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CUBOSOME PROCESSING
Industrial Nanoparticle Technology Development

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Cubosomes are nanoparticles but instead of the solid particles usually encountered, cubosomes are self-assembled liquid crystalline particles with a solid-like rheology that provides unique properties of practical interest. The discovery of cubosomes is a unique story and spans the fields of food science, differential geometry, biological membranes, and digestive processes. Despite the early realization of their potential, the manufacture of cubosomes on a large scale embodied difficulty because of their complex phase behaviour and viscous properties. This article reviews the development of several processes for practical manufacture and use of cubosomes in the consumer product industry, the intellectual property that resulted, and the eventual use of the patented technology.

Keywords: cubosome; nanoparticle; liquid crystal; self-assembly.

When asked to give a plenary talk at the UK Particle Technology Forum (PTF) on cubosomes I was simultaneously thrilled (my first plenary!) and nonplussed (have I anything new left to say on the subject?). The best approach in such a case is to think broadly and find a novel path that meets the objective. The cubosome project consumed nearly 3 years of my life at Procter and Gamble (P&G) and was a fascinating, fun pursuit. But unlike some academic research topics with decade time scales, industrial interests can be relatively short-lived. As a result, I had not done active research on cubosomes in 2 years when I came to UCL for the PTF. Nevertheless, although the technical work had been published, the background story of the work we did on cubosomes at P&G had not been told because of proprietary considerations. Given the 'Bridging the Chemistry/Chemical Engineering Interface' theme of the PTF in 2004, our work on cubosomes was especially relevant as it entailed collaboration between Matt Lynch, a chemist in P&G Corporate Research, and me, a chemical engineer in P&G Corporate Engineering. Also, the UK PTF places a strong emphasis on student involvement, and an overview of P&G's work on cubosomes provides unique insight into the type of work engineers with a background in Particle Technology can perform during industrial careers. Finally, in this age of excitement about nanotechnology, start-up companies, and invention, it is useful to speak frankly about the circuitous path often followed during industrial technology invention, process development, and the unexpected outcomes of such pursuits. Professor Seville's article should also be consulted for perspective on particle technology start-up companies and the associated financial rewards.

Cubosomes are nanoparticles, more accurately nanostructured particles (for a more detailed review, see Spicer, 2003), of a liquid crystalline phase with cubic crystallographic symmetry formed by the self-assembly of amphiphilic or surfactant-like molecules (Figure 1). That's right, although cubosomes are nanoparticles, they are not solids. However, the cubic phases are unique in that they possess very high solid-like viscosities because of their intriguing bicontinuous structures [meaning they enclose two distinct regions of water separated by a contorted bilayer of surfactant (Scriven, 1976)]. As a result cubic phases can be fractured and dispersed to form particulate dispersions that are colloidally, if not thermodynamically, stable for long times. Certain surfactants will spontaneously form cubic phases when combined with water above a certain level and the first determination of their molecular structure was ingeniously carried out by Luzzati and Husson (1962), Luzzati *et al.* (1968), Larsson (1983) and Hyde *et al.* (1984) between 1960 and 1985. Kåre Larsson is unanimously credited with discovering that these phases can exist as dispersed particles as well as in the bulk (Larsson, 1989), an observation made from studies of human fat digestion (Patton and Carey, 1979). Larsson's trailblazing work earned him the Rhodia European Prize for colloid and interface work in 2001. So you see that discovery, even in an exciting area like nanoparticles, can come at unexpected moments within seemingly unrelated areas of study. Larsson named the particles he discovered 'cubosomes' to reflect their cubic molecular crystallographic symmetry and their similarity to liposomes (also known as vesicles: dispersed nanoparticles of lamellar liquid crystalline phase). Because cubosomes can form from biological lipids like monoglycerides, can

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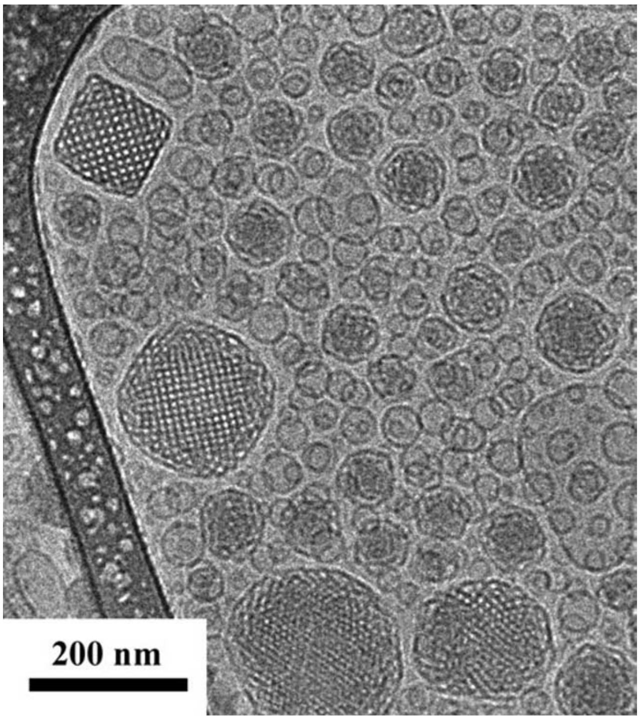

Figure 1. Cryotransmission electron microscope (cryo-TEM) image of cubosomes. Cubosomes are the square and rounded particles with internal cubic lattices visible. Also seen are vesicles, a less structured liquid crystalline particle similar to biological cell membranes.

solubilize numerous biologically active molecules including proteins (Buchheim and Larsson, 1987), and possess a tortuous microstructure (Anderson and Wennerström, 1990), their application as drug (and other active ingredient) delivery vehicles was pursued (Lawrence, 1994).

In 1999 P&G had already begun applying technologies that blended aspects of pharmaceutical products (delivery to and through skin) and consumer products (emphasis on softening and conditioning of skin rather than physiological effects). Cubosomes were an excellent example because they allowed a wide variety of active ingredients to be delivered, their use required knowledge of surfactant aqueous phase behaviour, and the surfactant most commonly used to form cubosomes, glycerol monoolein, is a food-grade material that is inexpensive and broadly safe for use. We became aware of the unique properties of cubosomes through the efforts of Prof Barry Ninham of Australian National University and Prof Stig Friberg of Clarkson University who had both worked for years with the Australian and Swedish researchers at the centre of the now-classic work that highlighted the cubic phases' relevance to areas as diverse as differential geometry, material science, plant biology, and even the origins of life on Earth (Hyde *et al.*, 1997).

As industrialists and engineers we realized that, although cubosomes were intriguing with fascinating properties and potential, their flexible, efficient, and economical manufacture would be difficult (if not impossible) using the technology and understanding available at the time. The published (Ljusberg-Wahren *et al.*, 1996) processes for cubosome production relied on the top-down approach to nanoparticle production: make the extremely viscous bulk cubic phase by hydrating molten lipid mixed with block copolymer (for steric stabilization of the resulting particles) and then use very high energy (ultrasound or high pressure homogenization were most commonly cited) to disperse the cubic phase into nanoparticles. The problem of course is that such unit operations can require multiple passes to achieve the desired particle size distribution and the high energy input can be an obstacle to using many temperature-sensitive active ingredients. The assignment was thus easily stated: develop a process to produce cubosomes that did not require high energy processing. The crucial aspect of the work rested on the application of particle technology: although cubosomes were perceived as exotic nanoparticles because of their liquid crystalline nature, they could be treated the same as solid nanoparticles because of their high viscosity. As a result, our objective became the production of cubosomes using a bottom-up technique, starting from a molecular solution rather than a bulk material.

Similar approaches had been applied to form vesicles (Friberg *et al.*, 1997) by using a hydrotrope solvent to dissolve the viscous liquid crystalline bulk phase (and avoid its formation entirely) but then add excess water to reduce the liquid crystalline phase's solubility and crystallize it as discrete particles. The key to making such a process work is the use of a hydrotrope, defined as a material with hydrophilic and hydrophobic character but no surfactant properties, instead of a solvent. Use of a solvent would have prevented the liquid crystalline phase from forming even after dilution, whereas the hydrotrope only prevents liquid crystal formation at high concentrations. Design of such a process requires knowledge of the full system phase behavior, so after some trial and error the ternary ethanol–monoolein–water system was chosen and its phase diagram constructed (Spicer *et al.*, 2001). Figure 2 shows the full phase diagram used to design the cubosome dilution process. Single phase regions are labelled, indicating the formation of two cubic phases and a lamellar liquid crystalline phase, all viscous liquid crystals. Cubosomes form between a cubic phase and the water–ethanol mixture, where two-phase cubic-fluid equilibrium exists. The single

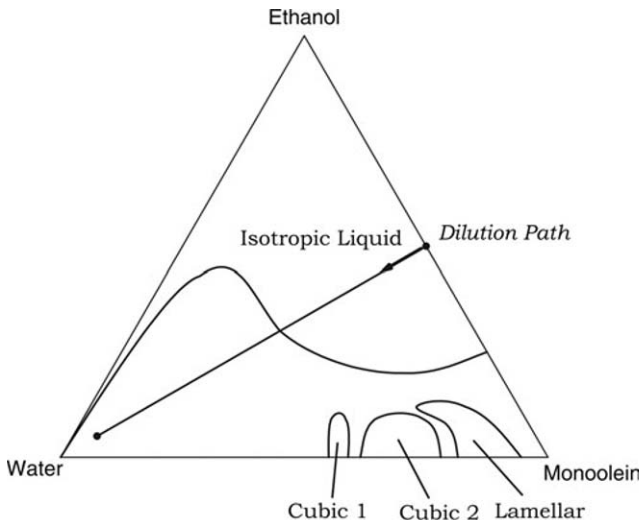

Figure 2. Ternary phase diagram for a typical process forming cubosomes via dilution.