

MICROENCAPSULATION AND RECENT TRENDS IN DRUG DELIVERY: AN OVERVIEW

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ABSTRACT

Novel drug delivery systems have several advantages over conventional multi dose therapy. Much research effort in developing novel drug delivery system has been focused on controlled release and sustained release dosage forms. Now considerable efforts are being made to deliver the drug in such a manner so as to get optimum benefits. 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. Microencapsulation is a process where by small discrete solid particles or small liquid droplets are surrounded and enclosed by an intact shell. Microencapsulation is used to modify and delayed drug release form pharmaceutical dosage forms. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor. The intent of the paper is to highlight the potential of microencapsulation technique as a vital technique in novel drug delivery.

KEYWORDS: Microspheres, controlled release, sustained release, target site, therapeutic efficacy, novel drug delivery.

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 gelatin 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] The first research leading to the development of microencapsulation procedures for the Pharmaceuticals was published by Bungen burg de Jong and Kan in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin Coacervation process. 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.^[2] 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 protiens or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200 μm .^[3]

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. 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 200 μm . 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 &/or enhance its shelf life.^[4] Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials. Several of these properties can be attained by macro packaging techniques; however, the uniqueness of microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and not has been technically feasible.

Microencapsulation

- This technique can be used for converting liquid drugs in a free flowing powder.
- The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
- Incompatibility among the drugs can be prevented by microencapsulation.
- Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.
- Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
- Alteration in site of absorption can also be achieved by microencapsulation.
- Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.^[5]
- Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability.

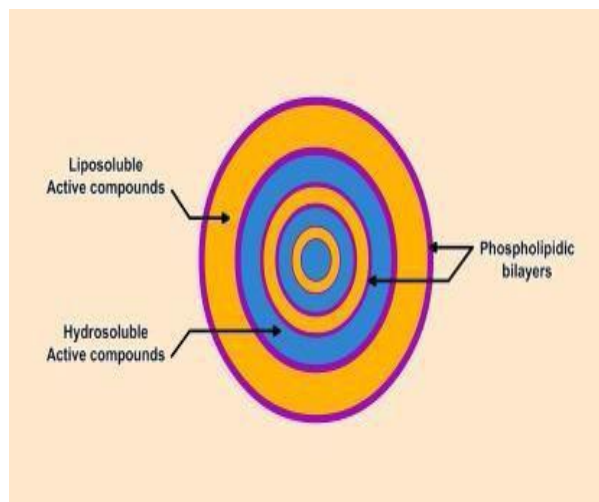


Fig. 1: Microencapsulation process.

The Reasons for Microencapsulation

The reasons for microencapsulation are countless. 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 odor of the core,^[6] or as complex as increasing the selectivity of an adsorption or extraction process.

Fundamental Considerations

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods .

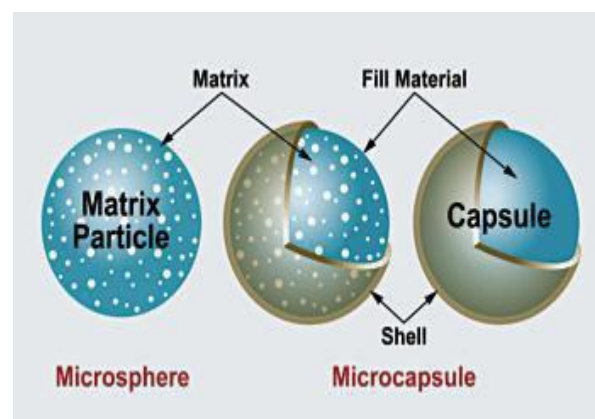


Fig. 2: Microsphere & microcapsule.

Core Material

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition

of the core material can be varied as the liquid core can include dispersed and/or dissolved material. The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators. The ability to vary the core materials composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsules properties.^[7]

Coating Material

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer the product requirements i.e. 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, 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 gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate and styrene maleic anhydride. The film thickness can be varied considerably,^[8] depending on the surface area of the material to be coated and other physical characteristics of the system. 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 gelatin capsules, suspensions, and other dosage forms.

Release Mechanisms

Mechanisms of drug release from microspheres are

1. Degradation controlled monolithic system

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on,^[9] degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

2. Diffusion controlled monolithic system

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.

3. Diffusion controlled reservoir system

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is

completed. In this case, drug release is unaffected by the degradation of the matrix.

4. Erosion

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc.^[10-11]

Techniques to Manufacture Microcapsules

Preparation of microspheres should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size,^[12] and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification.^[13,14]



Fig. 3: Microencapsulation techniques.

Microencapsulation Methods

- Air suspension
- Coacervation phase separation
- Multiorifice-centrifugal process
- Spray drying and congealing
- Pan coating
- Solvent evaporation techniques
- Polymerization

Air Suspension

Microencapsulation by air suspension technique consist of the dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating

material, usually a polymer solution, is spray applied to the moving particles. During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated, perhaps several hundred times during processing, depending on the purpose of microencapsulation the coating thickness desired or whether the core material particles are thoroughly encapsulated. The supporting air stream also serves to dry the product while it is being encapsulated. Drying rates are directly related to the volume temperature of the supporting air stream.^[15]

Coacervation Phase Separation

Microencapsulation by coacervation phase separation is generally attributed to The National Cash Register (NCR) Corporation and the patents of B.K. Green et al. The process consists of three steps.^[16]

- Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase.
- Deposition of the liquid polymer coating on the core material.
- Rigidizing the coating usually by thermal, cross linking or desolvation techniques to form a Microcapsule.^[17]

In step 2, the deposition of the liquid polymer around the interface formed between the core material and the liquid vehicle phase. In many cases physical or chemical changes in the coating polymer solution can be induced so that phase separation of the polymer will occur. Droplets of concentrated polymer solution will form and coalesce to yield a two phase liquid-liquid system. In cases in which the coating material is an immiscible polymer of insoluble liquid polymer it may be added directly. Also monomers can be dissolved in the liquid vehicle phase and subsequently polymerized at interface. Equipment required for microencapsulation this method is relatively simple; it consists mainly of jacketed tanks with variable speed agitators.

Multiorific-Centrifugal Process

The Southwest Research Institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to hurl a core material particle through an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation. Processing variables include the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity and surface tension of the core material.^[18] The multiorifice-centrifugal process is capable for microencapsulating liquids and solids of varied size ranges, with diverse coating materials. The encapsulated product can be supplied as slurry in the hardening media or as a dry powder. Production rates of 50 to 75 pounds per hour have been achieved with the process.

Pan Coating

The microencapsulation of relatively large particles by pan methods has become wide spread in the pharmaceutical industry. With respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating and there process has been extensively employed for the preparation of controlled release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and the coated with protective layers of various polymers. In practice, the coating is applied as a solution or as an atomized spray to the.^[19] desired solid core material in the coating pan. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in drying oven.

Spray Drying and Spray Congealing

Spray drying and spray congealing methods have been used for many years as microencapsulation techniques. Because of certain similarities of the two processes, they are discussed together. Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby relatively rapid solidification of the coating is effected.^[20] The principal difference between the two methods, for purpose of this discussion, is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing method however is accomplished by thermally congealing a molten coating material or solidifying a dissolved coating introducing the coating core material mixture into a nonsolvent. Removal of the nonsolvent or solvent from the coated product is then accomplished by sorption extraction or evaporation techniques.

Solvent Evaporation

Solvent evaporation techniques are carried out in a liquid manufacturing vehicle (O/W emulsion) which is prepared by agitation of two immiscible liquids. The process involves dissolving microcapsule coating (polymer) in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material (drug) to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core – coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain appropriate size microcapsules. Agitation of system is continued until the solvent partitions into the aqueous phase and is removed by evaporation.^[21] This process results in hardened microspheres which contain the active moiety. Several methods can be used to achieve dispersion of the oil phase in the continuous phase. The most common method is the use of a propeller style blade attached to a

variable speed motor. Various process variables include methods of forming dispersions, Evaporation rate of the solvent for the coating polymer, temperature cycles and agitation rates. Important factors that must be considered when preparing microcapsules by solvent evaporation techniques include choice of vehicle phase and solvent for the polymer coating, as these choice greatly influence microcapsule properties as well as the choice of solvent recovery techniques.^[22] The solvent evaporation technique to produce microcapsules is applicable to a wide variety of liquid and solid core materials. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings.

Polymerization

A relatively new microencapsulation method utilizes polymerization techniques to form protective microcapsule coatings in situ. The methods involve the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas, and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface.

Application of Microencapsulation

There are many reasons why drugs and related chemicals have been microencapsulated. The technology has been used widely in the design of controlled release and sustained release dosage forms.^[23-25]



Fig. 9: Applications of microencapsulation

- Many drugs have been microencapsulated to reduce gastric and other G.I. tract irritations. Sustained release Aspirin.
- To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.

- Preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.
- A liquid can be converted to a pseudo-solid for easy handling and storage. eg. Eprazinone
- Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.
- Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odor and volatility.
- Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g. vitamin A
- Separation of incompatible substance has been achieved by encapsulation.
- Cell immobilization: In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.
- Beverage production.
- Protection of molecules from other compounds.
- Drug delivery: Controlled release delivery systems.
- Quality and safety in food, agricultural & environmental sectors.
- Soil inoculation.
- In textiles: means of imparting finishes.

Physicochemical Evaluation Characterization

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.^[26,27]

Sieve analysis

Separation of the microspheres into various size fractions can be determined by using a mechanical sieve shaker (Sieving machine, Retsch, Germany). A series of five standard stainless steel sieves (20, 30, 45, 60 and 80 mesh) are arranged in the order of decreasing aperture size. Five grams of drug loaded microspheres are placed on the upper-most sieve. The sieves are shaken for a period of about 10 min, and then the particles on the screen are weighed.^[28]

Morphology of microspheres

The surface morphologies of microspheres are examined by a scanning electron microscope (XL 30 SEM Philips, Eindhoven, and The Netherlands). The microspheres are mounted onto a copper cylinder (10 mm in diameter, 10 mm in height) by using a double-sided adhesive tape. The specimens are coated at a current of 10 mA for 4 min using an ion sputtering device (JFC-1100E, Jeol, Japan).^[29]

Atomic force microscopy (AFM)

A Multimode Atomic Force Microscope from Digital Instrument is used to study the surface morphology of the microspheres. The samples are mounted on metal

slabs using double-sided adhesive tapes and observed under microscope that is maintained in a constant-temperature and vibration-free environment.^[30]

Particle size

Particle size determination approximately 30 mg microparticles is redispersed in 2–3 ml distilled water, containing 0.1% (m/m) Tween 20 for 3 min, using ultrasound and then transferred into the small volume recirculating unit, operating at 60 ml/s. The microparticle size can be determined by laser diffractometry using a Malvern Mastersizer X (Malvern Instruments, UK).^[31]

Polymer solubility in the solvents

Solution turbidity is a strong indication of solvent power. The cloud point can be used for the determination of the solubility of the polymer in different organic solvent.

Viscosity of the polymer solutions

The absolute viscosity, kinematic viscosity, and the intrinsic viscosity of the polymer solutions in different solvents can be measured by a U-tube viscometer (viscometer constant at 40°C is 0.0038 mm²/s/s) at 25 ± 0.10°C in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution.^[32]

Density determination

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and density of the microsphere carrier is determined.^[33]

Bulk density

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an auto trap (Quantach- Rome, FL, USA) until the microsphere bed volume is stabilized. The bulk density is estimated by the ratio of microsphere weight to the final volume of the tapped microsphere bed.

Capture efficiency

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement.

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence

of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200° within a minute of deposition of microspheres.^[34]

In vitro methods

There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating *in vivo* conditions has led to development of a number of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.^[35]

Beaker method

The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed from 60-300 rpm.

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements (paddle and basket). Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

Advantages

- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.
- The size, surface charge and surface hydrophilicity of microspheres have been found to be important in determining the fate of particles *in vivo*.
- Studies on the macrophage uptake of microspheres have demonstrated their potential in targeting drugs to pathogens residing intracellularly.

CONCLUSION

The microencapsulation technique offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action. In future by combining various other approaches, microencapsulation technique will find the vital place in novel drug delivery system.

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