ELSEVIER

Carbohydrate Polymers 34 (1997) 421–436

Abstracts

Gluportwo, 2nd International Meeting of the Portuguese Carbohydrate Chemistry Group, Abstracts of papers

Antisense Drugs: Low-cost Multi-ton Manufacture for Market

Yogesh S. Sanghvi*, V.T. Ravikumar, Anthony Scozzari and Douglas L. Cole
Isis Pharmaceuticals, Development Chemistry, 2292 Faraday Avenue, Carlsbad, CA 92008, USA

Over the last decade, the biotechnology industry has witnessed a tumultuous growth in antisense based therapeutics. This is evidenced by a significant rise in the number of oligonucleotides entering into human clinical trials. Therefore, antisense technology represents a major paradigm shift for the biotech-based drug discovery in the nineties, with impressive capabilities to target a host of diseases well into the coming millennium.

Interestingly, all of the first generation antisense drugs belong to a common class of modification, popularly known as Phosphorothioates. The first generation drugs are manufactured from four simple phosphoramidite building-blocks. These blocks are currently prepared from natural 2′-deoxynucleosides, which are generally isolated from fish milt. Recently, however, chemical synthesis of thymidine has been accomplished on multi-ton scale and synthesis of other 2′-deoxynucleosides is under investigation.

The availability of raw materials and the recent advances made in automated solid-phase synthesis of oligonucleotides, now enables the large-scale manufacturing of antisense drugs at relative ease. This presentation will focus on the various technological advances made at Isis. Particularly, development of new synthetic approaches for effective assembly of oligonucleotides on solid-support, use of novel reagents for improved efficiency and lowering the cost of oligonucleotides, state-of-the-art purification techniques that allow enhanced full-length purity of oligonucleotides and excellent recovery yields. In summary, we will describe our vision of low-cost multi-ton manufacturing of antisense phosphorothioate oligonucleotide for the market.

Approaching Sucrose Crystallization at a Molecular Level: Role of Water Structure and Interactions

Mohamed Mathlouthi
Faculté des Sciences, Université de Reims Champagne-Ardenne, Moulin de la Housse BP 1039, F-51687 Reims Cedex 2, France

IT is well known that molecular associations take place in sucrose solutions. We have made the demonstration of the existence of these interactions and of their different nature (water-water, water-sucrose, sucrose-sucrose) as a function of concentration some years ago. The clustering of hydrated sucrose molecules in swarms called "protonuclei" was also found to occur in saturated sucrose solutions.

The rate of sucrose crystallization in supersaturated solutions is known to include at least two steps: the diffusion of sucrose from the bulk solution to the thin layer at the interface crystal/solution and the incorporation of sucrose molecules in the crystal after the release of their hydratation water.

Among the energy barriers encountered in the "hurdle race" of the crystallisation process, viscosity seems to be a minor one and the desassociation of hydration water a major one. These hypothesis were given some 20 years ago by Professor Andrew Van Hook.

We will attempt to show that the dehydration of sucrose molecules prior to their incorporation to the crystal plays an important part in the crystallization process and propose to conceive the mechanism of crystal growth as mainly based on the release of water molecules and their diffusion in the bulk solution rather than a migration of sucrose from the solution to the crystal.

Biopolymers Used in Microspheres and Microcapsules

Renée van Schijndel*, Jeroen van Soest, Henk Verduin and Herman Feil
ATO-DLO, P.O. Box 17, 6700 AA Wageningen, The Netherlands

Microcapsules are defined as particles with sizes in the range of 50 nm to 2 mm consisting of a polymer matrix and an 'encapsulated' or bound active component. Polymer microspheres are described as empty microcapsules. Interest in the fundamental and applicative research of these materials is immense. The choice of the manufacturing process depends on the nature of the starting materials. Frequently used methods are suspension-emulsion polymerization from monomeric materials or suspension-emulsion crosslinking from polymeric starting materials.

Traditionally, microspheres were produced from synthetic polymers such as polyacrylates. Also, agarose and cellulose-based supports in chromatographic packing materials were applied. Although there were attempts in grafting of polysaccharides with synthetic polymers such as in starch-polyacrylate microparticles, recently microspheres were prepared solely from biopolymers such as chitosan and starch.

Starch is used in various non-food products such as bioplastics. Starch is available in large quantities, renewable and cheap. At ATO-DLO a range of starch-based microspheres were prepared by several new routes based on emulsion crosslinking or polymerization. The size of the particles range from 100 nm to several mm. The particle size could be controlled by the amount of energy during emulsification and emulsion composition. A polydispersity can be obtained of less than 30%. Furthermore, they have unique colloidal and emulsifying properties.

Starch microparticles were prepared with a broad range of structural and functional differences. This opened the door to