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MICROENCAPSULATION: A REVIEW A NOVEL APPROACH IN DRUG DELIVERY

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ABSTRACT

The review of Microencapsulation is a well-established dedicated to the preparation, properties and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and-tested techniques relevant to micro and nano particles and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology and research applications. The Microparticulate offers a variety of opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. Microencapsulation technology can protect active materials against environment, stabilize them, prevent or suppress volatilization. Microencapsulation technology can provide new forms and features and many polymeric drug delivery systems, biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. Its scope extends beyond conventional microcapsules to all other small particulate systems such as self assembling structures that involve preparative manipulation. The review covers encapsulation materials, physics of release through the capsule wall and / or desorption from carrier, techniques of preparation, many uses to which microcapsules.

KEYWORDS: Microencapsule, core material, coating material.

INTRODUCTION

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. 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 tumour. The concept of miroencapsulation 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, 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 macropackaging 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.[1-5]

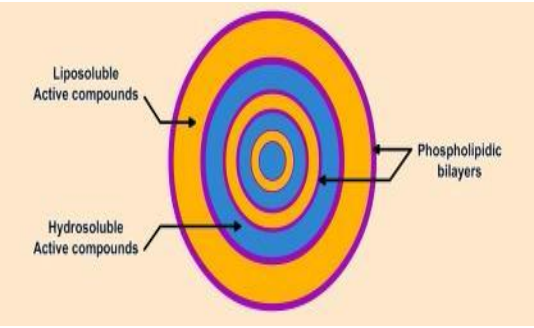

Figure 1: Microencapsulation process

Reasons for microencapsulation

The primary reason for microencapsulation is found to be either for sustained or prolonged drug release. This technique has been widely used for masking taste and odor of many drugs to improve patient compliance. 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. Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability.[6-9]

ADVANTAGES[10]

1. An effective protection of the encapsulated active agent against (e.g. enzymatic) degradation
2. The possibility to accurately control the release rate of the incorporated drug over periods of hours to months.
3. An easy administration (compared to alternative parenteral controlled release dosage forms, such as macro-sized implants).
4. Desired, pre-programmed drug release profiles can be provided which match the therapeutic needs of the patient.

RELEASE MECHANISMS

Mechanisms of drug release from microspheres are.

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 degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

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.

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.

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.

Basic consideration of microencapsulation technique[11-15]: 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.

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. 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.

1. 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.
2. 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.
3.
4. 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.

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.
- **Water insoluble resins** – Ethylcellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), cellulose nitrate, Silicones, Poly lactideco glycolide.
- **Waxes and lipids** – Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.
- **Enteric resins** – Shellac, Cellulose acetate phthalate, Zein

c. 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.

SYNTHETIC POLYMERS

Non-biodegradable

1. PMMA
2. Acrolein
3. Glycidyl methacrylate
4. Epoxy polymers

Biodegradable

1. Lactides and glycolides and their copolymers
2. Polyalkyl cyano acrylates
3. Polyanhydrides
4. Corbopol

NATURAL MATERIALS

A. Proteins
B. Albumins
C. Gelatin
D. Collagen
E. Carbohydrates
F. Starch, Agarose
G. Carrageenan
H. Chitosan
I. Chemically modified carbohydrates
J. DEAE cellulose
K. Poly (acryl) dextran
L. Poly (acryl) starch

METHODS OF MICROENCAPSULATION

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

1. Air suspension coating
2. 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
3. Pan coating
4. Multi orifice centrifugal process.
5. Spray drying and spray congealing
6. Polymerization
7. Melt dispersion technique

1. Air-suspension coating[17-20]

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. Air-suspension coating of particles by solutions or melts gives better control and flexibility. The particles are coated while suspended in an upward-moving air stream. They are supported by a perforated plate having different patterns of holes inside and outside a cylindrical insert. Just sufficient air is permitted to rise through the outer annular space to fluidize the settling particles. Most of the rising air (usually heated) flows inside the cylinder, causing the particles to rise rapidly. At the top, as the air stream diverges and slows, they settle back onto the outer bed and move downward to repeat the cycle. The particles pass through the inner cylinder many times in a few minutes methods. The air suspension process offers a wide variety of coating materials candidates for microencapsulation. The process has the capability of applying coatings in the form of solvent solutions, aqueous solution, emulsions, dispersions or hot melts in equipment ranging in capacities from one pound to 990 pounds. Core materials comprised of micron or submicron particles can be effectively encapsulated by air suspension techniques, but agglomeration of the particles to some larger size is normally achieved.

2. Coacervation and microencapsulation

Coacervation is a colloid phenomenon. If one starts with a solution of a colloid in an appropriate solvent, then according to the nature of the colloid, various changes can bring about a reduction of the solubility of the colloid. As a result of this reduction a large part of the colloid can be separated out into a new phase. The original one phase system becomes two phases. One is rich and the other is poor in colloid concentration. The colloid-rich phase in a dispersed state appears as amorphous liquid droplets called coacervate droplets. Upon standing these coalesce into one clear homogenous colloid-rich liquid layer, known as the coacervate layer which can be deposited so as to produce the wall material of the resultant capsules. Coacervation may be initiated in a number of different ways. Examples are changing the temperature, changing the pH or adding a second substance such as a concentrated aqueous ionic salt solution or a non-solvent. As the coacervate forms, it must wet the suspended core particles or core droplets and coalesce into a continuous coating for the process of microencapsulation to occur. The final step for microencapsulation is the hardening of the coacervate wall and the isolation of the microcapsules, usually the most difficult step in the total process.[21]

This process of microencapsulation is generally referred to The National Cash Register (NCR) Corporation and the patents of B.K. Green. This process consists of three Steps.

• 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 of the coating material

Step-1: The first step of coacervation phase separation involves the formation of three immiscible chemical phases: a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for polymer. The coating material phase consists of a polymer in a liquid phase, is formed by using one of the of phase separation- coacervation method, i.e. .by changing the temperature of the polymer solution, by adding a solution, or by inducing a polymer- polymer interaction.

Step-2: It involves the deposition of the liquid polymer coating upon the core material. This is done by controlled mixing of liquid coating material and the core material in the manufacturing vehicle. The liquid coating polymer deposited on the core material if the polymer is adsorbed at the interface formed between the core material and liquid phase. The reduction in the total free interfacial energy of the system help to promote the deposition of the coating material, brought by the decrease of the coating material surface area during coalescence of the liquid polymer droplets.

Step-3: In the last step rigidizing of the coating material done by the thermal, cross linking desolvation techniques, to forms a self supporting microcapsule.

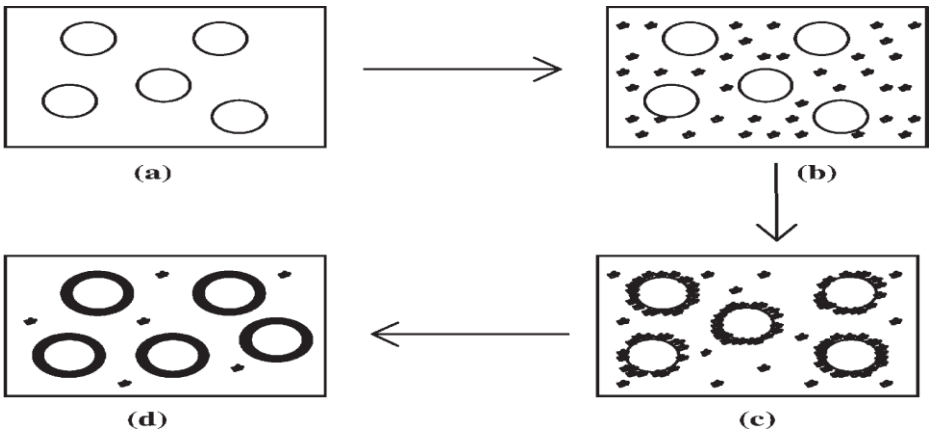

Fig. 4: Coacervation process: (a) Core material dispersion in solution of shell polymer; (b) Separation of coacervate from solution; (c) Coating of core material by micro droplets of coacervate; (d) Coalescence of coacervate to form continuous shell around core particles.

3. Multiorifice centrifugal process[22-24]

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 an 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.

4. Pan coatings[25-26]

The microcapsulation of relatively large particles by pan coating method 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 is being applied in the coating pans.

5. Spray–drying[27-31]

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages is the ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300 m Pa.s. 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 (and formation) of the coating is affected. The principal 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 a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, 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 non-solvent. Removal of the non-solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques. In practice, microencapsulation by spray drying is conducted by dispersing a core material in a coating solution, in which the coating substance is dissolved and in which the core material is insoluble, and then by atomizing the mixture into air stream. The air, usually heated, supplies the latent heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product.

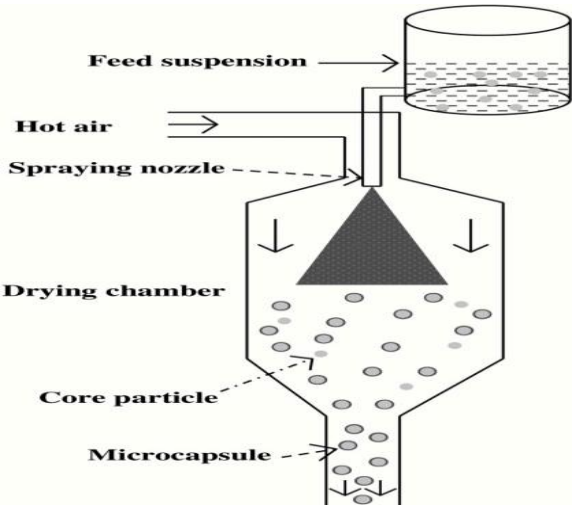

Fig. 8: Spray Dryer

The equipment components of a standard spray dryer include an air heater, atomizer, main spray chamber, blower or fan, cyclone and product collector. Microencapsulation by spray congealing can be accomplished with spray drying equipment when the protective coating is applied as a melt. General process variables and conditions are quite similar to those already described, except that the core material is dispersed in a coating material melt rather than a coating solution.

Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cool air stream. Waxes, fatty acids and alcohols, polymers and sugars, which are solids at room temperature but meltable at reasonable temperatures, are applicable to spray congealing techniques. Typically, the particle size of spray congealed products can be accurately controlled when spray drying equipment is used, and has been found to be a function of the feed rate, the atomizing wheel velocity, dispersion of feed material viscosity, and variables.

Chemical methods

6. Solvent evaporation[31]

This technique has been used by companies including the NCR Company, Gavaert Photo Production NV, and Fuji Photo Film Co., Ltd. to produce microcapsules. The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, 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 coating 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 dispersed in the polymer solution, polymer shrinks around the core. In the case in which core material is dissolved in the coating polymer solution, a matrix - type microcapsule is formed. Once all the solvent for the polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. 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. Example: Evaluation of sucrose esters as alternative surfactants in microencapsulation of proteins by the solvent evaporation method.[32]

7. Polymerization

The method involves 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.[33-36]

8. Melt-dispersion technique

In this technique the coating material is melted by heating upto 80°C. The drug is suspended in it and then emulsified in water containing emulsifying agent at 80°C under stirring. Microcapsules are formed as the temperature of the system reaches to room temperature.[37-41]

Characterization of microcapsule

The characterization of the micro particulate 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.

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.[42]

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.

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.[43]

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)[44]

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 400C is 0.0038 mm) at 25 ± 0.10C in a thermostatic bath. The polymer solutions are allowed to stand for 24 h prior to measurement to ensure complete polymer dissolution.[45]

Density determination

The density of the microspheres can be measured by using a multi volume pychnometer. Accurately weighed sample in a cup is placed into the multi volume pychnometer. 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.[46]

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. The percent encapsulation efficiency is calculated using following equation.

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.[47]

***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.[48]

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 over head stirrer. Volume of the medium used in the literature for the studies varies from 50-500 ml and the stirrer speed form 60-300 rpm.[48]

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.[48]

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.[37-39]

- To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.
- 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.
- 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 palmitate.
- 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.

CONCLUSION

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. 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. Microencapsulation is both an art and a science. There's no ONE way to do it, and each new application provides a fresh challenge. Solving these riddles requires experience, skill and the mastery of many different technologies.

REFERENCESS

1. Dziezak JD, (Microencapsulation and encapsulated ingredients), Food Technology, 1988; 42(4): 136-51.
2. Fergason JL, (Polymer encapsulated nematic liquid crystals for display and light control applications), SID Int. Symp Digest, 1985; 16: 68-70.
3. Green BK & Schleicher L, The National Cash Register Company, Dayton, Ohio, Oil containing microscopic capsules and method of making them, US Patent 2,800,457.23 July 1957; 11.
4. Green BK, The National Cash Register Company, Dayton, Ohio, Oil containing microscopic capsules and methodof making them, US Patent 2,800,458, 23 July 1957,
5. Jackson LS & Lee K, (Microencapsulation and encapsulated ingredients), Lebensmittel WissenschaftTechnol, 1991; 24: 289-97.
6. Mars GJ & Scher HB, (Controlled delivery of crop protecting agents), Wilkens, R.M. (Ed.) Taylor and Francis, London, 1990; 65-90.
7. Scher, H. B. In Proceedings of the 5th International Congress of Pesticides Chemistry, edited by Miyamoto, J.& Kearney, P C Pergamon Press, Oxford., 1982; 295-300.
8. Schnoring H, Dahm M & Pampus G, Fed. Rep. of Germany, Process for the Production of Microcapsules, US Patent 4,379,071, 5 April 1983. 9pp.
9. Gohel MC, Amin AF. (Formulation optimization of controlled release diclofenac sodium microspheres using factorial design). J. of Controlled Release, 1998; 51: 115-122.
10. Gunder W, Lippold BH, Lippold BC. (Release of drugs from ethyl cellulose microcapsules (diffusion pellets) with pore formers and pore fusion). Euro J Pharm Sci, 1995; 3: 203–214.
11. Green B K and Schleicher L: US patent, 2800457, CA 1957, 51; 15842d 1957; 13-627.
12. Ghulam Murtaza, Mahmood Ahamd, Naveed Akhtar and Fatima Rasool. (A comparative study of various microencapsulation techniques: effect of polymer

viscosity on microcapsule characteristics). Pak. J. Pharm. Sci., 2009; 3: 291-300.
13. Hausberger AG, Deluca PP. (Characterization of biodegra- dable poly(D,Llactide-co-glycolide) polymers and micro- spheres) J. Pharm. Biomed. Anal, 1995; 13: 747–760.
14. Higuchi T: (Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solidmatrices). J. Pharm Sci, 1963; 52: 1145–1149.
15. Haznedar S, Dortue B. (Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide). Int J of Pharm, 2004; 269: 131–140.
16. Guo, JH. (Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation in vitro adhesive and release properties). Drug Dev.Ind.pharm, 1994; 20: 315-325.
17. Hora MS, Rana RK, Nunberg JH, Tice TR, Gilley RM and Hudson ME. (Release of human serum albumin from PLGA microspheres). Pharm Res, 1990; 7: 1190-1194.
18. Ishida, M, Nambu N, Nagai T. (Highly viscous gel ointment containing carbapol for application to the oral mucosa). Chem. pharm Bull. 1983; 31: 4561.
19. Jackson, LS and Lee K. (Microencapsulation and the food industry. Lebennsmittel-Wissenschaft Techonologie). Ret on Cont Rel, 1991; 5: 199-205.
20. Jegat C, Taverdet J L. (Stirring speed influence study on microencapsulation process and the drug release from microcapsules). Polymer Bulletin, 2000; 44: 345–351
21. Jain N K., Controlled and Novel drug delivery. CBS Publisher, 1997; 236-237.
22. Jian You, Fu-de Cui, Xu Han, Yongsheng Wang, Lei Yang, Ying-Wei Yu, Qing-po. Literature of Biointerfaces, 2006; 35-41
23. James S. Encylopedia of PharmaceuticalTechonology, 2005; 3: 1325-1333.
24. Khawla A, Abu izza, Lucila Garcia-Contreras, Robert Lu D. (Selection of better methed for the preparationof microspheres by applyinghierarchy process). J. Pharm Sci., 1996; 85: 144-149.
25. Khawla A, Abu izza, Lucila Garcia-Contreras, Robert Lu D. (Selection of better method for the preparation of microspheres by applying hierarchy process). J. Pharm Sci, 1996; 85: 572-575
26. Kreitz M, Brannon-peppas L, Mathiowitz E. (Microencapsulation Encyclopedia of controlled drug delivery). John Wiley Sons publishers, 1999; 493-553.
27. Kesting RE. Synthetic Polymeric Membranes, A Structural Perspective A Wiley-Interscience Publication, Wiley, 1985; 2nd Edition: 525.
28. Korsmeye RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharmacet, 1983; 15: 25–35.
29. Lachman LA, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishng House. 3:414-415.
30. Leon, L, Herbert AL, Joseph LK. (The Theory and Practice of Industrial Pharmacy. Varghese Publishing House)., 1990; 3: 412-428.
31. Lopez, CR, Portero A, Vila-Jato, JC, Alonso MJ. (Design and Evaluation of Chitosan/Ethylcellulose mucoadhesive bilayered devices for buccal drug delivery). J. Control. Re, 1998; 55: 143-152.
32. Li SP, Kowarski CR, Feld KM and Grim WM (Recent advances in microencapsulation technology and equipment). Drug Dev. Ind. Pharm, 1988; 14: 353-376.
33. Lu W and Park TG, (Protein release from poly (lactic-co-glycolic acid) microspheres: protein stability problems). PDA J Pharm Sci Technol, 1995; 49: 13-19.
34. Nagai T, Machida Y, Suzuki Y, Ikura H. (Method & preparation for administration to the mucosa & preparation for administration to the mucosa of the oral or nasal cavity) US patent NO.4226848. 1980.
35. Nikhil K Sachan. (Controlled drug delivery through microencapsulation.) Assam India, Dibrugarh University 2005; 1-3.
36. Nack H, (Microencapsulation techniques, application and problems. J.Soc.Cosmetic Chemists), 1970; 21: 85-98.
37. Nokhodchi A, Zakeri-Milani P, Valizadeh H and Hassan-Zadeh D: (Evaluation of microcapsules of acetyl salicylic acid prepared with cellulose acetate phthalate, ethyl cellulose or their mixtures by an emulsion non-solvent addition technique) Ars Pharmaceutical, 2002; 43: 135–147
38. O'Donnell PB, McGinity JW. (Preparation of microspheres by solvent evaporation technique). Adv Drug Delivery Reviews, 1997; 28: 25-42.
39. Pao-Chu Wua, Yaw-Bin Huanga, Jui- Sheng Changa, Ming-Jun Tsaib, Yi-Hung Tsaia. (Design and evaluation of sustained release microspheres of potassium chloride prepared by Eudragit). Euro. J. of Pharma. Sciences, 2003; 19: 115–122.
40. Parodi, B, Russo E, Caviglioli G, Cafaggi S, Binardi G.(Development &characterization of a buccoadhesive dosage form of Oxydodone hydrochloride). Drug Dev.Ind.pharm, 1996; 22: 445-450.
41. Rao MRP, Borate SG, Thanki KC, Ranpise AA, Parikh GN. (Development and in vitro evaluation of floating rosiglitazone maleate microspheres) Drug Dev Ind Pharm, 2009; 35: 834-842.
42. Reis MAA, Sinisterra RD, Belchior JD. (An alternative approach based on artificial neural networks to study controlled drug release). J. Pharma Sci, 2004; 93: 418–430.
43. Rowe, E.L.(U.S. Patent 3 336) 155: 1967.
44. Tanaka W, Akito E, Yoshida K, Terada T, Ninomiya H. (Pharmaceutical preparations for oral cavity administration). US patent., 4059686., 1977.
45. Venkatesan P, Muralidharan C, Manavalan R, Valliappan K. (Selection of better method for the preparation of microspheres by applying Analytic

Hierarchy Process). J. Pharm. Sci. & Res., 2009; 1: 64-78.
46. Venkatesh H. (A buccal delivery system of Salbutamol Sulphate). J. Pharm. Sci. & Res., 1989; 3: 53-55
47. Vyas SP and Khar RK. (Targeted and Controlled drug delivery), 07 Edition: 418.
48. Yi-Yan Yang, Hui-Hui Chia, Tai-Shung Chung. (Effect of preparation temperature on the characteristics and release profiles of PLGA microspheres containing protein fabricated by double-emulsion solvent extraction / evaporation method)