

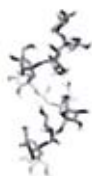
Formulation Development of Poorly Soluble Drugs

Compounds with poor water solubility are increasingly posing challenges in the development of new drugs.

OctoPlus offers several formulation solutions specifically aimed at this group of compounds, either based on generally available formulation strategies or through proprietary, patent-protected technologies.

Our established expertise and technologies, together with our experienced team can help you meet your goals in the development of poorly soluble drugs during lead discovery, lead optimisation and drug development. In addition, the patent-protected technologies we offer provide the potential for life cycle extension of established drugs through the development of better, more convenient dosage forms.

Figure 1. 3-dimensional structure of inulin



General formulation strategies for poorly water-soluble compounds

OctoPlus offers a full range of established formulation technologies to improve solubility or bioavailability of compounds. These technologies offer the potential to increase solubility of compounds using well-established techniques and excipients for various different administration routes. It is often well worth exploring whether compounds can benefit from these formulation strategies. OctoPlus has developed a screening program in which several formulation technologies are tested. This provides the poorly soluble compound with a rapid and expeditious manner to determine which strategy offers the highest improvement in solubility. After the initial screening program, the best suited technology will be used in further formulation development.

Specialized formulation technologies for poorly soluble compounds

OctoPlus offers several specialized technologies to improve solubility and bioavailability of compounds, such as liposomes, mixed micelles and the excipient inulin.

Liposomes / mixed micells

Low soluble compounds can be solubilized in the hydrophobic space of mixed micelles and liposomes. The liposome family consists of vesicular structures that can be used as carriers for drugs and antigens. They consist of bilayers composed of (phospho)lipids. These vesicular structures vary in size, bilayer rigidity, bilayer geometry and charge. They can be as small as 30 nm and as large as 30 μm . By selecting the proper lipid(s) the bilayer can be neutral or positively or negatively charged. Bilayer rigidity depends on the lipid choice as well, and plays a critical role, e.g. in drug/ antigen release kinetics and stability on storage. Depending on their physico-chemical characteristics liposomes can successfully alter the disposition and improve the therapeutic potential of a drug.

Mixed micelles do not have a double layer, but do have a hydrophobic core in which low soluble compounds can dissolve. Also for this group of particles different compounds can be chosen to increase solubilization. However, compared to liposomes, mixed micelles offer a little less flexibility in the choice of their physico-chemical characteristics.

The behavior of liposomes and the fate of the liposome-associated drugs in vivo strongly depend on their physicochemical properties. Moreover, pharmaceutically important issues such as preparation strategy and sufficient shelf life also depend on the chosen liposome: its bilayer composition, liposome size and manufacturing protocol.



Examples for the use of liposomes include the following:

- + liposomes are excellent solubilisers of lipophilic drugs allowing intravenous administration of these often poorly water soluble compounds
- + liposomes can enhance the immune response against antigens in vaccines
- + liposomes can be used in dermatological preparations to enhance skin penetration
- + liposomes can be used for slow release of the associated drug after intramuscular or subcutaneous injection
- + liposomes can be used for passive targeting of the associated compounds to macrophages, to tumor tissue or inflammation sites
- + homing devices can be attached to liposomes for active targeting to diseased sites
- + cationic liposomal structures are successfully being used as synthetic gene transfection systems

References

- 1 Van Drooge et al., J. Controlled Rel. 97:441-452, 2004
- 2 Crommelin D.J., et al., J. Liposome Res., 13:33-36, 2003
- 3 Crommelin D.J., et al., J. Controlled Rel., 62:245-51, 1999

OctoPlus' role in the formulation of pharmaceutical liposomes

OctoPlus has developed several different liposome formulations for the delivery of drugs, antigens and genetic material. OctoPlus' staff is globally recognized for its expertise in liposome formulation. We have worked together with our sponsors on the formulation and analytical aspects of liposomes and developed several batches for clinical studies (at present up to 10 liter batch size for parenterally administered liposomes). Ample attention is being paid to reach the desired shelf life (> 2 years). Successfully used (freeze) drying protocols are available to speed up the formulation process for our clients. Liposome batches for clinical studies can be prepared in our filling and finishing facilities under GMP conditions. OctoPlus produces different types of liposomes using standard preparation procedures under aseptic conditions. Extruders and / or high shear homogenizers are used to obtain the proper particle size dimensions.

Inulin glasses

Inulin is a novel excipient offering unique advantages to increase the solubility of lipophilic compounds. Inulin is a naturally occurring fructose polymer (Figure 1). The compound has a long history of safe parenteral use in medicine as the gold standard to measure the glomerular filtration rate. Furthermore, the compound has obtained GRAS status (Generally Recognized As Safe) from regulatory authorities, facilitating use in oral applications.

Mixing an inulin solution with a drug solution followed by freeze-drying under appropriate conditions, results in the formation of a sugar glass. Uniquely for inulin, the dissolution profile of the lipophilic compound incorporated is closely related to the dissolution of this sugar glass as shown in Figure 2. This leads to a strongly enhanced, reliable dissolution for the low soluble active component.

The sugar glasses that emerge from this process also protect the compound against physical and chemical degradation, thereby increasing stability. The inulin formulation technology is suitable for oral and pulmonary application. It was discovered by professor Frijlink and co-workers from Groningen University and is patent protected.

Analytical techniques

OctoPlus offers a full set of analytical techniques to support formulation development and manufacturing of products based on poorly water-soluble compounds. Examples of available analytical techniques specifically for poorly soluble compounds are:

- dissolution
- particle size measurement
- porosimetry

In addition, an extensive range of other analytical techniques is available such as LC-MS and HPLC to cover all analytical requirements for formulation development and release of final product.

For more information on general Formulation Development please refer to our factsheet on the subject.

Manufacturing of clinical trial material

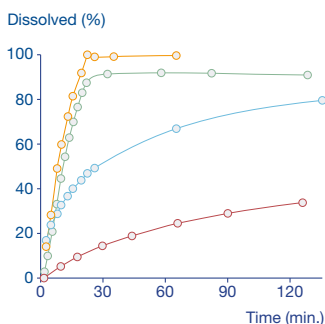
OctoPlus operates a fully licensed cGMP Pilot Plant for manufacturing and release of final product for clinical trials. With this plant, and through OctoPlus' network of contract manufacturers, we offer our clients the possibility to swiftly move from formulation development through to manufacturing of material for clinical trials, thereby saving valuable time and money.

For more information on Clinical Trial Manufacturing at OctoPlus, please refer to our factsheet on the subject.

Person to contact

Gerben Moolhuizen, Chief Business Officer
OctoPlus
Zernikedreef 12
2333 CL Leiden, the Netherlands
Telephone +31(0)71 524 40 44
Fax +31(0)71 524 40 43
E-mail octoplus@octoplus.nl
Website www.octoplus.nl

Figure 2. Significant increase in dissolution rate and dissolved amount of diazepam after creation of sugar glass with inulin. Inulin glass: dissolution of inulin (○) and diazepam included in the inulin glass (◇) are almost similar. Physical mixture: dissolution of inulin (○) and diazepam (◇) is slower, the maximum concentration is lower and the compounds dissolve independently from each other.



Examples of formulation technologies available at OctoPlus are:

- + bile salts
- + emulsions
- + solid dispersions
- + oily depot formulations
- + Hydroxy Propyl (Methyl) Cellulose
- + cyclodextrins

In our hands, liposome formulation includes the process of carefully deciding on the following issues to meet all the demands of our client:

- + strategy to prepare the liposomes (including the choice of the proper equipment)
- + lipid components of the bilayers
- + bilayer charge
- + bilayer rigidity
- + preferred liposome size
- + excipients, including buffers and lyoprotectants
- + lipid suppliers

To fully characterize phospholipids and liposomes, procedures and methods have been developed to monitor:

- + impurity profiles and hydrolysis: HPLC, HPTLC, LC-MS
- + size and charge: (dynamic) light scattering equipment
- + bilayer melting: differential scanning calorimetry