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# MICROENCAPSULATION: REVIEW ON NOVEL APPROACHES

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## INTRODUCTION

### Microencapsulation:

Microencapsulation is a rapidly expanding technology. It is the process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. 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. Microencapsulation is receiving considerable attention fundamentally, developmentally and commercially[1].

The term microcapsule is defined as a spherical particle with size varying from 50nm to 2mm, containing a core substance. Microspheres are in strict sense, spherical empty particles. However the terms microcapsule and microsphere are often used synonymously. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200µm. Solid biodegradable microcapsules incorporating a drug dispersed or dissolved throughout the particle matrix have the potential for the controlled release of drug. These carries received much attention not only for prolonged release but also for the targeting of the anticancer drug to the tumor.

The concept of miroencapsulation[2] was initially utilized in carbonless copy papers. More recently it has received increasing attention in pharmaceutical and biomedical applications. The first research leading to the development of micro-encapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and

Kass in 1931 and dealt with the preparation of gelatin spheres and the use of gelatin coacervation process for coating. In the late 1930s, Green and co-workers of National cash register co. Dayton, Ohio, developed the gelatin coacervation process. Since then may other coating materials and processes of application have been developed by the pharmaceutical industry for the microencapsulation of medicines? Over the last 25 years numerous patents have been taken out by pharmaceutical companies for microencapsulated drugs.

**Fundamental considerations:**

Microencapsulation often 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. The intended physical characters of the encapsulated product and the intended use of the final product must also be considered.(Leon Lachman et.al)

**a. 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 a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators.

**b. Coating materials**

The coating material should be capable of forming a film that is cohesive with the core materials, be chemically compatible and non reactive with the core material and provide the desired coating properties such as strength, flexibility impermeability, optical properties and stability. The total thickness of the coatings achieved with microencapsulation techniques is microscopic in size.

**c. Selected stability, release and other properties**

Three important areas of current microencapsulation application are the stabilization of core materials, the control of the release or availability of core materials and separation of chemically reactive ingredients within a tablet or powder mixture. A wide variety of mechanisms is available to release encapsulated core

materials; such as disruption of the coating can occur by pressure, shear or abrasion forces, permeability changes brought about enzymatically etc., improved gastro tolerability of drugs can be obtained by microencapsulation.

**d. Physical character of the final product**

Microcapsules should have desirable physical properties like ability to flow, to be compacted or to be suspended and the capsule wall must be capable of resisting the pressure during compression etc.

**COATING MATERIALS[3]:**

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation or microcapsules. These materials include the polymers of natural and synthetic origin and also modified natural substances. Some of the polymers used in the preparation of the microcapsules are classified and listed below.

**Synthetic Polymers**

Non-biodegradable

- PMMA
- Acrolein
- Glycidyl methacrylate
- Epoxy polymers

Biodegradable

- Lactides and glycolides and their copolymers
- Polyalkyl cyano acrylates
- Polyanhydrides
- Carbopol

**Natural Materials**

Proteins

- Albumins
- Gelatin
- Collagen
- Carbohydrates
- Starch
- Agarose
- Carrageenan
- Chitosan

Chemically modified carbohydrates

- DEAE cellulose
- Poly (acryl) dextran
- Poly (acryl) starch

**Prerequisites for ideal microparticulate carriers:**

The materials utilized for the preparation of microparticulates should ideally fulfill the following prerequisites:

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability

- Water solubility or dispersability
- Bioresorbability
- Targetability
- Polyvalent

**METHODS OF MICROENCAPSULATION[4]**

Preparation of microcapsules as prolonged action dosage form can be achieved by various techniques under following headings.

1. *Coacervation phase separation*
    a. By temperature change
    b. By incompatible polymer addition
    c. By non-solvent addition
    d. By salt addition
    e. By polymer-polymer interaction
    f. By solvent evaporation
2. *Multi orifice centrifugal process*.
3. *Pan coating*
4. *Air suspension coating*
5. *Spray drying and spray congealing*
6. *Polymerization*
7. *Melt dispersion technique.*

**1. Coacervation phase separation**:

Microencapsulation by coacervation phase separation is generally attributed to the national cash register (NCR) corporation and the patents of Green et.al. The general outline of the processes consists of three steps carried out under continuous agitation.

1. Formation of three immiscible chemical phases.
2. Disposition of the coating, and
3. Rigidization of the coating

a. *By thermal change*: Phase separation of the dissolved polymer occurs in the form of immiscible liquid droplets, and if a core material is present in the system, under proper polymer concentration, temperature and agitation conditions, the liquid polymer droplets coalesce around the dispersed core material particles, thus forming the embryonic microcapsules. As the temperature decreases, one phase becomes polymer-poor (the microencapsulation vehicle phase) and the second phase. (the coating material phase) becomes polymer-rich.

b. *By incompatible polymer addition*: It involves liquid phase separation of a polymers coating material and microencapsulation can be accomplished by utilizing the incompatibility of dissimilar polymers existing in a common solvent.

c. *By non-solvent addition:* A liquid that is a non-solvent for a given polymer can be added to a solution of the polymer to induce phase separation. The resulting immiscible liquid polymer can be utilized to effect microencapsulation of an immiscible core material.

d. *By salt addition:* There are two types of coacervation: simple and complex. Simple coacervation involves the use of only one colloid, e.g. gelatin in water, and involves removal of the associated water from around the dispersed colloid by agents with a greater affinity for water, such as various alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form the coacervate. Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are most frequently used, and the coacervation is accomplished mainly by charge neutralization of the colloids carrying opposite charges rather than by dehydration.

e. *By polymer-polymer interaction*: The interaction of oppositely charged poly electrolytes can result in the formation of a complex having such reduce solubility that phase separation occurs.

f. *By solvent evaporation:* The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent, which is dispersed in volatile solvents, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer. In the case in which the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The solvent evaporation technique to product microcapsules is applicable to a wide variety of core materials. The core materials may be either water soluble or water insoluble materials.

**2. Multiorifice – centrifugal process**:

The South-West 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 therapy 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 of the coating material and the viscosity and surface tension of the core material. This method is capable of microencapsulating liquids and solids of varied size ranges, with diverse coating materials.

**3. Pan coatings:**

The microcapsulation of relatively large particles by pan coating method has become wide spread in the pharmaceutical industry and solid particles greater than 600 µg in size are generally considered essential for effective coating. The coating is applied as a solution or as an automized spray to the desired solid core passed over the coated materials during coatings are being applied in the coating pans.

**4. Air suspension coating:**

The process consists of the dispersing of solid particulate core materials in a supporting air stream and the spray coating of the air suspended particles. Within coating chambers, 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.

**5. Spray drying and spray congealing:**

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in liquified coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby relatively rapid solidification of the coating is effected. The principle difference between the two methods, is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of 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 by solidifying the dissolved coating by 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.

**6. Polymerization:**

The method involve the reaction of monomeric unit located at the interface existing between a core material 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 e.g., microcapsules containing protein solutions by incorporating the protein in the aqueous diamine phase.

**7. Melt-dispersion technique:**

In this technique the coating material is melted by heating upto $80^{o}$C. The drug is suspended in it and then emulsified in water containing emulsifying agent at $80^{o}$C under stirring. Microcapsules are formed as the temperature of the system reaches to room temperature.

**APPLICATIONS OF MICROENCAPSULATION:** (Chowdary, 1992)

**Pharmaceutical**

- To mask the taste of bitter drugs.
- To provide protection to the core material against atmospheric effects.
- In the design of controlled and sustained release dosage form.
- To reduce gastric and other G.I. tract irritation.
- To decrease the volatility
- To reduce toxic hazards.
- To reduce hygroscopicity.
- To increase flow properties.
- For the separation of incompatible substances.
- For liquid –solid conversions.

**Biomedical:**

- *As artificial cells*: to remove or convert unwanted metabolites or toxins from the body; for the treatment of chronic renal failure and congenital enzyme deficiency.
- *Liposomes*: entrapment of enzymes with in concentric layers of lipids; used for the entrapment of enzyme for enzyme studies, for enzyme and drug targeting.
- Magnetic microcapsules: for drug targeting.

**Characterization of microcapsules** (vyas etal,2002)

The characterization of microcapsule carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. The parameters that are generally evaluated for characterization of microcapsules are:

1. **Particle size and shape:** The most widely used procedure to visualize microcapsule are conventional light microscopy, and Scanning electron microscopy (SEM). Both techniques can be used to determine the shape and outer structure of microcapsule. SEM provides higher resolution in contrast to the light microscopy. It allows investigation of the microsphere surfaces and after particles are cross sectioned, it can also be used for the investigation of double walled systems. Confocal laser scanning microscopy (CLSM) is applied as a nondestructive visualization technique, which allows characterization of structures not only on surface, but also inside particle.

2. **Fourier trans form –infrared spectroscopy: (FTIR**)

   FTIR is used to determine the degradation of the polymeric matrix of the carrier system, and also interaction between drug and polymer system if present.

3. **Density determination**

   The density of the microcapsule can be measured by using a multi volume

   pychnometer. Accurately weighed sample in a cup is placed in pychnometer, helium is introduced at a constant pressure in chamber and allowed to expand. The expansion results in a decrease in pressure within the chamber. From two pressure readings the volume and hence density of microcapsule can be determined.

4. **Isoelectric point:**

   The micro electrophoresis is an apparatus used to measure electrophoretic mobility of microsphere from which the isoelectric point can be determined. The electrophoretic mobility can be related to surface contained charge, ionisable behavior or ion absorption nature of microsphere.

5. **Capture efficiency**

   The capture efficiency of microcapsule or the percent drug entrapment can be determined by allowing washed microcapsule to lyse. The lysate is then subjected to determination of active constituents as per monograph. The percent encapsulation efficiency is calculated using following equation

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

**6. Contact angle**

The angle of contact is measured to determine the wetting property of microcapsule. It determines the nature of microsphere in terms of hydrophilicity or hydrophobicity. The angle of contact is measured at the solid/air/water surface by placing a droplet in circular cell mounted above the objective of inverted microscope. Contact angle is measured at 20$^{o}$C within a minute of decomposition of microsphere.

**7. In-vitro release studies:**

Release studies for microcapsules can be carried out in different pH condition like pH 1.2 and pH 7.4 using USP rotating basket or paddle apparatus. The samples are taken at specific time intervals and are replaced by same amount of fresh medium. The samples withdrawn are analyzed as per the monograph requirement and release profile is determined using the plot of amount released as a function of time.

**KINETICS OF DRUG RELEASE**

Release of the active constituent is an important consideration in case of microcapsules.Many therotically possible mechanisms may be considered for the release of the drug from the microparticulates.

1. Liberation due to polymer erosion or degradation
2. Self diffusion through the pore
3. Release from the surface of the polymer.
4. Pulsed delivery initiated by the application of an oscillating or sonic field.

In most of the cases, a combination of more than one mechanism for drug release may operate, so the distinction amongst the mechanisms is not always trivial. The release profile from the microcapsules depends on the nature of the polymer used in the preparation as well as on the nature of the active drug.

Attempts to model drug release from microcapsule have been reported and in the treatment of their data, it was assumed that drug release was confined to any of the order such as zero order or first order processes. One

indication of mechanism can be obtained using a plot of log of cumulative percentage of drug remaining in the matrix against time.

First order release[5] would be linear as predicted by following equation.

$$\text{Log } C = \text{Log } Co - Kt/2.303 \quad \text{———-————(1)}$$

Where, C = Amount of drug left in the matrix

Co = Initial amount of drug in the matrix

K = First order rate constant, (time $^{-1}$)

t = time, either in hours or minutes

The *in-vitro* drug release data obtained from selected batch of microcapsules was treated according to equation (1) by plotting log of cumulative % of drug remaining against time. Next, an attempt was made to see whether the drug release is by diffusion. For system, which will release the drug by diffusion, were proposed by Higuchi[6].

$$Q = [D\epsilon/\tau\ (2A - \epsilon\ C_s)\ C_s\ t]^{1/2} \quad \text{---------- (2)}$$

Where, Q = Weight in grams of drug released per unit surface area.

D = Diffusion co-efficient of drug in the release medium.

ε = Porosity of the matrix.

Cs = Solubility of drug in the microcapsule expressed as gm/ml.

A = Total concentration of drug in matrix

τ =Tortuosity of the matrix

t = Time

The assumption made in the deriving equation (2) is as follows:

- A pseudo steady state is maintained during release.
- A » Cs i.e., excess solute is present.
- C = 0 solution at all times (perfect sink).

- Drug particles are much smaller than those in the matrix.
- The diffusion coefficient remains constant.
- No interaction between the drug and the matrix occurs.

For the purpose of data treatment, equation is usually reduced to,

$Q = Kt^{1/2}$ ----------(3)

Therefore a plot of amount of drug released verses the square root of time should be

linear if the drug release from the matrix is diffusion controlled.

Precisely, to know the exact mechanism of drug release, whether it is by diffusion or with combination of diffusion and erosion control, the data has also been plotted according to equation as suggested by Korsemeyer[7], they used a simple empirical equation to describe the general solute release behavior from control release polymer matrices.

$\frac{M_t}{M\infty} = Kt^{n \ldots}$ ---------- (4)

$\frac{M_t}{M\infty}$ = the fraction of drug release

K = Kinetic rate constant

t = Release time.

n = Diffusional exponent for drug release.

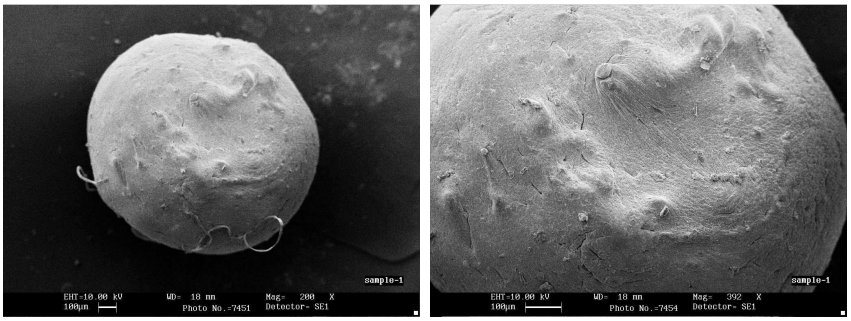
The value of 'n' gives an indication of the release mechanism. For non –Fickian release, the 'n' value falls between 0.5 and 1.0, while in the case of Fickian diffusion, $n \leq 0.5$ for zero order release (case II transport) $n = 1$ and for super case II transport $n > 1$.

The *in-vitro* drug release data obtained from microcapsules was treated according to equation (4) by plotting log cumulative percentage of drug release Vs log time.

In the present study, the release data obtained were plotted according to the above equations. These graphs are shown in results.

**Fig-1: SEM Photographs of Carbopol-alginate Microcapsule (CPA11) of Nitrofurantoin.**

**A. Single**




B. Surface

**Fig-2: SEM Photographs of Chitosan-alginate Microcapsule (CHA1150) of Nitrofurantoin.**

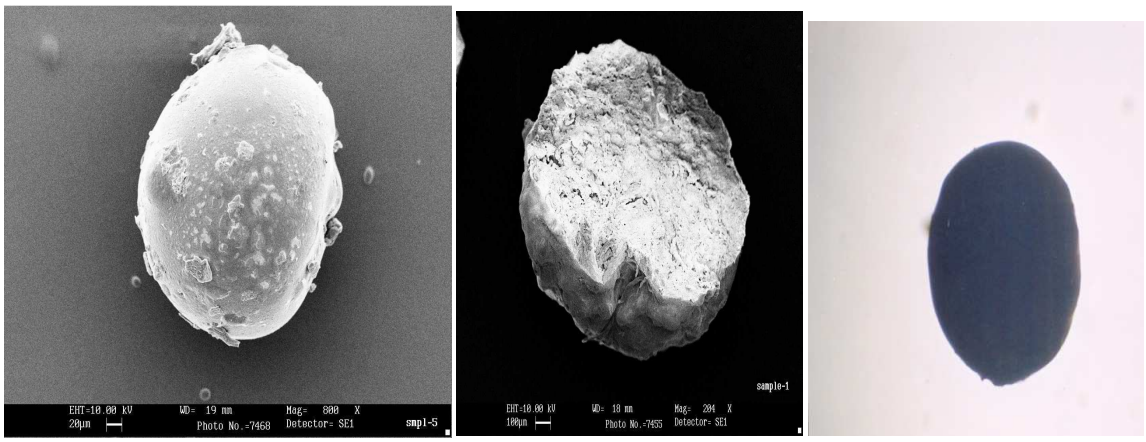
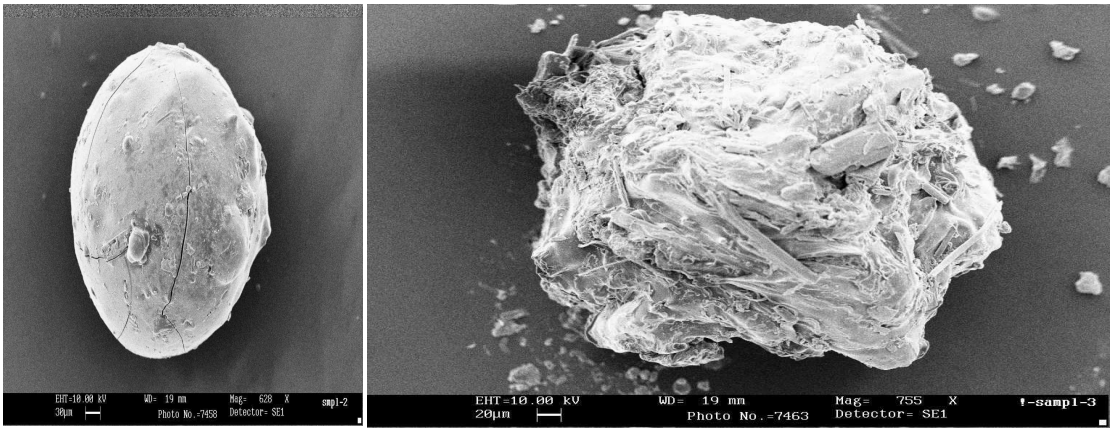



**Fig-3: scanning and optical view of microencapsules.**



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