-Review-

# Various Types and Manufacturing Techniques of Nano and Micro Capsules for Nanofood

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## ABSTRACT

Nano and micro capsulation (NM capsulation) involve the incorporation for nanofood materials, enzymes, cells or other materials in small capsules. Since Kim D. M. (2001) showed that a new type of food called firstly the name of nanofood, which means nanotechnology for food, and the encapsulated materials can be protected from moisture, heat or other extreme conditions, thus enhancing their stability and maintaining viability applications for this nanofood technique have increased in the food. NM capsules for nanofood is also utilized to mask odours or tastes. Various techniques are employed to form the capsules, including spray drying, spray chilling or spray cooling, extrusion coating, fluidized bed coating, liposome entrapment, coacervation, inclusion complexation, centrifugal extrusion and rotational suspension separation. Each of these techniques is discussed in this review. A wide variety of nanofood is NM capsulated - flavouring agents, acids, bases, artificial sweeteners, colourants, preservatives, leavening agents, antioxidants, agents with undesirable flavours, odours and nutrients, among others. The use of NM capsulation for sweeteners such as aspartame and flavors in chewing gum is well known. Fats, starches, dextrins, alginates, protein and lipid materials can be employed as encapsulating materials. Various methods exist to release the ingredients from the capsules. Release can be site-specific, stage-specific or signaled by changes in pH, temperature, irradiation or osmotic shock. NM capsulation for the nanofood, the most common method is by solvent-activated release. The addition of water to dry beverages or cake mixes is an example. Liposomes have been applied in cheese-making, and its use in the preparation of nanofood emulsions such as spreads, margarine and mayonnaise is a developing area. Most recent developments include the NM capsulation for nanofood in the areas of controlled release, carrier materials, preparation methods and sweetener immobilization. New markets are being developed and current research is underway to reduce the high production costs and lack of food-grade materials.

(Key words: nanofood; nano and micro capsulation (NM capsulation); manufacturing techniques; nanofood materials; food-grade materials)

### T. Introduction

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Approximately 30 years ago, nano and micro capsulation (NM capsulation) processes were developed. It involves the coating or entrapment of a pure material or a mixture into another material. The coated or entrapped material is usually a liquid but can be a solid or gas.

This material is also known as the core material, actives, fill, internal phase or payload. The coating material can also be called the capsule, wall material, membrane, carrier or shell. The purpose of NM capsulation is to protect its contents from the environment which can be destructive while allowing small molecules to pass in and out of the membrane. Natural examples include birds' egg shells, plant seeds, bacterial spores, skin and seashells.

Early versions of NM capsules were impermeable and were broken apart, most often by mechanical means, for the inner ingredients to become active. Examples included controlled release of flavours and aromas, perfumes, drugs, detoxicants, fertilizers and precursors in textiles and printing (Seiss & Divies, 1981; Kim et al., 2001, 2002, 2003, 2004). Enzymes, plant, animal or microbial cells could be NM capsulated to allow substrates to enter the membrane and products to leave. This concept was instrumental in the development of artificial kidneys since detoxifying enzymes could be placed in semi permeable membranes (Chang, 1978) and performs the function of the kidney. Nylon membranes have been used by Desoize (1986) to NM capsulate and cross-link enzymes such as casein and pepsin. Examples of enzyme NM capsulation include juice clarification with pectin esterase, sucrose inversion by invertase and milk coagulation with rennet (Lee, 1996; Kim et al, 2003, 2004).

An important bacteria used in the industry, lactic acid bacteria, was first immobilized in 1975 on Berl saddles and Lactobacillus lactis was NM capsulated in alginate gel beads years later (Linko, 1985). Seiss and Divies (1981) suggested that immobilized lactic acid bacteria could be used to continuously produce yoghurt. However, the alginate beads of L. lactis susp. cremoris leaked large quantities of cells. Other membranes such as poly-L-lysine, nylon and polyethyleneimine to coat alginate beads have also recently been examined (Larisch, 1990) but did not show any improvement in lactic acid production as compared to free cells.

NM capsulation involves the incorporation of various ingredients within a NM capsule of approximately 5 nm to 300 micron in diameter (Lee, 1996; Kim et al., 2001,

2002, 2003, 2004). The NM capsule can be made of sugars, gums, proteins, natural and modified polysaccharides, lipids and synthetic polymers. The advantages of NM capsulation include improved flow properties and easier handling since they are solid instead of liquid. Stability of the NM capsulated material can be improved due to protection from moisture or heat. NM capsulation can be of many different forms such as a simple membrane coating, a wall or membrane of spherical or irregular shaped, a multiwall structure with walls of the same or varying compositions or numerous cores within the same walled structure as shown in Fig. 1. Currently, almost any material can be NM capsulated for the purpose of isolation, purification or slow release.

For many years, this technique has been used in the food and pharmaceutical industry for time-release, enhanced stability of formulations and flavors masking. Since Kim D. M. (2001) showed that a new type of food called firstly the nanofood, which means nanotechnology for food, prescription nanofood and nanofood materials have been encapsulated. Therefore, these applications, in addition to many others, would be useful in the food industry.

Applications have been slower in increasing since the technique was thought to be too expensive and highly specific. However, since production volumes have increased and more cost-effective preparation techniques and materials have been developed, the number of NM capsulated nanofood products has significantly increased.

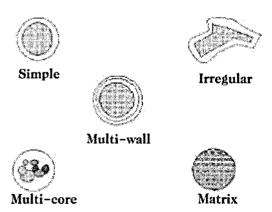


Fig. 1. Various forms of NM capsules.

NM capsulated nanofood products can improve nutrition since the extensive storage of many products can result in the loss of nutritional value by enabling the addition of oxidation-sensitive vitamins, minerals and proteins to various products (Kim et al, 2001, 2002, 2003, 2004, 2005).

A wide variety of processes have been developed to prepare food grade NM capsules. The most common techniques are spray drying (Kim et al., 2001, 2002, 2003 and Bruschi, Cardoso, Lucchesi, & Gremião, 2003), emulsifying-crosslinking (Kim et al., 2003 and Ishizaka & Koishi, 1981) or coacervation (Mauguet et al., 2002). No organic solvents are required for this method, and encapsulation is achieved under mild conditions, thereby minimizing destruction of sensitive nutraceutical compounds. More importantly, globular proteins such as whey proteins have the ability to denature, dissociate, and aggregate under different conditions of pH, ionic strength, and temperature to form capsules with size ranging from 40 nm to 200 microns. These properties can be judiciously exploited to formulate active-nano molecule- loaded capsules of specific size.

In the same way that the prefix 'micro' came into widespread use during the 1980s, the prefix 'nano' has been co-opted to describe the current generation of dimension-reducing technologies (Kim et al., 2001, 2002, 2003, 2004). Technology for nanofood originally refers to the development of functional nanofood materials at a length scale of less than 100 nm (Kim et al., 2001, 2002, 2003, 2004). Although the applications of nano-scale capsules in therapeutic systems have been well documented and various systems have been designed for intelligent, modulated, and selective delivery of drugs to specific areas in the body in order to maximize drug action and minimize side effects, nanotechniques are relatively new in the nanofood industry. Due to their sub-cellular size, nanoparticles offer promising means of improving the bioavailability of nutraceutical compounds, especially poorly soluble substances such as functional lipids (e.g. carotenoids, phytosterols, ω-3 fatty acids), natural antioxidants, and numerous other compounds that are widely used as active ingredients in various food

products. They can dramatically prolong compound residence time in the GI tract by decreasing the influence of intestinal clearance mechanisms and increasing the surface available to interact with the biological support (Peppas, 1995, Kawashim, 2001 and Kim et al., 2003, 2004). They can also penetrate deeply into tissues through fine capillaries, cross the epithelial lining fenestration (e.g. in the liver) and are generally taken up efficiently by cells (Schäfer et al., 1992, Desai et al., 1997, Desai et al., 1996 and Lamprecht et al., 2004), thus allowing efficient delivery of active compounds to target sites in the body.

As demonstrated by the above examples, new functions such as improved solubility, targetability, and adhesion to tissues arise from nanosizing. Nevertheless, the potential of nanofood science cannot be fully appreciated yet because of insufficient knowledge of the physicochemical aspects of nanocapsule systems organization and of the interactions between bioactive molecules and their carrier matrices. Further advances are needed in order to turn the concept of nanosizing into a realistic practical technique for the next generation for nanofood.

# II. Manufacturing Techniques

Various techniques are used for NM capsulation (Dziezak, 1988; Kim et al., 2001, 2002, 2003, 2004). In general, three steps are involved: formation of the wall around the material, ensuring that leakage does not occur, and ensuring that undesired materials are kept out. These NM capsulation techniques include spray drying, spray chilling or spray cooling, extrusion coating, fluidized bed coating, liposome entrapment, coacervation, inclusion complexation, centrifugal extrusion and rotational suspension separation. Each of these methods will be discussed in the following sections.

#### 1. Spray Drying

Since spray drying is an economical, effective method for protecting materials and specialized equipment is not required, it is most widely employed, particularly for

flavours. It is also used for dehydration of materials such as powdered milk. For NM capsulation purposes, modified starch, maltodextrin, gum or others are hydrated to be used as the carrier or wall material. The material for NM capsulation is homogenized with the carrier material usually at a ratio of 1: 4. The mixture is then fed into a spray dryer and atomized with a nozzle or spinning wheel. Water is evaporated by the hot air contacting the atomized material. The capsules are then collected after they fall to the bottom of the drier.

Recent developments have been in the use of new carrier materials and a newly designed spray dryer. Colloides Naturels (Thevenet, 1995) and TIC Gums (Reineccius et al., 1995) have developed new combinations of gum arabic starches to increase the retention of volatiles and shelf-life of the NM capsules. In particular, Risch and Reineccius (1988) enhanced the etention of orange oil and decreased oxidation by using gum arabic. Bhandari et al., (1992) showed that a new type of dryer called the Leaflish spray dryer, which uses a high air velocity with a temperature of 300 to 400°C, was effective for encapsulating citral and linally acetate without degradation. A disadvantage is that a separate agglomeration step is required to prevent separation or to render the obtained powder soluble. A chief advantage is that this technique can be used for heat-labile materials.

#### 2. Spray Chilling or Spray Cooling

In spray chilling, the material to be NM capsulated is mixed with the carrier and atomized by cooled or chilled air as opposed to heated air as in spray drying (Risch, 1995; Kim et al., 2003). The outer material is usually vegetable oil in the case of spray cooling (45 to 122°C) or a hydrogenated or fractionated vegetable oil in the case of spray chilling (32 to 42°C). The disadvantage of the latter method is that special handling and storage conditions could be required (Taylor, 1983). Spray chilling is usually used for ferrous sulfate, vitamin, and mineral or acidulent NM capsulation. Frozen liquids, heat-sensitive materials and those not soluble in the usual solvents can be NM capsulated in this manner. These materials are then released as the wall material is melted. Applications of spray chilling can include: dry soup mixes, foods with high fat contents and bakery products (Blenford, 1986).

#### Extrusion

Extrusion was first patented in 1995 (Swisher, 1995) and further developed by the same group. At this time, citrus oils were dispersed in corn syrup solids and glycerine at 125°C as heated by steam, poured into a chamber pressurized by nitrogen and extruded into a dehydrating liquid such as isopropyl alcohol. The solidified material is then separated into small pieces (1mm) and vacuum-dried. Several factors were later found to improve the quality of the NM capsules including the dextrose equivalent of the corn syrup, emulsifier and flavors oil content and emulsification pressure (Crocker & Pritchett, 1978; Kim et al., 2001, 2002, 2003, 2004, 2005). The advantage of extrusion is that the material is totally isolated by the wall material and that any core is washed from the outside. It is mainly used for visible flavors pieces, vitamin C, colors and extension of shelf-life up to at least 2 years. Dry food applications include drink, cake, cocktail and gelatin dessert mixes since the encapsulated materials are soluble in hot or cold water. Numerous flavors have also been NM capsulated by this method (Risch, 1988; Kim et al., 2002, 2003, 2004).

#### 4. Fluidized Bed Coating

NM capsules are suspended in a temperature and humidity-controlled chamber of high velocity air where the coating material is atomized (DeZarn, 1995 and Kim et al., 2001, 2002, 2003). Optimal results are obtained with NM capsule sizes between 50 nm and 500 microns. NM capsule size distribution should also be narrow. The amount of material that coats the NM capsules is dependent on the length of time that the NM capsules are in the chamber. This technique is applicable for hot-melt coatings such as hydrogenated vegetable oil, stearines,

fatty acids, emulsifiers and waxes or solvent-based coatings such as starches, gums, maltodextrins. For hot melts, cool air is used to harden the carrier, whereas for solvent-based coatings, hot air is used to evaporate the solvent. Hot-melt ingredients release their contents by increasing the temperature or physical breakage, whereas water-soluble coatings release their contents when water is added. Fluidized bed NM capsulation can be used to isolate iron from ascorbic acid in multivitamins and in small tablets such as children's vitamins. Many fortified nanofood, nutritional mixes and dry mixes contain fluidized bed-NM capsulated materials. Citric acid, lactic acid, sorbic acid, vitamin C, sodium bicarbonate in baked goods, and salt added to pretzels and meats are all NM capsulated.

#### 5. Liposome Entrapment

One type of capsule with more versatile properties and less fragility than those made of fat is liposomes. They have been used for delivery of vaccines, hormones, enzymes, vitamins, and nanofood materials in to the body (Gregoriadis, 1984; Kim et al., 2001, 2002, 2003, 2004). They consist of one or more layers of lipids and thus are nontoxic and acceptable for foods. Permeability, stability, surface activity and affinity can be varied through size and lipid composition variations. They can range from 25 nm to several microns in diameter, are easy to make and can be stored by freeze-drying. Kirby and Gregoriadis (1984) have devised a method to NM capsulate at high efficiency that is easy to scale-up and uses mild conditions appropriate for enzymes.

Phospholipids make up the outer layer or layers of liposomes (Fig. 2A). The hydrophilic portion of the lipids is oriented towards the aqueous phase and the hydrophobic groups associate with the hydrophobic ones of other lipid molecules. Folding of the lipid sheet into a spherical shape forms a very stable capsule due to there being no interaction of the lipids with water (Fig. 2B). Aqueous or lipid-soluble materials, but not both, are entrapped in these membranes. Mainly flavour agents are encapsulated in this manner. Liposomes can range from

a few nanometers to micron. They were initially developed for medical purposes (New, 1990) and then were used for cosmetics (Ghychy & Gareiss, 1993). Food and nanofood applications of liposomes in cheese-making (Fig. 3) were described by Kirby (1993) and Kim et al. (2004).

The most common phospholipid in lectin, phosphatidyl choline, is insoluble in water and is inexpensively isolated from soy or egg yolk. The composition of the phospholipids and the process used determine if a single or multiple layers are formed (Martin, 1990). Fatty acids also make up liposomes and their degree of saturation is dependent on the source. Animal sources provide more saturated fatty acids. They influence the transition temperature that is the conversion from a gel to the more leaky liquid form.

Although sugars and large polar molecules cannot permeate through a liposome bilayer, small lipophilic molecules can. They will only permeate through the membrane, though, if they are soluble in the outside liquid. Hydroxyl ions, protein, and molecules potassium ions permeate very slowly.

Liposomes are made by three different procedures. The lipid formulation is mixed with a solvent system such as 2:1 chloroform: methanol. The volume of solvent is decreased and the film of lipids/solvent is then redispersed

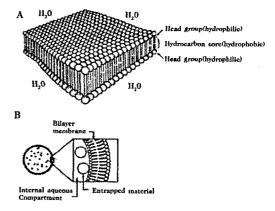


Fig. 2. Schematic diagram of a sheet of lipid bilayer (A) and the liposome formed from the lipids (B).

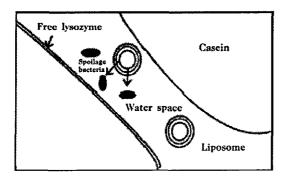


Fig. 3. NM capsulation of lysozyme in liposomes to prevent spoilage in cheese by bacteria.

in an aqueous phase. This step forms the liposomes and it can be done in different ways including physical, two-phase and detergent solubilization. The liposomes are then recovered from the water (New, 1993).

The phospholopids in the liposomes oxidize or hydrolyze over time. Maximum stability can be ensured by using freshly prepared lipid and solvents to prepare the liposomes, avoiding exposure of the liposomes to oxygen as much as possible, limiting excessive temperatures, adding antioxidants and metal chelators to avoid charge neutralization by metals and using proper storage conditions. Hydrolysis can be minimized by using pure solvents and removing as much of the water as possible.

Holding the temperature above the phase transition temperature helps to avoid annealing or fusion. Liposomes smaller than 40 nm are more likely to fuse than larger ones. Since neutral liposomes will still aggregate due to van der Waals forces, addition of 5% phosphatidic acid or phosphatidyl glycerol can reduce this.

#### 6. Coacervation

National Cash Register Company patented this technique for carbonless paper in the 1990s (Risch, 1995). Particle sizes of a few submicrons to a centimeter are obtained. Food grade materials have only recently been used as the carrier. This method, although efficient, is expensive. It consists of dissolving a gelling protein, followed by emulsification of a material such as flavour

oil into the protein. The coating in liquid form is removed from a polymer solution, coats the material to be NM capsulated, solidified and collected by centrifugation or filtration. Drying can be accomplished by spray or fluidized bed drying. The factors, pH, temperature and composition are all important in making the NM capsules.

Coacervation can be simple with only one colloidal solute such as gelatin, or complex, with, for example, gelatin and gum acacia (Luzzi & Gerraughty, 1994). Gelatin and gum acacia are used together since at low pH, each has an opposite charge, causing attraction and the formation of an insoluble complex. This viscous solution is more common and can be used to coat flavors oil droplets suspended in an aqueous medium (Bakan, 1999). Lowering the temperature hardens the wall material but it can be softened again by addition of bases, acids, heat or dilution. This process is irreversible if divalent salts or aldehydes are added.

Hydrophilic coatings such as gelatin can be used to NM capsulate hydrophobic substances including citrus or vegetable oils or vitamin A. Hot water, pressure or chemical reaction can be used to release the contents. The coating can also be hydrophobic and the core may be water soluble or immiscible (Balassa & Fanger, 1991; Kim et al., 2002, 2003).

#### 7. Inclusion Complexation

In this technique,  $\beta$ -cyclodextrin is used since the centre is hydrophobic while the outer surface is hydrophilic due to its seven glucose units linked 1 to 4. In the centre of the cyclodextrin, water molecules are replaced by less polar molecules (Risch, 1995). The complex then precipitates out of solution (Reineccius & Risch, 1986). Only water can serve as the suspension medium. The precipitate is recovered and dried by conventional means. Binding by the cyclodextrin can occur up to 200 °C. The moisture and temperature conditions of the mouth, however, allow release of the bound material.

Garlic and onion oils can be complexed as odour less compounds by cyclodextrin. Vitamins A, E and K that

are fat-soluble can also be stabilized in this manner (Kim et al., 2003). Cyclodextrin, however, is only approved for use with foods in Japan and Eastern Europe (Dziezak, 1988).

# 8. Rotational or Centrifugal Suspension Separation

The steps in rotational suspension separation, which is a relatively new technique (Sparks, 1989; Kim et al., 2001, 2002, 2003), involve mixing the core and wall materials and then adding to a rotating disk. The core materials then leave the disk with a coating of residual liquid. The NM capsules are then dried or chilled after removal from the disk. The whole process can take between a few seconds to minutes. Solids, liquids or suspensions of 30 nm to 200 microns can be NM capsulated in this manner. Coatings can be 1 to 200 microns in thickness and include fats, polyethylene glycol (PEG), diglycerides and other meltable substances. Since this is a continuous, high-speed method that can coat particles, it is highly suitable for nanofood. One application is to protect nanofood that are sensitive to or readily absorb moisture such as aspartame, vitamins or methionine (Sparks et al., 1993; Kim et al., 2002, 2003).

# Nanofood Materials

The types of nanofood materials (Kim et al., 2002, 2003, 2004) that can be NM capsulated are shown in Table 1. Most of the uses of NM capsulation in nanofood are for masking odours or tastes. The NM capsules are usually water-soluble and are dissolved when water is added. Flavour oil NM capsulated in a food-grade hydrocolloid is such an example. NM capsulation also enables materials such as enzymes to maintain their viability for extended periods of time as shown in Fig. 4. Addition of enzymes unprotected to nanofood exposes them to ions, protons, radicals, inhibitors, etc. that cause instability and inactivity. The NM capsule can shield the

Table 1. Various nanofood materials that have been NM capsulated

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Type of nanofood materials
Flavoring agents such as oil, spices, seasonings and sweeteners Acids, alkalis, buffers
Redox agents (bleaching, maturing)
Enzymes or microorganisms
Artificial sweeteners
Leavening agents
Preservatives
Colourants
Cross-linking and setting agents
Agents with undesirable flavours and odours
Essential oils, amino acids, vitamins and minerals

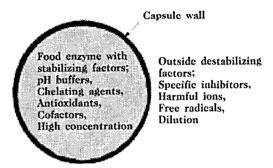


Fig. 4. Benefits of NM capsulating enzymes.

enzyme from these actors.

Acidulents are added to processing and preservation aids, and flavour modifiers. Since they interact with gums, starches, proteins and pectins, they can develop a wide range of textures. NM capulation of these agents can increase the shelf-life of citrus flavours and starchcontaining nanofood and prevent loss of flavour and colour since their release is controlled (Dziezak, 1988 and Kim et al., 2002, 2003, 2004). Hygroscopicity and dusting can also be reduced.

Adipic, fumaric, citric, lactic and ascorbic acids have all been NM capsulated. Ascorbic acid is added to bread to improve its quality. The NM capsulated form can protect this acid from the water and oxygen in the bread that causes degradation. Citric acid is added to tea (Dziezak, 1988) to increase tartness but it can react with the tannins and cause discolouring of the tea bag. NM

capsulation can avoid this problem while maintaining the function of the citric acid. In cured meats such as pepperoni, hard salami and summer sausages, lactic and citric acids enhance the flavours of these meats. Usually this is accomplished by fermentation that is hard to control. Direct addition is not an option since the acids react with the foods. An alternative is to use NM capsulated acids. NM capsulation with fat avoids premature acidity and meat stiffening, and bypasses the fermentation step. Other potential applications include desserts, baking mixes and pet foods.

B-carotene, turmeric and other natural colours are not very soluble and can cause dust problems during handling. The advantages of NM capsulating these materials include: extending shelf-life from 6 months to 2 years (Kim et al, 2002, 2003, 2004), easier handling, improved solubility and stability.

NM capsulation of citrus oils, other flavouring agents and spices enhance stability. Menthol, peppermint, spearmint, and other flavours in their NM capsulated forms are gaining popularity in microwavable and extruded foods because of their stability at high temperatures for short periods of time. Fat-NM capsulated cinnamon does not allow this flavour to interfere with yeast growth in baked goods.

Sodium bicarbonate used as a leavening agent can be NM capsulated to reduce its reaction with acid or water and provide uniform performance. Fat and oil coatings are typical to NM capsulate leavening agents in pizza doughs.

The advantage of NM capsulating sodium chloride with partially hydrogenated vegetable oil is to increase ability to flow and reduce clumping and caking. Sodium chloride decreases colour degradation, rancidity, and helps tc control water absorption and the growth of yeast. This is particularly applicable for yeast doughs, pretzel snacks and pulverized meats.

Sweeteners can be degraded by temperature and moisture. Sugar and the artificial sweetener, aspartame, is NM capsulated with fats in chewing gum. These sweeteners are released slowly during chewing and moisture in the mouth. Aspartame (Nutra Sweet) can be protected from

high temperatures in baking goods by NM capsulation. Sweetness would normally be lost as the aspartame breaks down to aspartic acid and phenylalanine (Gibbs et al., 1996: Kim et al., 2003).

Vitamins and minerals are usually added to breakfast cereals, dairy products (Kim et al., 2003, 2004), infant and pet foods. By NM capsulating both water and fat-soluble vitamins, off flavours can be avoided and stability can be increased. Flow properties are also enhanced (Kim et al., 2002, 2003, 2004).

#### IV. Conclusions

Numerous developments have been made in the field of NM capsulated nanofood materials. Manufacturing techniques include spray drying, spray chilling or spray cooling, extrusion coating, fluidized bed coating, liposome entrapment, coacervation, inclusion complexation, centrifugal extrusion and rotational suspension separation. There are many requirements for the controlled and sustained release of nanofood materials. New markets will be developed as advances in NM capsulation continue. Coacervation seems to be particularly promising since the cost can be reduced due to the requirement for lower levels of food ingredients. In addition, flavours are more stable after processing with microwave, heat, oven drying and frying.

Limitations in many of the NM capsulation techniques have occurred due to high costs of production and the lack of food-grade available materials. Research is necessary to eliminate these limitations. NM capsulation currently is an art that is difficult for the food scientist to master. The food scientist does not have the information available in databases to enable him to make informed choices concerning the most appropriate material and NM capsulation process. For example, the appropriate blends of starches and maltodextrins as NM capsulating materials could prove highly beneficial. The development of cyclodextrins has led to new products with longer shelf-life, reduced volatility and protection of heat-labile substances.

Preliminary indications are that liposomes have many

benefits for the food industry including protection of materials until desired release or targeted delivery. There is a great deal of research that needs to be done concerning the use of liposomes in the food industry. Unlike the pharmaceutical industry, which can tolerate high costs, manufacturing costs will have to be reduced for nanofood applications.

# V. Acknowledgements

This research was supported in part by 2005-B0000002 from Korea Bio-Hub Program of Korea Ministry of Commerce, Industry & Energy.

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