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# Microencapsulation: Convenient mode of drug delivery in novel drug delivery system

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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 tumour. The intent of the paper is to highlight the potential of microencapsulation technique as a vital technique in novel drug delivery.

Key-Words: Microencapsulation, controlled drug delivery system, microspheres as carriers for drugs.

## Introduction

Microencapsulation is a process by which solids, liquids or even gases may be covered in microscopic particles formation of very thin coatings of core material around the substances that are to be coated. 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.

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Accurately formulated controlled drug delivery system can overcome some of the problems of conventional dosage form and increase the therapeutic efficacy and also improve the patient compliance of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the therapeutic agent to the target tissue/cell in the optimal amount in the proper period of time there by causing minimising the toxicity and side effects [2].

**Etiology**

There are various reasons for microencapsulation. 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 process.

**Core material**

The core material is 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.

**Coating material**

The selection of appropriate coating material decides the physical and chemical properties of the resultant product. 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. Generally hydrophilic polymers, hydrophobic polymers (or) a combination of both are used for the microencapsulation process.

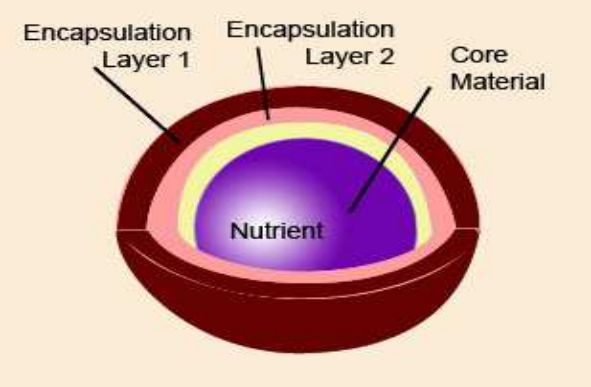


**Fig. 1: Microencapsulation**

**Mechanisms behind the drug release**

There are various mechanisms of drug release that are proposed for microencapsulation [6].

i. The coating is dissolved away from around the core such as when a liquid flavouring oil is used in a dry powdered beverage mix
ii. A compressive force in terms of a 2 point or a 12 point force breaks open the capsule by mechanical means
iii. The coating melts away from the core releasing the core in an environment such as that occurring during baking
iv. The capsule is broken open in a shear mode such as that in a waring blender or a Z-blade type mixer
v. The core diffuses through the coating at a slow rate due to the influence of an exterior fluid such as water or by an elevated temperature.

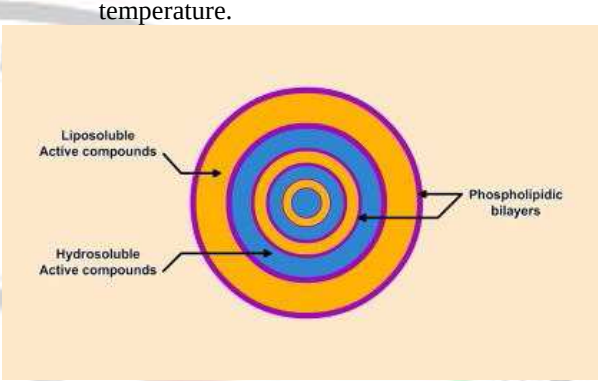


**Fig. 2: Microencapsulation process**

**Methods of preparation**

There are some conditions which are to be maintained during preparation of microencapsulated product. They are as follows**:**

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

**Microencapsulation methods** [4]

1) Air suspension
2) Coacervation phase separation
3) Multiorifice-centrifugal process
4) Pan coating
5) Polymerization
6) Spray drying and congealing
7) Solvent evaporation techniques

**Air suspension**

Microencapsulation by air suspension technique consist of the dispersing of solid, particulate core materials in a supporting air stream and the spraying of coating solution 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 of the chamber, where a coating material, usually a polymer solution, is applied by spraying to the moving particles. During each cycle 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.

**Coacervation pahse 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 [7]:

a) Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase.
b) Deposition of the liquid polymer coating on the core material.
c) Rigidizing the coating usually by thermal, cross linking or desolvation techniques to form a microcapsule.

In second step, 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.

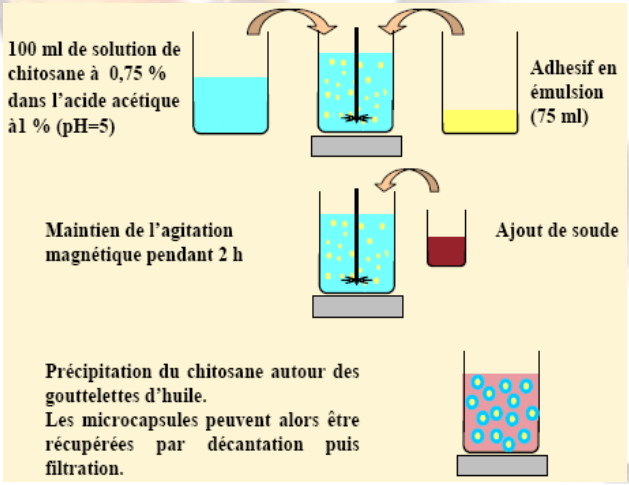


**Fig. 3: Coacervation pahse separation technique**

**Multiorific-centrifugal process**

The Southwest Research Institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes centrifugal forces to push 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. 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 s a dry powder.

**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 of controlled release preparation. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds and the coated with protective lagers of various polymers. In practice, the coating is applied as a solution or as an atomized spray to the 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.

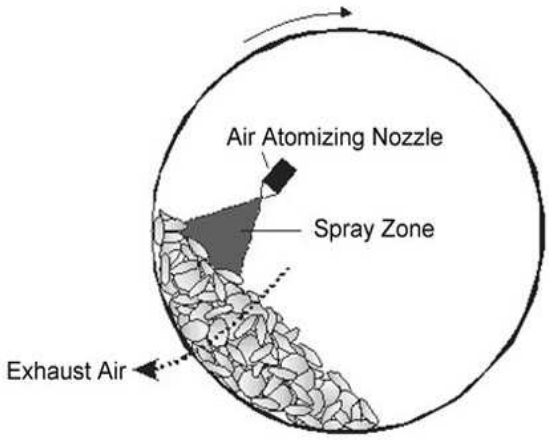


**Fig. 4: Representation of a typical pan coating**


**Fig. 5: List of variables affecting pan coating process[8]**

**Polymerization**

A relatively new microencapsulation method utilizes polymerization techniques to from 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.

**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 affected. 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 by solidifying a 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 sorptionextraction 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.

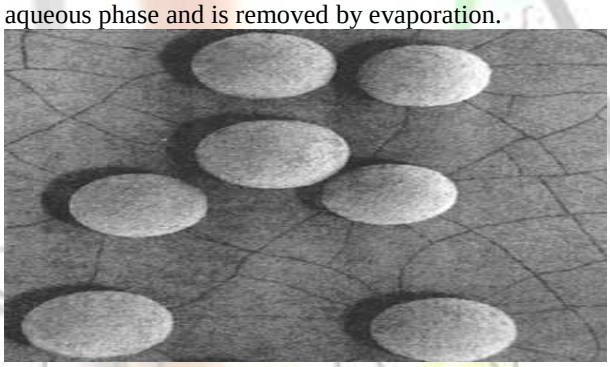

**Fig. 6: Scanning electron micrograph of cellulose esters (CAB381-20) matrix microspheres 250-355 mm sieve fraction prepared using the emulsion solvent evaporation method[9].**

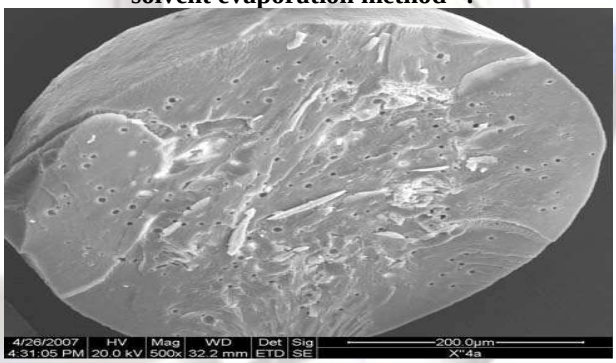


**Fig. 7: Cross-sectional view of a cleaved microsphere preparation from a 300-425mm sieve fraction after buffer dissolution [10-11].**

**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 [12, 13].

**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 [14].

**Morphology of microspheres**

The surface morphologies of microencaosulated product are examined by a scanning electron microscope (XL 30 SEM Philips, Eindhoven, and The Netherlands). The microencapsulated product is 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) [14, 15].

**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) [17].

**Polymer solubility in the solvents**

Solution turbidity is a strong indication of solvent power [18]. The cloud point can be used for the determination of the solubility of the polymer in different organic solvents [19].

**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 0C is 0.0038 mm2/s /s) at 25 ± 0.1˚C in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution [15].

**Bulk density**

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an autotrap (Quantach- rome, FL, USA) until the microsphere bed volume is stabilised. The bulk density is estimated by the ratio of microencapsulated product weight to the final volume of the tapped microsphere bed [16-23].

**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 [13]. The percent encapsulation efficiency is calculated using following equation:

% Entrapment = Actual content/Theoretical content x 100.

**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 200C within a minute of deposition of microspheres [13].

***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 [29, 30, 31, 32 and 33].

**Dissolution apparatus**

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle [24, 25, 26, 27, and 28]. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

**Application of microencapsulation**

The technology has been used widely in the design of controlled release and sustained release dosage forms.

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

been reported to cause significantly less G.I. bleeding than conventional preparations.

C. A liquid can be converted to a pseudo-solid for easy handling and storage. eg.Eprazinone.
D. Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.
E. Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g.Vit.A.Palmitate.
F. Separation of incompatible substance has been achieved by encapsulation

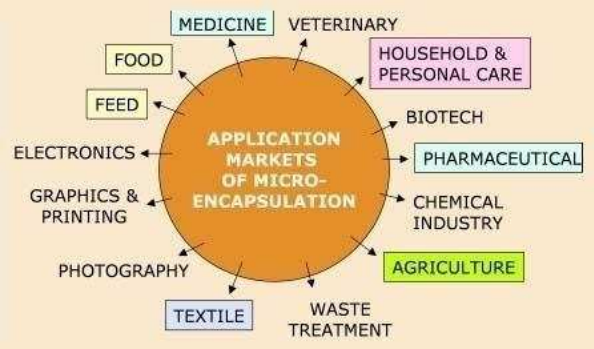


**Fig. 8: Application of microencapsulation**

**EXAMPLES OF SOME MICROENCAPSULATED DRUGS** [2]

| *Drug / Core material* | *Characteristic property* | *Purpose of encapsulation* | *Final product form* |
|---|---|---|---|
| Actaminophen | Slightly water soluble solid | Taste masking | Tablet |
| Aspirin | Slightly water soluble solid | Taste masking, sustained release, reduced gastric irritation, separation of incompatibles | Tablet or capsule |
| Islet of Langerhans | Viable cells | Sustained normalization of diabetic condition | Injectable |
| Isosorbide dinitrate | Water soluble solid | Sustained release | Capsules |
| Menthol | Volatile solution | Reduction of volatility, sustained release | Lotion |
| Progesterone | Slightly water soluble solid | Sustained release | Varied |
| Potassium chloride | Highly water soluble solid | Reduced gastric irritation | Capsule |
| Urease | Water soluble enzyme | Permselectivity of enzyme, substrate, and reaction products. | Dispersion |
| Vitamin A palmitate | Nonvolatile liquid | Stabilization to oxidation | Dry powder |

## Conclusion

The very much popular microencapsulation technique is the most convenient way of protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This drug delivery system gives accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue. In future by combining various other approaches, microencapsulation technique will find the vital place in novel drug delivery system.

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