Sunsari Technical College Journal, Volume 1, Issue 1, October 2012
ISSN 2091-2102

Review Article

MICROENCAPSULATION FOR CONTROLLED DRUG DELIVERY: A COMPREHENSIVE REVIEW

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ABSTRACT

Microencapsulation is described as a process of enclosing micron sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment as well as control the drug release profile. Microencapsulated particle is having diameter between 3 [-] 800µm which differ them from other technologies such as nanotechnology and macroparticle in their morphology and internal structure. This review paper will address the background of microencapsulation technology, commonly used microencapsulation methods with its advantages and disadvantages and its applications in pharmaceutical field. This article also gives an overview on the general aspects and recent advances in drug-loaded microparticles to improve the efficiency of various medical treatments. The review paper will also address about the other factors affecting microencapsulation and its limitation. The article will also discuss about various findings described in the published scientific journals and patent literatures. Based on the existing results and authors' reflection, this review gives rise to reasoning and suggested choices of process parameters and microencapsulation procedure.

Key words: Application of medicine, microcapsule, microencapsulation technology, control drug delivery , polymer

Introduction

The word 'capsule' implies a core and shell structure, and the term 'microcapsules' states the membrane enclosed particles or droplets dispersed in solid matrix lacking a distinctive external wall phase as well as intermediate types.[1] Microcapsules according to the French Pharmacopoeia are solid material consisting of a solid envelope containing a liquid or solid or a pasty substance. The microcapsules occur in the form of powder with particles less than 1250 ìm in diameter. . Starting first as an art than a science, nowadays the topic of microencapsulation is extensively studied inside major pharmaceutical companies and universities as well as research institutes. Microencapsulation can be defined as small entities that contain an active agent or core material surrounded by a shell or embedded into a matrix structure. Commercial microparticles have a diameter 3 and 800 micrometers and contain 10-90% w/w core. A wide range of core materials has been encapsulated,

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including adhesives, agrochemicals, live cells, active enzymes, flavors, fragrances, pharmaceuticals and ink. Morphologically, two general structures exist: microcapsules and microspheres.[2]

Microencapsulation of pharmaceuticals was first investigated in the year 1931 by preparing spheres of gelatin using coacervation technique. Processes and materials used for coating have since been developed by the pharmaceutical industry to aid in formulation of various dosage forms such as tablets, capsules, injectables, powders and topical. [3] The more recent result of pharmaceutical research is that the absorption rate of a drug can be controlled by controlling its rate of release from the dosage form .The controlled released dosage forms are so designed and formulated as having the sustained action, sustained release, prolonged action, delayed action and timed release medication. [4]This has been done by developing the new drug entities, discovering of new polymeric materials that are suitable for prolonging the drug release, safety, improvement in therapeutic efficacy. [5]

Reasons for Microencapsulation[6]

1. The main reason for microencapsulation is for sustained or prolonged release of the drug
2. This technique has been widely used for masking the organoleptic properties like taste and odor of many drugs and thus improves patient compliance e.g. Paracetamol, nitrofurantoine for masking the bitter taste.
3. By using microencapsulation techniques the liquid drugs can be converted in a free flowing powder.
4. The drugs sensitive to moisture, light and oxygen can be protected by microencapsulation. For example, nifedipine is protected from photo instability.
5. Microencapsulation technique is also helpful to prevent the incompability between drugs.
6. The drugs which are volatile in nature may vaporize at room temperature. Drugs like Aspirin and peppermint oil can be prevented by microencapsulation.
7. Reduction in toxicity and GI irritation including with KCL and ferrous sulphate can be achieved by microencapsulation.
8. Microencapsulation has also been employed to change the site of absorption. This application has been useful for those drugs which have the toxicity at lower pH.
9. Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability, as prevent from oxidation.
10. Microencapsulation method has also been employed to prepare intrauterine contraceptive device.

Mechanism and Kinetics of Drug Release

Major mechanisms of drug release from microcapsules include diffusion, dissolution, osmosis and erosion. [7]

1. Diffusion is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels[8] Thus, the overall release depends on, (1) the rate at which dissolution fluid penetrates the wall of microcapsules, (2) the rate at which drug dissolves in the dissolution fluid, and (3) the rate at which the dissolved drug leak out and disperse from the surface.[9] The kinetics of such drug release obeys Higuchi's equation [10] as below:

$Q = [D/J (2A – å C_S) C_S t]^{1/2}$

Where Q is the amount of drug released per unit area of exposed surface in time t; D is the diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; 'C' is the solubility of drug in permeating dissolution fluid ; a is the porosity of the wall of microcapsule; J is the tortuosity of the capillary system in the wall. The above equation can be simplified to Q = vt where **v** is the apparent release rate.

2. Dissolution: Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the dissolution fluid [8] Thickness of coat and its solubility in the dissolution fluid influence the release rate. [11]

3. Osmosis: The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat.
4. Erosion: Erosion of coat due to pH and/or enzymatic hydrolysis causes drug release [12] with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol.

The drug release from microcapsules has become complicated because of great diversity in physical forms of microcapsules with size, shape and arrangement of the core and coat materials.[13,14] The physiochemical properties of core materials like solubility, diffusibility and partition coefficient and of coating materials like variable porosity, thickness and inertness which makes difficult to modeling of drug release. However, based on various studies concerning with the release characteristics, the following considerations can be made-

1) Drug release rate from microcapsules follow the zero order kinetic.
2) Microcapsules of monolithic type have the t1/2 dependant release rate for the first half of the total drug release and thereafter turn down exponentially.
3) Microcapsules of monolithic type having large excess of dissolved drug, the release rate are t1/2 dependant throughout almost the entire drug release.

MATERIALS FOR MICROENCAPSULATION

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 materials. The solid core be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators. The variation in the core material composition provides definite flexibility and utilization of this characteristic then allows effective design and development of the preferred microcapsule properties. [15]

Liquid Core Material Examples: [16]

Perfumes, Solvents, Vegetable Oils, Pesticides, Dyes, Catalysts, Bleaches, Cosmetics, Insecticides, Sugars,Salts,Acids, Pigments, Fungicides, Nutrients

Solid Core Material Examples:

Dextrins , Bases ,Herbicides , Pharmaceuticals , Biocides , Minerals

Coating material:

A wide variety of coating materials are available for microencapsulation. Some patent innovative coating polymers have also been developed for some special applications particularly among the bioadhesives and mucoadhesives. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. They include inert polymers such as ethyl cellulose and pH sensitive ones, such as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linking. [17]

Table 1: Example of coating materials [18]

Water Soluble resins	Water insoluble resins	Waxes and resins	Enteric resins
Gellatin	Ethyl Cellulose	Paraffin	Shellac
Starch	Polyethylene	Beeswax	Cellulose Acetate Pthalate
Polyvinylpyrrolidine	Polyamide	Stearic acid	Zein
Hydroxyethylcellulose	Polymethacrylate	Steryl Alcohol	

Table 2: Microencapsulation methods [15]

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

Pan coating [19]

The pan coating process, widely used in the pharmaceutical industries, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly. The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly with respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating, and the process has been extensively employed for the preparation of controlled - release beads

Air suspension

The air suspension coating process was invented by Professor Dale E. Wurster while at the Department of Pharmacy, University of Wisconsin. Air suspension apparatus consists of different sections such as control panel, coating chamber, air distribution plate, nozzle for applying film coatings. Within the coating chamber of air suspension apparatus particles are suspended on an upward moving air stream. In the coating zone, coating material is applied by spraying to the moving core particles. The design and operating parameters of the chamber affect the recirculating flow of the core particles through the coating zone. The core material receives an increment of coating material, usually a polymer solution during each pass through the coating zone. The cyclic process is repeated until desired coating thickness is achieved. The supporting air stream helps to dry the product during encapsulation.[20] Air suspension techniques are generally applicable only to encapsulate the solid core materials. The rate of drug release from the microcapsules was highly dependent on the encapsulating materials. [21]

Coacervation-Phase Separation

The general outline of the coacervation-phase separation processes consist of three steps carried out under continuous agitation: A liquid manufacturing vehicle phase, a core material phase, and a coating material phase. To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. [22]

Multi orifice-Centrifugal process

In this process, a jet of core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air it breaks, owing to Rayleigh instability, into droplets of core, each coated with the wall solution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporated from the wall solution. Since most of the droplets are within ± 10% of the mean diameter, they land in a narrow ring around the spray nozzle. [23]

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. The device has a rotating cylinder which has three circumferential grooves. 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.[23,24]

Spray Drying and Spray congealing:

Spray drying and spray congealing methods have been used as microencapsulation techniques for many years. The main difference between the two methods is by which coating solidification is completed. In the case of spray drying, the coating solidification is effected by rapid evaporation of a solvent in which the coating material is dissolved. In spray congealing method the coating solidification is completed by thermally or by solidifying the dissolved coating by introducing the core material mixture into a nonsolvent. Removal of the nonsolvent from the coated product is then accomplished by sorption, evaporation or extraction techniques.[24]

Solvent Evaporation

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. [25]

Polymerization:

Polymerization is a new method of microencapsulation to form protective microcapsule coatings in situ. Microencapsulation by polymerization involved reaction between a core material substance and continuous phase in which the core material is dispersed. In polymerization a liquid or gaseous phase is used as continuous or core material and as a result the polymerization reaction occurs at a liquid-liquid, solid-liquid, liquid-gas, or solid-gas interface. [15, 26]

Collection of some interesting literatures on microencapuslatuion

K. Shekhar et al had studied formulation and evaluation of cefotaxime sodium microcapsules by solvent evaporation method using ethyl cellulose as polymer and found that upon increasing the polymer concentration the drug release was sustained. The study revealed that When drug and polymer ratio was too low (1:0.5) no spherical particles were obtained. Spherical particles were obtained, when the polymer and drug ratio was increased (1:1, 1:2, 1:2.5, 1:3). [27]

Santhosh KM, Chowdary KA and Sammaiah G studied controlled release formulation and evaluation of aceclofenac by microencapsulation using sodium Alginate as coat material in combination with some mucoadhesive polymers such as sodium CMC and Carbopol and found that microencapsulation efficiency found more in Carbopol than Sodium CMC. The microcapsules with Carbopol exhibited good mucoadhesive property in the in vitro wash-off test. In vitro drug release studies of aceclofenac microcapsules were carried out up to 24hrs and release followed zero order Super case II mechanism.[28]

Pignatello R, Consoli P, and Puglisi G. had studied in vitro release kinetics of Tolmetin from tabletted Eudragit microparticle. In this study, microparticles were also prepared by adding MgO to the polymer matrix, to reduce the sensitivity of the drug to pH changes during its dissolution were studied. [29]

Sevgi F, Ozyazici and M, Güneri T had studied sustained-release dosage form of phenylpropanolamine hydrochloride. Microencapsulation and in vitro release kinetics and found that core:wall ratios of 1:1, 2:1 and 1:2 were prepared by the coacervation-phase separation method, using ethylcellulose as the coating material has good release profile in controlled release form. [30]

Kannan K, Karar PK and R. Manavalan, studied the formulation and evaluation of sustained release microspheres of acetazolamide by solvent evaporation technique using Eudragit RS and RL as polymer and found that particle sizes of the microcapsules were influenced by the concentration of Eudragit and stirring speed. They also showed that the in vitro study shows that the desired release rate is achieved by the combination of Eudragit RL and Eudragit RS. [31]

Chaudhary KPR and Dana SB studied ethyl cellulose coated microcapsule for the control release of Diclofenac sodium uing emulsion solvent evaporation method and found that drug release was slow over a period of 14-6 hour and more efficient. The drug release was first order andnon fickian diffusion. [31,32]

Shashikala P, Lavanya A and Rao MB studied microencapsulation for preparing sustained release drugs of formulation and evaluation of Isoxsuprine Hydrochloride tablets using different proportions of Ethylcellulose, Polyethylene glycol 6000 and Polyethylene glycol 4000 as the coat material. Phase separation technique was used with cyclohexane as the solvent. The prepared granules were found to be free flowing and spherical in shape. It was observed that the prepared formulation followed the Higuchi plot. The mechanism for drug release was suggested as diffusion. [33]

CONCLUSIONS

Since the concept of controlled drug delivery was introduced in 1970s, great progresses have been made in microencapsulation. The microencapsulation techniques offer various opportunities such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the core material. A single microencapsulation method cannot be universally applied for a variety of drug materials. In developing a new microparticle system for a given drug, it is important to understand the physicochemical properties of the drug and polymers that best match the properties and find an encapsulation method. However, most of the commonly used methods have several disadvantages such as unfavorable conditions for the core material, complexity in procedure and low encapsulation efficiency.

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