based on para-acyl-calixarenes have been prepared and studied. Through the work of various research groups, the carrier system SLN has been characterised intensively. For detailed information on production, characterisation and application, the reader is referred to the main review papers up to date. Typical atomic force microscopy (AFM) image of SLNs is presented in Figure 1.

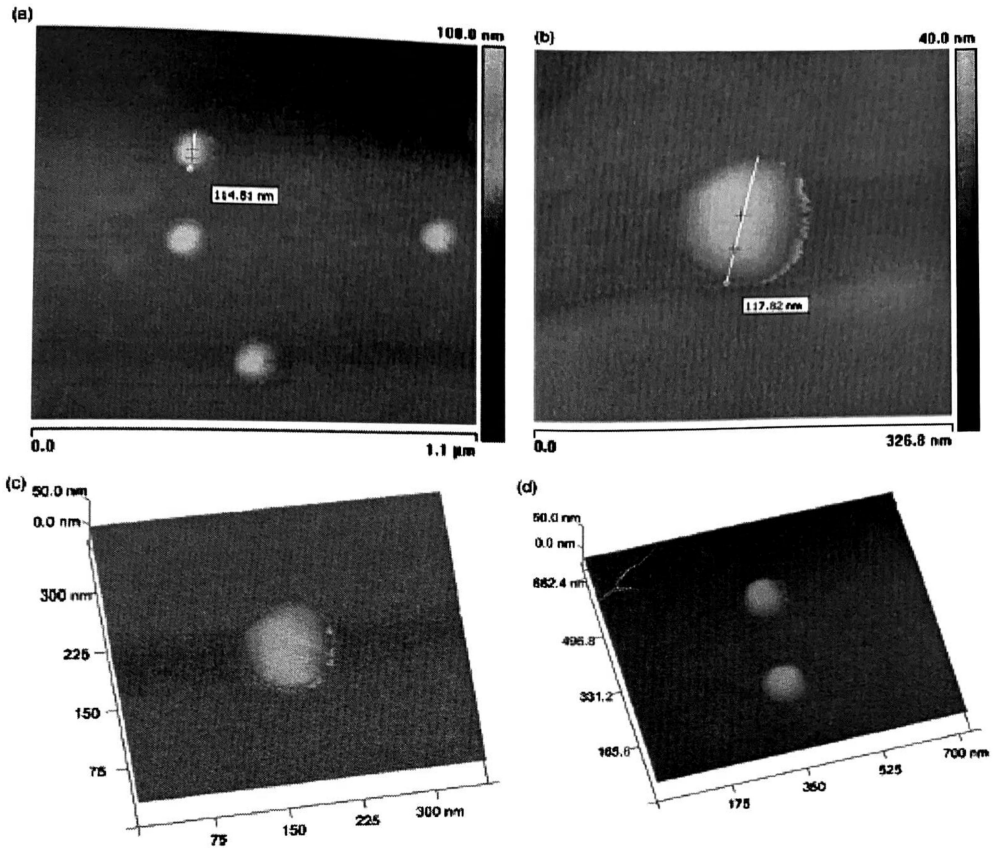

Figure 1. Typical atomic force microscopy (AFM) image of SLNs

Surfactants

In contrast to emulsions for parenteral nutrition which are normally stabilized by lecithin, the SLN can be stabilized by other surfactants or polymers and their mixtures. However, as a distinct advantage of SLN compared to polymeric nanoparticles they can be produced by high pressure homogenization identical to parenteral O/W emulsions. This is a technique well established on the large scale and already available in the pharmaceutical industry. The production lines for parenteral emulsions are in most cases equipped with temperature control units because an increased temperature facilitates emulsion production, this means that existing production lines can be used for producing SLN by the hot homogenization technique. Surfactants and co-surfactants include lecithin, bile salts, but also alcohols such as butanol. Excipients such as butanol are less favourable with respect to regulatory aspects. From the technical point of view precipitation of the lipid particles in water is a dilution of the system, that leads to a reduction of solid content of the SLN dispersion. For some technological operations it is highly desirable to have a high lipid solid content, e.g., 30%. An example is the transfer of the SLN dispersion to a dry product (e.g., tablet, pellet) by a granulation process. The SLN dispersion can be used as granulation liquid, but in the case of low particle content too much water needs to be removed.

Surfactants are compounds with two distinct regions in their chemical structure. One region has hydrophilic properties, the other having hydrophobic properties (Figure 2). The hydrophilic properties are usually conferred on molecule by the presence of ions, alcohol or carboxyl groups. Hydrophobic properties are due to long chain hydrocarbons which may also have a ring system attached to them.

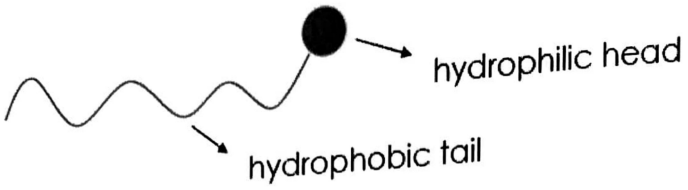

Figure 2. Typical structure of a surfactant

Surfactants can be defined into one of two categories; either ionic or non-ionic (Figure 3). The ionic group can also be sub-divided into cationic, anionic or zwitterionic (amphoteric) groups.

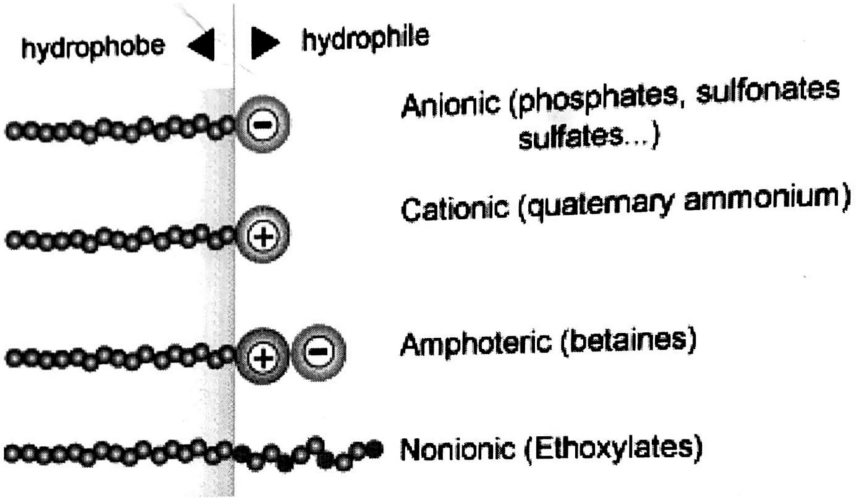

Figure 3: Different type of surfactants

Stability of SLNs

The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersion. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. However, this rule cannot strictly apply for systems which contain steric stabilizers because the adsorption of the steric stabilizer will decrease the zeta potential, due to the shift in the shear plane of the particle. The physical stability of SLN dispersions can be investigated intensively, e.g., by measurements of particle size (photon correlation spectroscopy, PCS; laser diffraction, LD), charge (ZP) and thermal analysis (differential scanning calorimetry, DSC).

METHOD

Formulations by the HPH/Ultrasonication methods

Students will be divided in two groups and they will swap mid-experiment to use either HPH or ultrasonication to prepare SLNs.

The SLN samples loaded with IBU as the model pharmacological active ingredient will be prepared by the following methods:

- Prepare 50 ml of hot water in a tall-form 100 ml beaker by heating the water on a hot plate, do not add a magnetic stirrer bar.
- 1 g of the SLN components (IBU/tristearin/poloxamer 407) at a ratio of 10/20/70 (w/w/w) is placed in a separate container and heated to a temperature above the melting point of the lipid (above 70°C) allowing the IBU and poloxamer 407 to dissolve in the molten lipid.
- The drug-containing melt lipid is then dispersed in distilled hot water (50ml). This is done by, adding, with aid of a syringe, the melted SLN components to the bottom of the beaker of hot water while mixing the water with a homogeniser, keep the beaker of water on a hot plate at all times. This process has to be carried out quickly to avoid crystallisation.
- The sample needs to be homogenised (15,000 rpm) with an Ultra Turrax K25 homogenizer to form a pre-emulsion for 3 min. The homogenizer needs to be observed, as the solution can sometimes overflow from the beaker. A white milky solution will be produced.
- The same process will be repeated but this time the IBU/lipid components will be dissolved in 2 ml Et-OH while SLN components will be dissolved in hot distilled water. (Students will swap to conduct this part of the work i.e., HPH group will perform this step using ultrasonic horn and *vice versa*.)

Particle size measurements and zeta potential

The particle size distribution and the zeta potential of the produced preparations will be determined by dynamic light scattering (PCS) using a Malvern Zetasizer Nano-ZS. The determined particle size range is 0.6 nm – 6 μm.

QUESTIONS

- What are advantages of the SLNs compared to other drug delivery systems?
- Which preparation SLN method is most suitable for the formulation of IBU nanosuspensions and why?
- What is the effect of different surfactants on the obtained SLN particle size with the following characteristics: a) Higher surfactant amounts and b) surfactants with longer lipid chains?
- Can SLNs be used for the development of sustained release formulations and how?