



Pulmonary Delivery of Biopharmaceuticals

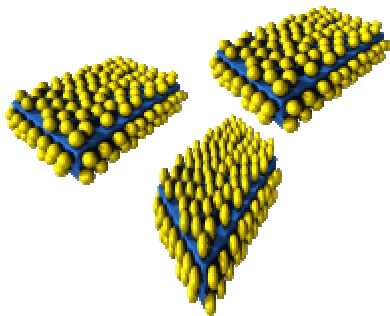
Initial Information on

Dry powder formulations of proteins including insulin

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INTRODUCTION

XstalBio specialises in the formulation of biomolecules in the form of particles engineered for advanced drug delivery. The company's proprietary technology is applicable to proteins, peptides, nucleic acids and vaccines and has the potential to improve therapeutic value, strengthen patent cover for new biological entities and extend product life-cycles.



The aerodynamic particles are based on protein-coated microcrystals (PCMC) and have a core composed of a water-soluble and crystalline pharmaceutical excipient, such as an amino acid, sugar or polyol (shown here in blue), on which is immobilised the therapeutic biomolecule (shown in yellow). The PCMC technology provides a highly differentiated method for preparing biomolecules as stable solid-state formulations and the particles may be engineered for a wide range of delivery options including pulmonary; parenteral; sustained release

and transdermal.

PCMC-based formulations are non-hygroscopic, stable at room temperature and can be delivered efficiently using standard dry-powder inhalers. The technology can be used to develop multi-dispensing systems (*i.e.* with powders open to the atmosphere).

The formulation and delivery of other biopharmaceuticals and small molecules is also possible.

Production of vaccine may be carried out in an easily scaled closed-loop continuous process with low capital investment and running costs. A GMP pilot plant is currently being developed in a licensed collaboration with a major European partner. XstalBio has exclusive rights to the three patent families underlying the PCMC technology and is currently working with several leading pharmaceutical companies.

THE TECHNOLOGY

PCMC may be prepared *via* either a batch or continuous co-precipitation process – in either case the rapid dehydration of the biomolecule leads to retention of a near-native conformation in the dry-state. **This is the key to the high stability** together with the crystalline non-hygroscopic particle core. Typically, formulations contain only two ingredients: buffered biomolecule and crystal-forming excipient: **NO other stabilisers** are required. The process is robust and can incorporate most additives arising from down-stream processing.

ADVANTAGES OF THE TECHNOLOGY

- **Particles** have narrow size distribution suitable for **inhalation** applications
- **Low water adsorption by the crystalline carrier:** for example, < 0.5 % increase in weight at a relative humidity (R.H.) of 75 %.
- **No change to particle morphology upon hydration:** dynamic vapour sorption (DVS), x-ray powder diffraction (XRD) and differential scanning calorimetry (DSC) all show that the core crystalline material remains unaltered.
- **No particle aggregation when exposed to high humidity:** multi-stage liquid impinger (MSLI); scanning electron microscopy (SEM); and TSI, particle size distribution analyser has all shown that there is negligible particle aggregation when exposed to high humidity (75 % R.H.).
- **> 50 % FPF routinely achievable:** as determined by MSLI.
- **Insulin-coated microcrystals remain fully active for > 1 year:** *ex-vivo* biological activity studies have shown that insulin-coated microcrystals remain fully active when stored “on the bench” without any attempt at maintaining control of temperature or humidity.
- **Payload versatility** with loading of biomolecule tailored according to the dosing regime (0.01 wt % to 40 wt %)
- Process **easily scaleable** with low capital investment and foot-print compared to freeze-drying and spray-drying technologies.
- PCMC formulation and particle engineering technology shown to be applicable to **antibodies, cytokines, hormones, plasmids and vaccines**
- **Very low residual levels of GRAS solvents** such as ethanol, isopropanol
- Highly **differentiated composition of matter** relative to particles produced by conventional techniques such as spray-drying
- **Partnership studies:** studies on marketed therapeutic proteins have shown that the proteins show excellent retention of bioactivity and very low levels of aggregation. Data also applicable to protein behaviour under accelerated stress conditions.

PATENT POSITION

Key Patents:

- Rapid Dehydration of Proteins (WO0069887) Granted/Pending World-Wide
- Pharmaceutical Composition (WO2004062560) Pending World-wide
- Process for Preparing Microcrystals (PCT/GB2005/0029) Pending

COLLABORATIONS

XstalBio is commercialising the PCMC patent portfolio on a product-by-product basis. Partners are being identified from pharmaceutical and biotechnology companies who are interested in developing advanced biopharmaceutical products (under license) by application of the PCMC technology to their proprietary biomolecules.

Pharmaceutical partners are being sought for licensing and co-development of the PCMC technology for their proprietary molecules.

Further information: can be obtained from our web-site (www.xstalbio.com) including copies of recent poster presentations

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