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A novel approach on microencapsulation in drug delivery system for cancer diagnosis

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ABSTRACT

The main objective of this article was to discuss on microencapsulation in drug delivery system for cancer diagnosis. Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles formation of thin coatings of wall material around the substances. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. The reasons for microencapsulation are countless. It is mainly used to increase the stability and life of the product being encapsulated, facilitate the manipulation of the product and control its liberation in an adequate time and space. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides. For over a half a century now, microencapsulation and encapsulated products have played a very important role in numerous industries like agriculture, chemical, pharmaceutical, cosmetic and the food industry.

Keywords: Microencapsulation, Cancer, Nova Caps®.

INTRODUCTION

Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles formation of thin coatings of wall material around the substances. The process had its origin in the late 1930s as a cleaner substitute for carbon paper and carbon ribbons as

sought by the business machines industry. The ultimate development in the 1950s of reproduction paper and ribbons that contained dyes in tiny Gelatine capsules released on impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials, including drugs [1, 2]. A well designed controlled drug delivery system

can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time thereby causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200µm. Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Microencapsulation includes Bio encapsulation which is more restricted to the entrapment of a biologically active substance (from DNA to entire cell or group of cells for example) generally to

improve its performance and /or enhance its shelf life [3, 4]. The reasons for microencapsulation are countless. It is mainly used to increase the stability and life of the product being encapsulated, facilitate the manipulation of the product and control its liberation in an adequate time and space. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack. In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsule, as in the controlled release of drugs or pesticides. The problem may be as simple as masking the taste or odour of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

In environmental science, a pesticide may be microencapsulated to minimize leaching or volatilization risks. [5-6]

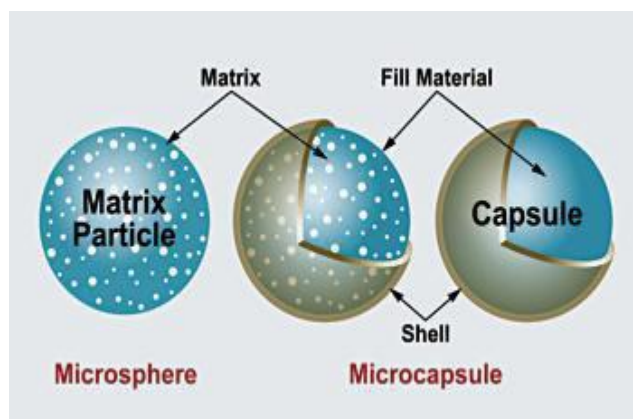


Figure 1: Formulation of Microcapsule

Advantages

This type of drug delivery systems mainly provides the encapsulated material to reach the area of action without getting adversely affected by the environment through which it passes. Pharmaceutical and biomedical advantages of micro particle include:

1. Taste and odour masking. Example: Fish oils, sulpha drugs.
2. Protection of drugs from environment.
3. Particle size reduction for enhancing solubility of the poorly soluble drug.

4. Sustained or controlled drug delivery Example: KCl (Potassium chloride), Ibuprofen.etc.
5. Targeted release of encapsulated material
6. Live cell encapsulation. Example: Resealed erythrocytes.
7. Conversion of liquid to free flowing solids.
8. Delay of volatilization.
9. Separation of incompatible components Example: Excipients, buffers and other drugs.
10. Improvement of flow property of the powder.
11. Safe handling of toxic substances.
12. Aid in dispersion of water insoluble substance in aqueous media [7]

Disadvantages

Although the advantages of micro particles are impressive there are certain limitations. These include:

1. The costs of the materials and processing of the controlled release preparation, which may be substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation / agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents and the cost, time probability of success in securing government registration of the product, if required [8].

Release mechanism of drug incase of micro encapsulation drug delivery system [9-10]

Mechanism for drug release from microspheres

Degradation controlled monolithic system

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attaches to the matrix and is released on the degradation of the matrix. The diffusion of the drug is slow as compare with degradation of the matrix.

Diffusion controlled drug release

In 1963 Folkman and Long systematically studied the slow release of drugs such as digitoxin, from the inside of silicon rubber tubing. In 1966 other researchers showed that when progesterone-loaded silicon rubber tubing was implanted in cattle, it was able to prevent the animal from becoming fertile for more than one year. Drug molecules need to diffuse through a polymer membrane or matrix to be released. It is divided into two classes:

Diffusion controlled reservoir system

The drug is surrounded by a polymer matrix. Here the active agent is encapsulated by rate controlling membrane through which the agent diffuses and the membrane eroded only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

Diffusion controlled monolirhic system

The drug is distributed throughout a polymer matrix. Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

Erosion

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like Glycerol mono stearate, Beeswax and Sterile alcohol etc.

Coating materials

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer the product requirements ie. Stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

Generally hydrophilic polymers and hydrophobic polymers (or) a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatine, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system [10]. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed

tablets, hard gelatine capsules, suspensions, and other dosage forms. The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and nonreactive with the core material; and provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability. The coating materials used in microencapsulation methods are amenable, to some extent, to in situ modification [11].

The selection of a given coating often can be aided by the review of existing literature and by the study of free or cast films, although practical use of free-film information often is impeded for the following reasons:

- Cast or free films prepared by the usual casting techniques yield films that are considerably thicker than those produced by the microencapsulation of small particles; hence, the results obtained from the cast films may not be extrapolate to the thin microcapsule coatings.
- The particular microencapsulation method employed for the deposition of a given coating produces specific and inherent properties that are difficult to simulate with existing film-casting methods.
- The coating substrate of core material may have a decisive effect on coating properties. Hence, the selection of a particular coating material involves consideration of both classic free-film data and applied results [12].

Coating material properties

- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific conditions.
- Film-forming, pliable, tasteless, stable.
- Non-hygroscopic, no high viscosity, economical.
- Soluble in an aqueous media or solvent, or melting.

- The coating can be flexible, brittle, hard, thin etc.

Examples of coating materials

- Water soluble resins – Gelatin, Gum Arabic, Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxyethylcellulose, Methylcellulose, Arabinogalactan, Polyvinyl alcohol, Polyacrylic acid.
- Waxes and lipids – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
- Water insoluble resins – Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), cellulose nitrate, Silicones, Poly lactideco glycolide.
- Enteric resins – Shellac, Cellulose acetate phthalate, Zein [13].

Clinical trials of cancer treatment using encapsulated cells to target Chemotherapy

The treatment of solid tumours like pancreatic cancer. The product consists of cells that have been genetically modified to over express a cytochrome P450 enzyme encapsulated in biologically inert cellulose sulphate polymers (Figure 2). The Nova Caps® product has already been tested in clinical trials in human patients suffering from pancreatic cancer, which has a very poor prognosis and represents an unmet medical need. In this clinical study, Nova Caps® were delivered by supra-selective catheterisation of blood vessels leading from the groin area to vessels feeding the pancreatic tumour where they are released and are flushed into smaller vessels where they become lodged (Figure 2). After successful instillation of Nova Caps®, the patient then received, via I.V infusion, low doses of the chemotherapeutic agent, ifosfamide, which is carried by the blood stream into the Nova Caps®

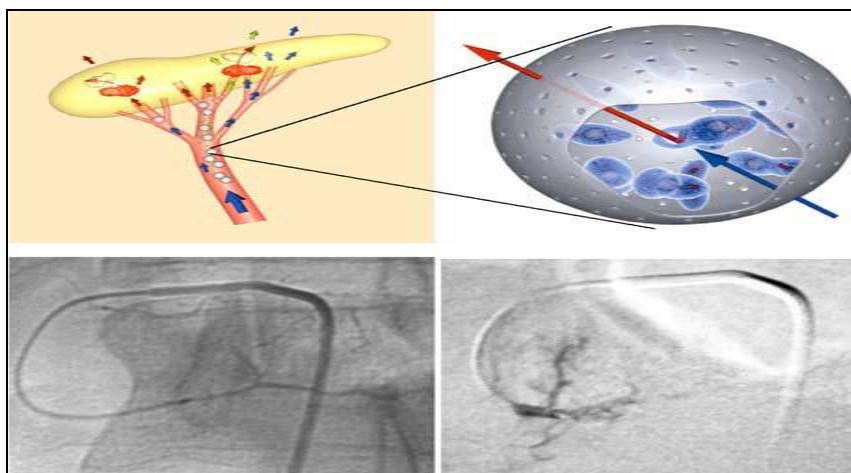


Figure 2: The Nova Caps® principle for the treatment of solid tumours Upper panel

Nova Caps® are delivered to a vessel feeding the pancreatic tumour using a supraselective catheter. Once released, the capsules are propelled by the blood flow into smaller vessels until they eventually become lodged. Two days later, ifosfamide (indicated by the blue arrow) is given I.V. and arrives at the capsule in the blood flow, which propels it into the capsule where it enters the cells that are over expressing a cytochrome P450 enzyme. Once in the cells, the ifosfamide is converted to the 4-hydroxyifosfamide intermediate which is then released from the cells and leaves the capsule (red arrow). The 4-hydroxyifosfamide is a short lived form that can pass freely across plasma membranes and enters surrounding cells, including the pancreatic cancer cells where it decays to phosphoramidate mustard which causes DNA cross linking. Any cells that attempt to undergo cell division then die, due to an accumulation of too many cross links which cannot be repaired. Lower panel: Angiogram from a patient treated with NovaCaps. Visible is the catheter and supraselective part of the catheter inserted into a vessel leading to the head of the pancreas, the site where the majority of pancreatic carcinomas arise. Left hand panel shows catheter before capsule delivery and the right hand panel after NovaCaps® delivery. Once inside the Nova Caps®, the Ifosfamide is metabolised by the cells within the Nova Caps® to a relatively short-lived, tumour toxic, product which is then released from the capsules and flows directly into the pancreas (Figure 2). Thus, in essence, Nova Caps® functions as a targeting device, increasing therapeutic efficacy while at the same time reducing the side

effects associated with more standard doses of chemotherapy. The feasibility of delivering Nova Caps® by this means was demonstrated in preclinical studies in a porcine model, and this data was used to support an application for a clinical trial in human patients. This phase I/II clinical trial, which involved the treatment of 14 patients suffering from pancreatic cancer with Nova Caps®, revealed that the application of Nova Caps® by this route is safe and Nova Caps® are well tolerated with no evidence of inflammatory or immune reactions. Additionally, there were no major toxicities beyond grade 2 associated with the low dose of ifosfamide that was used. The therapeutic benefit was also documented using the following parameters:

1. Quality of life, which was improved,
2. Tumour reduction observed in 4 patients with the other 10 patients showing stable disease,
3. 100% improvement in median survival over a control group, and
4. 1 year survival rates, which were twice as high as those documented after treatment with current gold standard treatment, Gemzar®.

In contrast to the more commonly used encapsulation of chemotherapeutics (i.e. formulations of chemotherapeutics), encapsulated cells over-expressing enzymes that can activate chemotherapeutic agents or pro drugs offer a promising means to treat tumours. Depending on the half-life of the activated drug, this type of approach can either be used locally or systemically. The first demonstration that this method could be used to treat solid tumours was provided in 1998,

using a mouse model of pancreatic cancer. In this study, feline kidney epithelial cells genetically modified to over-express a cytochrome P450 enzyme were encapsulated in polymers of cellulose sulphate and implanted into xenograft tumours. This was followed by administration of the chemotherapeutic agent ifosfamide. Tumour reductions and even complete loss of the tumour was observed in the treated mice group but not in control mice. This data could be reproduced using encapsulated HEK 293 cells over-expressing the same cytochrome P450 isoform. These encapsulated HEK293 cells were further developed for the initiation of a clinical trial. The prodrug activating strategy is not limited to the treatment of pancreatic cancer and has also been demonstrated to be efficacious in preclinical models of mammary cancer, and a mouse model of peritoneal spread from gastrointestinal cancer.

Samel and Lohr have tested the use of encapsulated cells expressing cytochrome P450 and ifosfamide in a mouse model of peritoneal spread from gastrointestinal cancer, since there is a lack of effective treatments for peritoneal spread. Adult Bal b/c mice were inoculated i.p. with 1×10^6 colon cancer cells that had previously been transfected with the green fluorescent protein (GFP) gene so that the tumour distribution in the peritoneal cavity as well as response to treatment could easily be measured. Two or five days later animals were randomly subjected to either i.p. treatment with ifosfamide alone or ifosfamide combined with microencapsulated cytochrome P450 expressing cells. Peritoneal tumour volume and tumour viability were assessed 10 days after tumour inoculation by means of fluorescence microscopy, spectroscopy and histology. Early i.p. treatment with ifosfamide and CYP2B1 cells resulted in a complete response. Treatment starting on day five as well as single-drug treatment with ifosfamide alone (without encapsulated cells) resulted in a partial response. This data suggest that targeted i.p. chemotherapy using a combination of a prodrug and its converting enzyme may be a successful treatment strategy for peritoneal spread from colorectal cancer, ivating cells. Sub sieve agarose capsules are about one-tenth the size of other encapsulated cell therapy products and are reported to have both higher mechanical stability and better molecular exchangeability than other systems, although this has not been rigorously

studied in a side by side comparison. In this study, cells that had been genetically modified to express the cytochrome P450 2B1 enzyme were encapsulated in sub sieve-size agarose capsules of ca.90 μm diameter. Changes in viability and function of the cells after encapsulation were measured in vitro and in a preformed tumour regression model in nude mice receiving the capsule implantation followed by administration of ifosfamide. Viable cells were detected for more than 1 month after encapsulation and they were able to activate ifosfamide. A more significant regression of preformed tumours in nude mice was observed in animals implanted with cell-containing capsules compared with those implanted with empty capsules [14-21].

Future Prospects of Microencapsulation

1. Microencapsulation can be defined as a process, which involves the complete envelopment of pre-selected core material(s) within a defined porous or impermeable membrane (shell) using various techniques, to give miniature sized particles ranging in size from 1-1000 μm . In practice, microencapsulation entails placing a spherical shell composed of a synthetic or natural polymer completely around another chemical. In a relatively simple form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Some materials like lipids and polymers, such as alginate, may be used as a mixture to trap the material of interest inside. Most microcapsules have pores with diameters between a few micrometers and a few millimeters. Many microcapsules however bear little resemblance to these simple spheres. The core may be a crystal, a jagged adsorbent particle, an emulsion, a Pickering emulsion, a suspension of solids, or a suspension of smaller microcapsules. The microcapsule even may have multiple walls.
2. Microencapsulation of oil ingredients, like omega-3, with sugar beet pectin could provide an alternative to more traditional encapsulating agents like milk proteins and gum Arabic. The incorporation of encapsulated hydrophilic actives into cosmetic aqueous formulations constitutes a challenge for two main intrinsic reasons: 1) the

encapsulation process normally takes place in aqueous media, and it's required to maintain the active in the core during the shell formation avoiding its migration to the continuous phase, and 2) leaking from the capsule core to the continuous phase during storage usually is a thermodynamically favoured process.

3. For over a half a century now, microencapsulation and encapsulated products have played a very important role in numerous industries like agriculture, chemical, pharmaceutical, cosmetic and the food industry. In recent decades these particles have been applied to numerous biotechnology and medical processes, including cell encapsulation for the generation of artificial implants, and the production of high density cell cultures [and the encapsulation of recombinant therapeutic proteins as a means of delivery.
4. Future prospects of microencapsulation of islets of Langerhans used sodium alginate and poly-L-lysine (PLL) to form the capsules [22-26].

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CONCLUSION

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimetres. The capsule protects the active ingredient from its surrounding environment until an appropriate time. Then, the material escapes through the capsule wall by various means, including rupture, dissolution, melting or diffusion. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion.

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