Microencapsulation: The Creation of Synthetic Fine Particles with Specified Properties

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1. Introduction

The aim of microencapsulation is to create synthetic powders or fine particle suspensions with required properties. Thus, in powder mixing technology a liquid component of the mixture can be transformed into a free flowing powder, which reduces the technical problems of creating a mixture with other powdered ingredients, and can be the basis of a strategy for preventing segregation in the assembled powder mixture.

For example, consider the formulation of a powder mixture in which one ingredient is a finely powdered toxic drug of relatively high density and another ingredient is a small amount of liquid which is compatible with the drug fine particles. The drug fine particles can be suspended in the liquid, and then the slurry spray dried to form a powder the grains of which can be regarded as heterogeneous microcapsules. One can adjust the size and the density of these microcapsules by adding hollow bubbles of a soluble cellulosic based material so that the overall density of the microcapsules and their size is comparable to an excipient powder with which the drug has to be mixed in the tabletting process. By adjusting the density of the microcapsules one eliminates the density driven segregation of the powder components in an ultimate mixture and by bulking them out with a bubble ingredient one is able to make it difficult for the heterogeneous microcapsules to migrate under the influence of vibration within the mixture.

Microencapsulation is one of those industrially important technologies in which successful solutions to technical problems tend to become closely guarded commercial secrets. For this reason the literature on the performance of microencapsulated products is sparse. For example, it has recently been announced that the artificial sweetener Aspartame (NutraSweet) has been successfully incorporated into microcapsules to enable the artificial sweetener to survive the heat of baking in products such as cakes. It is highly unlikely that the technical details of the process will be made available in the scientific literature to the company’s competitors.

The mainstay of the development of microencapsulation in industry are several companies that will create microcapsules on a custom basis. (A selection of these companies is listed in references 7 through 11.) In such a situation the purchaser of the microcapsules acquires the specialty knowledge of the creator of the capsules and appropriate secrecy contracts keep the information from emerging into the technical literature. One of the aims of this review is to direct the reader to sources of information on development possibilities for the evolution of microencapsulated products. The second aim of the review is to present an overview in the way in which microencapsulation technology promises to revolutionize various branches of applied science, and through such an overview to stimulate the reader to seek out innovative developments of new techniques for solving technical problems.

For some time scientists and technologists have been employing microencapsulation techniques without a clear understanding of the fact that the process they were using involved microencapsulation. Thus, in the mixing of powders, sometimes the practice of adding a very fine powder to a very coarse powder has been very successful despite, having considered the physical process of mixing the powders, the expectation that the fines would segregate through the assembled mixture as soon as the mixing process ceased. In such cases the finer powder is actually electrostatically coating the
coarser fineparticles to produce a heterogeneous microencapsulated system. Again in the pharmaceutical industry, flow agents are used to promote the movement of cohesive powders. The mechanisms employed by such flow agents (or glidants, as they are sometimes called) are not fully understood but, in the case of silica flow agents, the flow agent appears to coat the individual grains of the primary powder, increasing the friction between the grains and preventing packing. A different type of glidant added to pharmaceutical powders is powdered magnesium stearate. This powder appears to promote flow by de-dusting the powder as it creates heterogeneous microcapsules of agglomerated fines held together by the waxy stearate compound, a phenomenon described in the powder industry as spontaneous balling of the powder.

It is difficult to draw a sharp boundary between what should be considered as a microcapsule or as a coated tablet. Thus in the pharmaceutical industry one system for controlled release involves the packing of a capsule with millimeter sized encapsulated ingredients which have different coating thicknesses to create different dissolution rates in the stomach, thus releasing the drug over a period of time. Each different thickness of coated microcapsule contributes the drug to the body's circulation system at a different time interval. On the other hand a large coated tablet designed to protect drugs which can be destroyed by stomach fluids is not, strictly speaking, a microencapsulated system. However, the two systems, the micropills in a controlled release system and the large coated tablets, use the same technology.

Before proceeding to a discussion of some of the basic processes for microcapsulation it is necessary to summarize and develop some terminology.

In Figure 1 some of the vocabulary used in the description of microcapsules is illustrated with schematic drawings. The simplest form of microcapsule is known as a coherent, homogeneous element, simple microcapsule: in short form, a simple microcapsule shown in Figure 1(a). This is the type of microcapsule used to encapsulate a fuel such as kerosene with a thin gelatin wall so that the kerosene represents 99% of the volume of the microcapsule. Such capsules can then be pressed into bricks to make odorless stable bricks of fuel which can be transported over great distances safely and without having to carry containers. The basic simple microcapsule can be increased in complexity by adding more coherent layers to the original simple microcapsule. Thus in an agricultural application multiple layer simple microcapsules of the type shown in Figure 1(b) have been broadcast in one traverse of the field. The multiple layer capsule delivers an early season herbicide first, followed by the application of a fertilizer as the capsule continues to erode under the effect of weather. Finally a late season herbicide can be released from the remnants of the capsule to facilitate the harvesting of the crop.

In a heterogeneous simple microencapsulation, such as that shown in Figure 1(c), a microcapsule containing dispersed smaller droplets or fineparticles can be prepared at any level of complexity of dispersed material within the microcapsule. Obviously one can make composite microcapsules which have a heterogeneously structured core with a coherent coating about the outside. Toner beads (dry ink) used in xerography are actually microcapsules containing dispersed carbon black although more recent attempts to improve the performance of toner have looked at the possibility of coating carbon directly onto the outside of a resin fineparticle. More recent techniques of encapsulation have used heterogeneous coatings in which a sparse quantity of discrete coating material is placed around a core fineparticle as shown in Figure 1(d). The bonding between such coating fineparticles and the core can either be permanent or temporary. The heterogeneous type coating is the system used in the Mechanofusion and Hybridization techniques to be described in a later section. Workers in this area of microencapsulation use the specialized vocabulary indicated in Figure 1(d).

Another type of encapsulation uses a liquid to bond together smaller fineparticles to create heterogeneous crumbs. This technology, a form of heterogeneous microencapsulation, has been the subject of an extensive scientific literature in which granulated crumbs are sometimes fired to make the bonding permanent. The use of liquid to agglomerate fineparticles to form
The structure of a microcapsule can have various levels of complexity (and shape).

Technologies For Producing Microcapsules

In one review of the technology used to create microcapsules it is estimated that there are up to 25 different ways described in the scientific literature for making micro-capsules. In this review we will concentrate on a few of the major methods which should acquaint the reader with the basic concepts of the technology and introduce the methodologies available.

The Wurster Process. One of the most widely used methods of microencapsulation was developed by Wurster at the University of Wisconsin in Madison. The patents for this process are now vested in a corporation known as The Coating Place Inc. The Wurster technique for creating microcapsules is essentially a spouted fluidized bed system in which the moving fine-
particles are coated with the appropriate material. The basic equipment used in the process is illustrated in Figure 2. The powder grains to be coated are air fluidized. As they move up through the center of the fluidized bed they are sprayed with the coating material. At the top of the central cylinder the coated fineparticles fall back down the outside to recirculate for a second coating to be applied. One of the advantages of this procedure is that coatings of any given thickness can be built up on the powder grains by repeated circulation of the material. If one attempts to use this technique with very fine powders the most difficult part of the process is to fluidize the powder grains. The circulating action of the fluidized bed also results in each increment of the coating being dried in the downward portion of the circulation trajectory. One has to be cautious with some materials to avoid explosions since a dry circulating system can build up an electrostatic charge, and there is a danger of explosion in some situations. Other manufacturers use similar air circulation systems in fluidized bed equipment. Thus the two systems of Figure 3(a) and (b) are described in the trade literature of the Glatt corporation.

![Figure 3](image)

**Fig. 3** Variations in the configuration of air fluidized - spray coating have been discovered by other manufacturers of microencapsulation equipment.

Microencapsulation System Developed by the South West Research Institute. The basic system developed at the South West Research Institute for creating microcapsules is shown in Figure 4. The core material is fed to a spinning disc at the center of the equipment. Core droplets, or grains of the powder to be encapsulated, are thrown off of the disc towards an outer cylinder containing many small holes around the periphery of the disc. The coating material is fed to this outer disc in liquid form so that it coats the holes in the cylinder with a thin film of the coating material. The core droplets or fineparticles pass through this film, which is constantly renewed, they are coated and then fall out into the outer container where they can be hardened by physical or chemical methods.

Electrostatic Coating Techniques. Several techniques for mixing core and coating fineparticles which have been given opposite electrostatic charges to attract them to each other have been developed. In this section we will describe the basic system developed by Leiberman and co-workers at the Illinois Institute of Technology Research Institute (IITRI) Chicago. The
In the SWRI technique for creating microcapsules a spinning disc is used to fling droplets, or fine particles, through a film coating material. The system used by Lieberman and co-workers is illustrated in Figure 5. In this technique the core material can be either solid or liquid. The usual choice of coating is a liquid for ease in subsequent handling of encapsulated fine particles. Typical coating materials used by Lieberman and co-workers include a wax that solidifies on cooling, a dissolved polymer resin that forms a skin upon the evaporation of a solvent, a polymeric skin formed by interfacial action between a component in the core material, and liquid coatings that solidify upon exposure to a suitable gas phase. The two components to be turned into a microencapsulated system are fed into a reaction chamber which can be heated. The aerosol fine particles are given an ionic charge of the appropriate sign using sub-corona discharge systems. To achieve sufficient encapsulation the system must be designed to achieve a high rate of collision between the two types of aerosol in a turbulent supportive air or gas system. If there is any danger of explosion appropriate supportive gas systems such as nitrogen must be used. In this process one must choose the coating substance so that it will wet, i.e. spread out on, the core material and cover it completely. If the core is also liquid the coating must have a lower surface tension otherwise the desired encapsulation will not be achieved. In Figure 6 an encapsulated sodium chloride crystal system coated by this procedure is shown.

Coacervation Technique for Producing Microcapsules. The process known as coacervation was developed by colloid chemists Kruyt and colleagues in the 1930’s and remained a technology without an application until it was further developed by scientists at the National Cash Register company to create microcapsules for use in carbonless copy paper. (See discussion later in this review of applications of microcapsules in business systems.) The basic technique is illustrated in Figure 7. The core material to be encapsulated is placed in an immiscible liquid to form liquid droplets. The coating material is also suspended in the liquid medium or actually dissolved in this support material. To induce the process known as coacervation the temperature, pH or other environmental conditions are changed in such a way that the wall material comes out of solution and aggregates around a core droplet to form continuous encapsulating walls. Then in the final stage of the process these capsules are hardened.

An alternative technique for creating microcapsules out of the suspension of coacervated droplets is to spray dry the resulting slurry to create heterogeneously encapsulated composite microcapsules. A third avenue for creating microcapsules with coacervated suspensions is to add another ingredient that gels the support.
Unencapsulated

Encapsulated

Fig. 6 Electronmicrographs of sodium chloride crystals, magnified 30,000 times, with and without carboxymethylcellulose encapsulation using the electrostatically charged aerosol system.

Dispersion of internal phase in vehicle phase

Coacervation induced

Fluid wall deposition

Wall solidifies

Fig. 7 The coacervation process starts with an emulsion of two immiscible liquids and then a wall is formed around the droplets by changing the physical and chemical properties of the supporting liquid.

Dry Powder Encapsulation Technology. The most recently developed system for creating microcapsules involves the mixing of two dry powders under high shear conditions so that one powder coats the other. Usually in this technique there has to be a considerable size difference in the two or more ingredients so that the encapsulated material adheres to the larger component of the mixture and the subsequent high shear treatment of the composite system embeds the encapsulating material into the core fineparticles. Note that in some discussions of this type of technology the core material is described as the host material and the encapsulating material is referred to as the guest fineparticles. In this discussion we prefer the term core and coating powders to differentiate between the two main members of the system. Dry encapsulation techniques using high shear conditions appear to have been simultaneously developed by two companies: Hosokawa Micron International Inc., and the Nara Machine Company Ltd. The system developed by Hosokawa is known by the name Mechanofusion whereas that developed by Nara is known as Hybridization. In the techni-
cal literature available at the time that this review was written the initial developments of the Mechanofusion system appear to be mainly in the material science and ceramic industry whereas the studies carried out using the Nara Machine process had found applications in the pharmaceutical industry. Since the two systems are very similar we will confine our discussion in this review to the Hosokawa Micron system of Mechanofusion. The basic equipment for this instrument is shown in Figure 8. As illustrated in Figure 8, in the Mechanofusion process a mixture of the two powders to be processed is compressed and sheared by a rotating cylindrical chamber which traps the mixture between the wall of the chamber and the head of a fixed element inside. As mentioned earlier, in this process one often uses coating powders of a very small size with core fine particles being considerably larger as illustrated for the powders shown in Figure 9. Titanium dioxide is an expensive white pigment which does not flow readily when placed in a powder mixture. By coating the titanium dioxide onto a carrier (core) fine particle maximum use is made of the expensive pigment which when spread out on the core of the resin generates maximum scattering power for the weight of the powder used. At the same time the microencapsulated powder flows much more readily than either of the constituent ingredients. It is not immediately obvious whether this change in flow properties comes from the fact that the stress of the microencapsulation process actually changes the oxide state of the titanium dioxide or whether the core plus microencapsulated powder constitutes an electrically charged system with desirable surface characteristics.

Industrial use of Microencapsulated Material

Microencapsulated Technology In Business Administration Systems. The first widespread use of microencapsulated products was the development of carbonless copy paper by the National Cash Register (NCR) company in 1954. The elimination of layers of carbon paper for making multiple copies of documents greatly facilitated the operation of computer printer systems and simplified completion of forms in triplicate etc. as required by many commercial and government operations. The layer of carbon paper between two ordinary pieces of paper was eliminated by coating the underside of the top paper with microcapsules of ink which in their microencapsulated state were transparent; then the lower paper which was to receive the copy was coated with special clay fine particles. In the early development of this type of paper it was common practice to include two initially colorless dyes, one of which gave an instant pattern of writing on the lower paper as the capsules were ruptured, and

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**Fig. 8** In the mechanofusion process a rotating cylinder stresses and shears the powders to be processed in the annular gap around the periphery of the milling chamber and the head of a fixed element inside.
another dye which gave a more permanent color to the writing after a short time.

The size of the microcapsules of ink has to be controlled closely since if the microcapsules are too small they will disperse into the matrix of cellulose fibers that constitutes the structure of the paper. On the other hand, if the microcapsules are too large, when they rupture they will spread out too far and form a poor quality boundary to the print lines of the copy.

To prevent premature release of ink onto the lower copy paper the manufacturers of carbonless copy paper place starch granules between the two sheets of paper. These granules hold the copies apart until the rupturing starts by the application of pressure.

The Post-it note stickers manufactured by 3M Company also make use of microencapsulation technology. The sticky part of such Post-it notes contains microencapsulated glue made from urea-formaldehyde which rupture under finger pressure. The spheres are between 15...
and 40 microns in diameter. Each time the note paper is pressed a few more spheres rupture to release a fresh film of glue. If one writes extensively with a ball point pen over the glue area of the Post-it note, one can sometimes create too strong a bond between the note intended to be removed and the lower piece of paper, resulting in damage to the lower document. This is because one has ruptured too many microspheres to make the material easily detachable.

Medical Applications of Encapsulated Materials.

One of the major uses of encapsulated material in the medical profession is to give a slow controlled release of medication to the patient. Another use of encapsulation is to hide the nasty taste of some medication. Particularly with children, there is often resistance by the patient to the swallowing of a foul tasting medication. If encapsulated in something like gelatin, the medication can be given as a spoonful of dry powder in a glass of water and swallowed without any taste sensation being felt by the patient. In the same way, medication for animals can be made up as a dry free-flowing tasteless powder and mixed with feedstuff.

Some liquid crystal compounds appear to have different colors as their temperature changes. Encapsulated liquid crystals can be used to take the temperature of a patient. In the simplest device which is available commercially, the letters N and F are printed in two different forms of encapsulated liquid crystals on a thin strip of plastic. This strip of plastic is then placed against the forehead of the patient. The liquid crystals are so chosen that if the person has a normal temperature, the letter N appears a strong blue. If, however, the person has a fever, the F shows as a bright green. The plastic strip can be used many times and is obviously easier to use than a thermometer made of mercury in glass.

Often in diseases of the circulation, doctors would like to know the distribution of body temperatures on the surface of the skin. This is not easy to determine with a traditional thermometer. However, if the skin is painted black and microencapsulated liquid crystals are sprayed onto the black surface, colored patterns made on the skin enable the doctor to see the temperature distribution of the skin. This can be then matched with deficiencies in the blood circulation of the patient. Tumors growing in the breast or other surface locations of the body are warmer than the surrounding tissue because of the concentration of blood in the growing tumor. For this reason, encapsulated liquid crystals are a useful diagnostic device for the early detection of breast cancer. Again, the surface of the skin could be sprayed black and then coated with encapsulated liquid crystals. The presence of a tumor would be indicated by a bright green spot in the patterns of the liquid crystal color contours.

A special type of pressure sensitive microcapsule, similar to those used in the carbonless copy paper, has been developed for use in rehabilitating leprosy patients. Patients who have suffered from a severe bout of leprosy lose the sense of feeling in their extremities. They have often lost fingers or toes so that they need to be taught new ways of doing simple tasks. Because of the lack of feeling in their extremities, they frequently apply excessive pressure in doing simple manual operations. This pressure is sufficient to damage the tissue to the point where further amputations are often necessary. In the same way, patients wearing special shoes designed to fit around their deformities may be subject to unfelt severe pressures which can further damage their remnant limbs. Special gloves or socks are provided with pressure sensitive capsules which release dyes when crushed. By studying the pattern of dye release, a patient can become aware of the areas of his hand or foot being subjected to dangerous pressures. This technique was developed at the U.S. Public Health Hospital at Carville, Louisiana.

The medical profession and the pharmaceutical industry have recognized for a long time that placing a drug into the general body circulation (described as systemic treatment) is inefficient. In recent years, there has been a big increase in efforts to develop targeted delivery of drugs. In targeted delivery, one delivers the drug to where it is needed without exposing the rest of the body to the therapeutic substance. For example, the Alza Corporation has developed an alternative system for administering hormone contraceptive preparations without taking the pill. The technique they use is a form
of encapsulation. To prevent pregnancy, the material is encapsulated into a strip of plastic. A relatively massive capsule can be prepared using microcapsules pressed into a block to create a porous body out of which the chemical can dissolve slowly. The strip of loaded plastic is positioned in the uterus on a cross bar. Experiments have shown that a year's protection against pregnancy can be achieved with the equivalent of one day's dose given in the form of pills. Not only is a much smaller amount of material required for this targeted delivery system, but also patients do not have to remind themselves of the need to take a pill according to a schedule. Furthermore, it is well known that the orally taken contraceptive pill has caused problems for some women with respect to blood clots. By delivering the contraceptive substance directly to the uterus, the problems associated with side effects in the bloodstream are avoided.

Another target delivery system developed by the Alza Corporation is used in the treatment of glaucoma. The medication is again dispersed throughout a plastic strip in such a way that it can dissolve out of the strip into the eye. This little plastic strip can be placed under the eyelid. It delivers a steady dosage of the necessary chemical over a period of up to two weeks. For elderly patients, this is much easier than having to administer eye drops. Furthermore, the steady delivery of the dose is better than the surges of medication associated with separate administration of eyedrops on an intermittent schedule. The strip of plastic is so designed that after it has given up its medication, it becomes stiff and pops out of the eye. Experimental work with liposomes to inject steroid drugs near to the place where they are required have shown that these oily droplets can be 50 to 100 times more effective than the straightforward injection of the steroid. For example, medical research workers at Cambridge, England have shown that liposome formulations of steroids injected into the joints of arthritic rabbits were effective at one-hundredth of the dose normally required to reduce swelling and temperature. It is believed that cell bodies in the joint which cause arthritis are the very cells which are intended by the body to clean up the fluid around the joints. It is a disturbance of this function that causes the inflammation of the joint. When these scavenger cells are presented with fat droplets in the fluid, they immediately attack them and absorb them so that the steroid preparation is delivered directly to those cells which need to be treated to reduce

The Greek word for fat is LIPO. This has given us several technical terms such as "lipid" which is defined as "any organic compound insoluble in water but soluble in a fat". Lipids, as a group of compounds, includes such substances as oils, fats, and steroids. The Greek word SOMA means "body". By emulsifying a drug with a fatty substance, one can obtain a compound droplet which is a form of microcapsule and is described as a "liposome". When injected into the human body, a liposome appears to be a normal fat droplet. Therefore, if we can load a liposome with a toxic drug which would normally damage body cells, the fat capsule is harmless until it reaches the parts of the body which deal with the particular fatty substance used to create the liposome, or until the capsule is broken up by special procedures. Liposomes must be small enough to travel through the bloodstream without causing obstructions to the blood flow.

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an adhesive strip, similar to a band-aid. To avail oneself of the medication, one affixes the strip to one's skin, in the same way that one applies a band-aid. The chemical then dissolves in the sweat of the surface of the body and moves through the skin into the body system. Travel sickness protection can be obtained in this way with a low dosage over long periods. This type of travel sickness medication has been used by astronauts in the United States Space Program.

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inflammation of the joint. The first human tests on injecting liposome forms of steroid drugs into arthritic joints were very promising.

One of the reasons why insulin must be injected rather than taken via the mouth is that the stomach chemicals destroy insulin. Professor Brenda Ryman of the Charing Cross Hospital in Great Britain has shown that diabetes can be treated effectively by giving insulin in liposome form through the mouth. The liposomes protect the insulin molecule from breakdown during its passage through the gut and ultimate absorption into the bloodstream.

Many people in South and Central America and in India, Pakistan, and parts of Africa suffer from a parasite which causes a disease known as “Leishmaniasis”. It is estimated that 100 million people suffer from the disease. The most commonly fatal form of this disease involves colonization of the liver, spleen, and bone marrow by the parasites. Toxic antimony based drugs are used to kill the parasites. However, the traditional treatment with the drug damages healthy parts of the body as well as the diseased parts. If these drugs are injected as liposomes into the veins, the blood circulation takes the fat capsules to the cleaning cells of the organs infected by the parasites. Field trials with liposome injections of antimony-based drugs into mice have been very successful, and initial work with humans is beginning. Drug delivery by liposome capsule appears also to offer better treatment for malaria, bilharzia (a disease affecting millions of people in underdeveloped countries) sleeping sickness, and leprosy.

Anti-cancer drugs often severely damage living cells and the amount that can be given to destroy the cancer is limited by the amount that normal cells can tolerate. Thus, treatment becomes a delicate balance between killing the cancer cells and not killing more of the normal tissues of the body than can be repaired by the human body. For specific cancers, such as cancers of the liver and the kidneys, liposome delivery of the anti-cancer drugs also appears to be very promising.

Thus, research work has been carried out at Northwick Park Hospital, Great Britain, into the delivery of the anti-cancer drug “actinomycin”, by liposome injection. Tests show that healthy tissues were largely protect-ed from the actinomycin by the liposomes which were selectively absorbed up to 50 times more rapidly by kidney tumors than by the surrounding tissue. This selective absorption appears to come from a combination of factors. First of all, the cancer cells seem able to absorb fatty compounds more quickly than similar tissues around them. Secondly, the rich supply of blood vessels which usually surrounds tumors brings a high concentration of the injected liposomes directly to the tumor cells. Thirdly, the liposomes appear to be broken down faster by tumor cells than by ordinary body cells.

A leader in the area of liposome drug delivery is Dr. Gregoriadis who is experimenting with techniques for attaching certain chemicals to the outside of the liposome bodies so that they go directly to the cancer tumor with even higher efficiency of delivery being achieved29. Other workers are exploiting the fact that liposomes can be sprayed directly into the lung so that they may prove very effective in treating lung cancer.

Drs. Weinstein and Magin of the U.S. National Cancer Institute, along with Dr. Yatvin of the University of Wisconsin, have developed a technique for releasing the drug from the liposome to the part of the body where it is required. In their experiments, a rat was injected with liposome drug formulations. At a particular part of the body where the drug was required, they raised the temperature of the body to 107 degrees Fahrenheit using infrared radiation. This temperature is just below that which causes damage to healthy cells but enough to melt the oily body of the liposomes to release the drug. This type of release mechanism is known as hyperthermia and appears to be another promising cancer treatment technique.

Yet another technique for carrying the liposomes to the immediate area where they are required has been described by workers at the Northwestern University Medical School in Chicago32. They packaged the anti-cancer drug, “adriamycin”, into microspheres of the protein albumin, which was also loaded with very small fineparticles of magnetite. These drug delivery microcapsules could then focus at the tumor in the body by using a magnetic field. By using the magnetic focussing of encapsulated drugs in the bloodstream, these workers
were able to produce useful therapy effect with one hundredth of the previous dosage used for treatment, and without damage to the immediate tissues en route to the tumor.

Preliminary work is under way to look at the possibility of using orally administered liposomes containing drug neutralizing companions to treat drug overdoses and that are being used to assist kidney machines in clearing poisons from the bloodstream. The use of fat encapsulated drugs is a rapidly growing area of research. Part of the success of future therapies will depend upon the ability of the scientist to create droplets of a given size and loaded in a given manner with different types of drugs.

One of the main problems arising in the body when kidneys do not function properly is the build-up of a chemical known as 'urea' in the bowels. Li has suggested that one way to remove urea from the patient's intestines is to take orally a mixture of two types of liquid membrane capsules. One type of capsules would contain an organic acid and the other would contain an enzyme to give off ammonia and carbon dioxide. These gases would move out of the capsule back into the gut. The carbon dioxide can be readily eliminated through the lung but the ammonia would diffuse into the acid-containing droplets and convert them into an ammonium compound. The constitution of the wall of the droplets would be designed so that the ammonium could not get out of the capsule which would be eliminated from the body by normal bowel processes. The dose which would have to be taken by the patient would look just like a spoonful of liquid since the little encapsulated drops would not be visible and could not be tasted by the patient. The simple mixture we have discussed would be an aid to a kidney machine but more complex systems are being investigated as possible replacements for kidney dialysis machines. (Complex application of liquid membrane encapsulated enzymes in medical practice have recently been described by Li.)

A complete description of the use of microencapsulated pharmaceuticals is beyond the scope of this discussion but the interested reader will find the technical publications full of interesting ideas.

Agricultural Uses of Microcapsules.

When fighting insect pests, scientists are trying to use natural enemies which they rear in captivity and release in the fields infested with the pest. The larvae of such friendly insects have to be fed. A useful application of encapsulation technology has been the manufacture of synthetic insect eggs which are microcapsules containing edible nutritious centres of the same size as the natural food of the larvae. The provision of such synthetic insect eggs removes the necessity of rearing another set of insects to provide food for the “friendly” insect to be used in pest control.

Any chemical substance emitted by an animal, fish, or insect as an odor which influences the behaviour of another member of the same species is described as a “pheromone”. Pheromones are now being used by scientists to attack insect pests. By isolating the odor which attracts male insects to the female, they are able to dope an insect killing device with the necessary perfume which attracts males to their doom. Pheromone chemicals are expensive and if they are simply dabbed onto the lure, they evaporate quickly. If, however, the pheromone is encapsulated in a porous microcapsule, the lure can be coated with the microcapsules and the odor will be given off for a period of weeks at a sufficient concentration to still attract the insects. Such pheromone microcapsules are being used to combat the gypsy moth and the spruce budworm. Pheromone-based strategies against insects have the advantage that the insects cannot develop defense mechanisms against them without interfering with their own reproduction program. Furthermore, the effectiveness of such procedures can be evaluated directly since the insects killed are brought into a central location. If the costs of the procedure can be lowered, such devices will probably be much more effective than indiscriminate spraying of large areas of forests. Again, unlike sprays, the pheromones are very specific against one type of insect and do not damage other friendly insects which are required for the normal functioning of a forest.

Encapsulated food, with the capsules being about one hundred microns in diameter, forms a useful food for small fish being reared in fish farms. The usual food for such fish is chopped up material which, if the fish do not eat immediately, can cause pollution through rotting in the
water. The encapsulated food, however, stays good until eaten and simulates the type of food eaten by the fish in their natural circumstances.

Experiments have been conducted with encapsulated pesticide for use against flies in cattle droppings. The encapsulated pesticide is fed to the cattle with their normal food. It is tasteless to the animal and passes through the digestive system to be released in the droppings, where it is most effective against the fly larvae which would breed in the droppings. Although such an application is still too expensive for general use, it has special applications in areas such as zoos, where there is a great need to protect the public from the swarms of flies that would breed on the dung from animals such as hippopotami, elephants, and other animals.

Experiments have been conducted by scientists at the United States Department of Agriculture to increase the percentage of unsaturated fat in milk. This was achieved by encapsulating a vegetable oil in the substance, “casein”. These microcapsules were placed in the grain ration given to cows. This increased the unsaturated fat content in their milk to a substantial degree. The same scientists conducted experiments in which calves were fed milk produced by cows that had been previously fed with the encapsulated oil. Examination of the tissue of the calves showed an increase in the unsaturated fat present in the meat to a substantial degree. The same scientists conducted experiments in which calves were fed milk produced by cows that had been previously fed with the encapsulated oil. Examination of the tissue of the calves showed an increase in the unsaturated fat present in the meat. Thus, microencapsulation of unsaturated oils could improve the quality of meat intended for human consumption. However, many tests would have to be performed before such meat was made available for retail sale.

The Pennwalt Corporation has developed encapsulated pesticides for use against different kinds of pests. Their process makes use of capsules with nylon-type porous walls. The trade name Penncap-M is an encapsulated form of the pesticide ‘methyl parathion’. They have found that this material is just as effective against the pests as the unencapsulated product but five times safer for the worker who must use material. In fact, the protection given to the worker by the capsule wall is sufficient for the material to be taken out of the dangerous category, and cans of the encapsulated pesticide do not need to be labelled with the skull and crossbones. When performing a test on a field of sweet corn, scientists found that they could reduce the amount of pesticide used to one quarter of a pound per acre, two to four times less than the amount used in the normal spraying treatment. Furthermore, in other tests, it was found that the encapsulated product controlled insects from five to seven days in the field, whereas the unencapsulated product was only effective for one to two days. Thus, not only is the amount required per spraying smaller, but also in crops requiring several treatments, the number of sprayings can be reduced thus saving energy and pesticide.

The Pennwalt Corporation has also carried out tests using encapsulated synthetic pyrethrins to combat cricket infestation. The microcapsules were still giving 100% kill of crickets 56 days after an application, whereas the normal spray of the same material had a kill of 85% after one day and 54% after four days. Another insecticide marketed by Pen­nwalt, which is non-toxic enough to be used by homeowners, persists only one day in the field. Greenhouse tests on an experimental microencapsulated formulation of the same material was still giving 100% kill of cockroaches after 12 weeks. Anyone who has tried to kill white flies by repeated daily sprayings over several weeks can appreciate the potential benefit of this approach.

An unexpected difficulty in the use of encapsulated pesticides was encountered in the United States, when it was found that some pesticide capsules had been made so like pollen grains that bees had no means of knowing which fine particles were pollen and which were pesticide. As a result, the pesticide capsules were collected and taken to the hive and stored as food. Later ingestion of the capsules caused high mortalities in the bee colonies. From this example, it is obvious that one must make sure that the microcapsules do not look like pollen to insects in our fields.

Starch xanthate capsules, manufactured by the process developed by Shasha and co-workers, have proven to be very useful in combating weeds. The herbicide to be used is encapsulated in the starch matrix and then placed on the field at the time of planting the seeds. The capsule does not release its chemical until the time when the weather conditions are suitable for seed germination, and so it can be spread well in advance of the time it is required
to control the weeds. Furthermore, it is possible to develop double encapsulated material, in which the prime capsule is given a second coating of starch xanthate. These double encapsulated materials take longer to release their material so they can be applied at the same time as the original capsules, but release a secondary dose of material later in the growing season. It is conceivable that by using different forms of capsules, one could have weed control and fertilizer material encapsulated so that they are released into the field at the appropriate times and the necessity for going over the field several times would be removed.

Nematodes are tiny thread-like parasitic worms that can cause problems for plants and animals. Plant parasitic nematodes are estimated to cause four billion dollars damage to U.S. agricultural products annually. To kill nematodes, one must treat the soil and this usually requires massive doses of the material in order to achieve a significant effect on the parasites. However, recent experiments with starch xanthate encapsulated pesticide have been very encouraging, in that when used in greenhouse tests, small doses were found to be effective for longer periods against the parasite.

Applications of Encapsulation Technology in the Food Industry

Perhaps the best known application of encapsulation technology in food science is the fact that encapsulated flavors retain their odour and taste much longer than free flavoring agents placed in such things as gelatin desserts and chewing gum. Much play in advertising has stressed the fact that “flavor buds” (ie. microcapsules) in the gelatin or the chewing gum give you longer lasting flavour. Another interesting application of encapsulated material is in the making and storing of frozen bread dough. In the traditional process for making bread, the bubbles for aerating the dough are made by the fermentation of yeast. The same effect can be achieved by using baking powder which when in contact with an acid, generates bubbles of carbon dioxide. Thus, many recipes call for sodium bicarbonate and tartaric acid to be placed in the mixture. In frozen dough, one does not want these bubbles to be generated until one is ready to cook the product. Therefore, the sodium bicarbonate and tartaric acid are encapsulated with a wall material that does not dissolve in the water of the frozen dough until the material is thawed out and heated.

Salt interferes with the action of yeast and in the domestic situation, one compensates for this by adding extra yeast to the mixture. In the mass baking of bread in large scale bakeries, this is not a satisfactory solution and a recent innovation using encapsulated salt promises to solve this problem. In this situation, the salt is coated with a wall which does not break down until the temperature of the baking bread or food product is reached. Such salt is known in the food industry as “enrobed” salt.

Vitamin C is not very stable on the shelf or in the cooking process. However, encapsulated vitamin C has a much improved shelf life. The wall substance can be designed to protect vitamin C even at normal baking temperatures so that the vitamin C is not degraded in a baked product and is still available for nutritional purposes. (Note: Even such well known compounds as aspirin tend to degenerate on the shelf, and encapsulation of aspirin increases the shelf life.) In the food industry, many of the capsule walls are made from specially treated oil which transform to a wax-like, edible, substance in the treatment process.

Iron deficiency is still a major problem among many groups in the United States. The treatment of the public bread supply with iron material to combat this problem is made difficult by the instability of some iron compounds during the baking process. Recently the development of encapsulated ferrous sulphate, which is readily available to the body, promises to overcome this problem.

Convenience foods flavored with citrus-type flavourings have a limited shelf life because of the incompatibility of the acid flavours with the other ingredients. This problem has largely been overcome by the use of encapsulated citrus flavors which do not come into contact with the other ingredients until a paste or other mixture is made.

Miscellaneous Applications of Microencapsulation Technology.

Some types of modern adhesives require the mixing of two components referred to as the resin and the hardener. These two chemicals
then interact to form the strong adhesive. It is not always convenient to make the mixture when carrying out the joining together of two components. It is now possible to make the two glue ingredients into microcapsules and coat the surfaces to be joined with dry capsules. These are brought together under pressure so that the capsules rupture and mix with each other. The wall of the capsule can be quite thin and its presence does not weaken the final joint.

Encapsulated glue is particularly useful in carrying out underwater repairs on boats or on structural systems such as oil rigs standing on the sea bed. For such applications, encapsulated specialist adhesives have been developed which set rock hard within 30 seconds of the rupturing of the microcapsules. When rivets are used to join two pieces of metal together, they are often coated with an anti-corrosion liquid. Again, the coating of each rivet as it is put into position is not always easy. A microencapsulated anti-corrosion fluid has been developed, which enables one to coat the rivets before they are handled. The act of driving the rivet into the hole ruptures the capsules releasing just the right amount of anti-corrosion fluid in the place where it is needed on the internal walls of the riveted joint.

In the home laundry, it is useful to use both a bleach in the early stages of the washing process followed by the addition of a whitening agent. The whitening agents in the powder are the little blue crystals. When they are coated on to the fabric, they absorb ultraviolet light, invisible to the eye, and give out extra light in the range of visible light. This make the fabric look brighter than white! Unfortunately, many brighteners are incompatible with bleaches. In the normal wash process, the bleach is used up in two to four minutes. If one encapsulated bleach and put it into a washing powder along with encapsulated brighteners, one could arrange for the bleach capsules to rupture as soon as water was added to the mixture but arrange for the capsules of brightener to be released five minutes after the wash process began. In this way, the whole system becomes one dry powder without the necessity to use separate bleach bottles. Ultimately, it would also be possible to develop washing powders in which softener was released from a third set of microcapsules, twenty to thirty minutes after the process began.

The removal of oil and fat stains from clothing often requires the use of an oil solvent which may be either toxic or inflammable. To store a bottle of such substance with subsequent overuse of the material forms a domestic hazard. A new product has been evolved in which a piece of disposable cleaning cloth is coated with encapsulated cleaning material. When a spot has to be removed from a fabric, the act of rubbing the spot with the coated disposable cleaning cloth ruptures the capsule to release a sufficient amount of fluid for the cleaning process. One could sell such a product in a package of ten cleaning tissues so that one could use them one at a time. It has been shown that encapsulated solvents can be stored for several years without the loss of significant amounts of solvent through the capsule wall, so that such a cleaning product would have a long shelf life (or purse life) and would be safe until needed.

In the design of rocket fuel, it is sometimes useful to include water in the fuel as a temperature moderator and also as a source of hydrogen and oxygen. To use the water as a liquid in the formulation of rocket fuel causes many problems. Encapsulated water, however, can be mixed with the other ingredients of the rocket fuel and pressed together to form a solid fuel combustion chamber. However, it is not easy to add water to gasoline in a uniform manner. Encapsulated water, however could be made of an appropriate size so that is remained in suspension in the fuel tank. The encapsulated water could assist in combustion by acting as extra hydrogen and oxygen fuel and also explosively disrupting in the heat of the combustion chamber to give a more finely divided spray of gasoline which would further improve the combustion process. Such an additive would increase the efficiency of the engine and reduce pollution. Many waxes would prove suitable as an encapsulation wall. Perhaps tomorrow’s motorists will buy fuel with added encapsulated water for better mileage.

In our discussion of medical applications of encapsulated products, it was mentioned that one can determine skin temperature by spraying encapsulated liquid crystals onto the skin. The same technique can be used to measure the temperature of moving mechanical parts. For example, liquid crystals have been sprayed onto
the outside of a wheel drum of a car and the
temperature rise, caused by the braking action,
appeared as colored contours on the drum.1–4

Anyone who consistently reads upscale
“women’s magazines” such as Vogue or
Mademoiselle must have noticed the prolifera­
tion of perfume ads employing microencapsula­
tion technology. A trace of perfume is held
inside a spot of weak adhesive until the opening
of the pages causes the microcapsules to burst
and release the scent. This phenomenon has led
creative marketers to add microencapsulated
fragrances to printing inks (such as chocolate to
brown ink, used to depict chocolate in newspaper advertising) in a continuing effort to
diversify a product’s appeal to the reader’s
senses.

Dry Microencapsulation
In Advanced Materials

Ceramicists have demonstrated that one can
make novel compounds out of metal and
ceramic material (cermets) by dry mixing the
ingredients followed by pressure treatment.
Thus in Figure 10 a novel material which con­
tains a conducting path of a metal network
formed by the collapsed coatings of metal coat­
ed ceramic material is shown. Such networks
can give materials with desired conductive
properties as well as tailormade strength
structure.5–18

This example is only meant to show the
possibilities inherent in applying microencap­
sulation technology to composite powders of
metal, ceramic and/or polymer constituents. A
review of such applications is beyond the scope
of this article.

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Fig. 10 Mechanofusion can create microcapsules of material
which can be compressed to create composite mate­
rials of desirable structure.

(a) X-ray micrograph (Ni. Kα )
of the microcapsule after 4500 s treating at 11.7 rps.
(b) and (c) Nickel network formed along the interface
between contiguous encapsulated fineparticles after hot
pressing, (b) 1μm nickel coated onto alloy particles,
(c) 0.02μm nickel coated onto alloy particles.
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