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Review Article

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Microencapsulation: Application and Recent Advances- A Review

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ABSTRACT

Microencapsulation is the process of encapsulating one material entirely within another on a very small scale, resulting in capsules ranging in size from less than 1-100. The encapsulation efficiency of the microcapsule is affected by various aspects such as polymer concentration, polymer solubility in solvent, solvent removal rate, organic solvent solubility in water, and so on. There are numerous strategies for achieving microencapsulation. The objective of microencapsulation of substances may be to restrict the core content within capsule walls for a certain period of time. Core materials, on the other hand, can be encapsulated so that the core material is released gradually through the capsule walls, a process called as controlled release or diffusion, or when an external condition activates the capsule walls.

Key Words: *Microencapsulation, Microcapsule, Encapsulation efficiency, Controlled release.*

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INTRODUCTION

Conservative dose formulations are swiftly absorbed, with the rising and falling parts of the concentration versus time curve indicating principally the rate of absorption and excretion. The medicine must be taken numerous times in this oral dose form, resulting in variable drug levels in plasma. This disadvantage can be overcome by developing sustained/controlled release dosage forms that provide drug release in sufficient amounts to maintain therapeutic drug levels over extended periods of time, with release profiles maintained by the system's special technological construction and design [1]. The goals of sustained/controlled release drug delivery include two critical aspects: spatial placement and drug delivery timing. Targeting a drug to a specific organ or tissue is referred to as spatial situation, whereas sequential delivery refers to managing the rate of drug delivery to the target tissue. A number of technological advances have been achieved solely to extend the duration of therapeutic activity and/or to target drug delivery to a tissue [2].Different types of sustained release dosage forms can be classified as the following [3, 4].

- Single unit (matrix tablets, coated tablets and micro capsule)
- Multiple units [granules, microcapsules and microspheres]
- Inert- insoluble matrix
- Water loving gel matrix (bio adhesive, erodible, non- erodible)
- Ion – exchange resins

Among the different types of SRDDS, microcapsules played the vital role in the development of dosage form for treating different ailments. Microcapsules are produced by microencapsulation technique. This technique has been widely employed in the design of controlled release and sustained release dosage forms. The microencapsulation is used for the manufacturing of sustained release dosage forms has been introduced by Smith, Nine and French in the early 1950's [5].

MICROCAPSULES

Mono or multinuclear materials enclosed by a coat or membrane are called as microcapsules.

MICROSPHERES

Microspheres are mononuclear or multinuclear materials encapsulated in a spherical coating matrix. Microcapsules for medical usage are made up of a solid or liquid core substance that contains one or more medications and is encased in a covering material. The core is also known as the nucleus, and the coating as the wall or sheet [6,7]. Microcapsules are made up of free-flowing powders of proteins or systemic polymers that are biodegradable and ideally have a particle size

of less than 200 m. Microcapsules made of biodegradable and non-biodegradable polymers have been studied for long-term and controlled release.[8-10] The word "microcapsule" refers to a spherical particle with a core portion material that ranges in size from 50 nanometres to 2 millimetres. Microspheres are spherically empty particles in the strictest sense. Nonetheless, the terms microcapsules and microspheres are often used synonymously. As well, some linked terms are used as well. For example, “micro-beads” and “beads” are used alternatively. Sphere and spherical particles are also in use for a large size and stiff morphology. Because of attractive properties and wider applications of microcapsules and microspheres, a survey of the applications in controlled drug release formulations is appropriate [11,12, 13]. While the word capsule implies a core and shell structure, the term microcapsules admits not only membrane enclosed particles or droplets but also dispersion in solid matrix lacking a characteristic exterior wall phase as well as intermediate types. The size range (2 to 2000μm approximately) distinguishes them from the smaller nano particles or nanocapsules. The scanning electron microscopy (SEM) has shown the structural features of microcapsules as to be varying and complex. The walled prototype may be mononuclear or may have multiple core structure. Also double or multiple concentric coating may be present. Aggregated microcapsules greatly vary in size and shape and may also posses additional external wall. The ideal microcapsules are accessible by using the liquid cores or forming the microcapsules as a liquid dispersed phase prior to the solidification. Although micro-structure of both membrane and interior can be detected by SEM of surfaces or sections, their physical quality, involving porosity, tortuousity and crystalinity, is difficult to be characterized quantitatively in microcapsules. However, some progress has been made, and efforts are continuing to calculate permeability and porosity from release data, dimensions, densities, and core/wall ratios. The effect of size and shape distribution has only been studied recently [14-16]

RELEASE MECHANISMS OF MICROENCAPSULATION

- The objective of this study to isolate core material from its surrounding; the wall must be ruptured at the time of use. Because of pressure or shear stress many walls are ruptured, as in the case of breaking dye particles during writing to form a copy. Releasing of Capsule contents are processed by melting the wall, or dissolving it under particular conditions. On the other hand, the wall is broken by solvent pressure, enzymetic attack, chemical reaction or slow disintegration.
- Microencapsulation can also be used to control or slow the release of a drug into the body. This may permit one controlled release dose to substitute for several doses of non-encapsulated drug and also may decrease toxic side effects for drugs by preventing high initial concentrations in the blood. There is usually a certain desired release pattern. In some cases, it is zero-order, i.e. the release rate is constant. In this case, the microcapsules deliver a fixed amount of drug per minute or hour during the period of their effectiveness. This can occur as long as a solid reservoir or dissolving drug is maintained in the microcapsule.
- The other typical release pattern is first-order in which the rate decreases exponentially with time until the drug source is exhausted. In this situation, a fixed amount of drug is in solution inside the microcapsule. The concentration difference between the inside and the outside of the capsule decreases continually as the drug diffuses.
- The other mechanisms that may take place in the liberation of the encapsulated material include biodegradation, osmotic pressure, diffusion, etc. Each one will depend on the composition of the capsule made and the environment it is in. Therefore, the liberation of the material may be affected with various mechanisms that act simultaneously.
- The release mechanism depends on the nature of application, for example, carbonless copy paper, scratch and sniff perfumes and self-healing structures rely on mechanical rupture of shell to release the core contents. The rupture may be caused by pressure as in case of carbonless copy paper and scratch and sniff perfumes or due to propagation of cracks as for self-healing structures.
- In the self-healing structures microcapsules act as means of storing and delivering insitu glue, to prevent the spread of cracks. Thus a microencapsulated healing agent and a catalyst known to trigger polymerization in the chosen agent are embedded in a composite matrix. Rupture of any microcapsules by an approaching crack defect releases the healing agent into the crack plane by capillary action. When the released healing agent comes in contact with the catalyst, the resulting polymerization bonds the crack face closed, stopping the defect in its track. For example urea formaldehyde microencapsulated dicyclopentadiene healing agent and Grubb's catalyst have been incorporated into an epoxy matrix to produce a polymer composite capable of self-healing.
- Detergent industry utilises dissolution of shell wall of powder detergents for release of encapsulated protease enzyme in order to remove bloodstains from the clothing.

APPLICATIONS OF MICROCAPSULE

Dosage formulations with a delayed release. Because microencapsulation is particularly beneficial for the manufacture of tablets, capsules, or parenteral dosage forms [31], the microencapsulated drug can be delivered. Microencapsulation can be utilised to create enteric-coated dosage forms, allowing the medication to be absorbed selectively in the intestine rather than the stomach [32]. It is useful for masking the taste of bitter medications [33, 34]. Microencapsulation has been employed mechanically to aid in the addition of oily pharmaceuticals to tablet dosage forms. This has been used to overcome problems inherent in producing tablets from otherwise tacky granulations and in direct compression to tablets [35,36]. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microencapsulation does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided [37,

38]. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible Aspirin-chlorpheniramine Maleate mixture was accomplished by micro-encapsulating both of them before mixing [39]. Microencapsulation can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation [40]. Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. The toxicity occurred due to handling of fumigants, herbicides, insecticides and pesticides have been advantageously decreased after microencapsulation [41]. The hygroscopic properties of many core materials may be reduced by microencapsulation [42]. Many drugs have been microencapsulated to reduce gastric irritation [43]. Microencapsulation method has also been proposed to prepare intrauterine contraceptive device [44,45]. In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles [46-49]. In such industrial applications, 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 citric acid in the food industry and chemical drugs in the pharmacy industry and fertilizers in the agro industry. Actually about any area in the industry could beneficiate from microencapsulation technologies. Microencapsulation can be found in various fields. In plant cell cultures microencapsulation, by mimicking cell natural environment, improves efficiency in production of different metabolites used for medical, pharmacological and cosmetic purposes. Human tissue are turned into bioartificial organs by encapsulation in natural polymers and transplanted to control hormone deficient diseases such as diabetes and severe cases of hepatic failure. In continuous fermentation processes immobilization is used to increase cell density, productivity and to avoid washout of the biological catalysts from the reactor. This has already been applied in ethanol and solvent production, sugar conversion or wastewater treatment. Today beer, wine, vinegar and other food drinks production are using immobilization technologies to boost yield, improve quality, change aromas, etc. Microencapsulation is often a necessity to solve simple problem like the difficulty to handle chemicals (detergents dangerous if directly exposed to human skin) as well as many other molecule inactive or incompatible if mixed in any formulation. Moreover, microencapsulation also allows preparing many formulations with lower chemical loads reducing significantly processes' cost. After designing the right biodegradable polymers, microencapsulation has permitted controlled release delivery systems. These revolutionary systems allow controlling the rate, duration and distribution of the active drug. With these systems, microparticles sensitive to the biological environment are designed to deliver an active drug in a site specific way (stomach, colon, specific organs). One of the main advantages of such systems is to protect sensitive drug from drastic environment (pH,) and to reduce the number of drug administration's for patient. Quality and safety in food, agricultural & environmental sectors: Development of the "biosensors" has been enhanced by encapsulated bio-systems used to control environmental pollution, food cold chain (abnormal temperature change). Applications of microcapsules in building construction materials An analysis of scientific articles and patents shows numerous possibilities of adding microencapsulated active ingredients into construction materials, such as cement, lime, concrete, mortar, artificial marble, sealants, paints and other coatings, and functionalized textiles.

RECENT ADVANCES IN MICROENCAPSULATION

Several technologies and techniques in the broad subject of microencapsulation may be useful for the creation of polymeric microparticles. The preparation process determines the kind and size of microparticles as well as the capacity of the components employed in microparticle formulations to interact. The word microparticle refers to systems with a diameter more than one micrometre and is commonly used to describe both microcapsules and microspheres. pharmaceuticals containing microparticles are used for a variety of objectives, including but not limited to controlled drug delivery, concealing the taste and odour of pharmaceuticals, protecting the drugs from degradation, and protecting the body from the toxic effects of the drugs. Polymeric carriers being essentially multi-disciplinary are commonly utilized in micro particle fabrication and they can be of an erodible or a non-erodible type [50]. Recently, numbers of publications and patents have been published. Hughes [51] provided a method of sustained delivery of an active drug to a posterior part of an eye of a mammal to treat or prevent a disease or condition affecting mammals. The method is comprised of administering an effective amount of an ester pro-drug of the active drug such as tazarotene (pro-drug of tazarotenic acid) subconjunctivally or particularly since a systemic administration requires high systemic concentration of the prodrug. The ester prodrug is contained in biodegradable polymeric microparticle system prepared using the o/w emulsion solvent evaporation methods. Lee et al.[52,53] prepared a composition in the form of thin film or strip composed of microspheres containing antibiotic such as minocycline HCl. It was made using a biodegradable polymer, prepared by a modified o/w emulsification technique followed by solvent evaporation. Water-soluble polysaccharide polymers such as pectin was used for making thin film or strip containing microspheres intended for local sustained release administration into the periodontal pocket. The thin film or strip is coated by spray-coating with cation salt aqueous solution of calcium or barium chlorides. In one embodiment, Traynor et al. used the o/w emulsion to produce sol-gel microcapsules (containing sunscreens) that are highly positively charged using non-ionizing cationic additives which can include cationic polymers [54]. An injectable slow-release partial opioid agonist or opioid antagonist in a poly (D, L-lactide) microspheres with a small amount of residual ethyl acetate was provided by Tice et al.[55] and Markland et al.[56] where an o/w emulsion is first prepared from an organic phase made of ethyl acetate and an aqueous phase comprised an aqueous ethyl acetate containing solution of polyvinyl alcohol. Microspheres are recovered by extraction with water. Wen and Anderson [57] prepared single wall biodegradable microspheres by extracting an o/w emulsion containing steroidal and non-steroidal anti-inflammatory agents. Otherwise, double wall microspheres were prepared.

Microspheres containing the active ingredient were then immobilized on a substrate surface in a polymeric matrix that is an implantable medical article or an *in situ* formed matrix. Solidification method of the hydrophilic capsule materials such as gelatin can be through rapidly lowering the temperature and subsequent dehydration. While such method achieved some significant commercial success, difficulties have sometimes been encountered in rapidly inducing solidification of the microencapsulating material. The use of various gel forming proteins (collagen and gelatine) and polysaccharides (agar, calcium alginate, and carrageenan) introduced a milder, biocompatible immobilization or isolation system. Obeidat and Price [58] employed a one step method for the preparation of microspheres having enteric and controlled release characteristics in one embodiment and swelling and controlled properties in another using the nonaqueous solvent evaporation method. Microspheres were especially useful for delivery of moderately non-polar active ingredients but can be formulated to deliver very soluble polar compounds. Delgado [59] developed a method for preparing enteric polymeric microparticles containing a proteinaceous antigen in a single or double emulsification process in which the enteric polymer acts as a stabilizer for the microparticles which are formed in the process. Single o/w or double w/o/w emulsion solvent evaporation method was utilized by Yamamoto et al.[60,61] to prepare microspheres with improved dispersibility by dispersing a w/o type emulsion in an outer aqueous phase that contains an osmotic pressure regulating agent[62]or to prepare sustained release microsphere containing a LHRH derivative or its salt in a large amount without containing gelatin by using a lactic acid-glycolic acid polymer or salts. When the low molecular weight of lactic acid-glycolic acid polymer fraction (8,000 to about 15,000) is contained in a large amount, LHRH derivative readily interacts with these polymers of high reactivity[63] or otherwise to produce a sustained-release composition which comprises emulsifying an aqueous solution containing LHRH derivative and an acid or a base with a solution of a biodegradable polymer[64] Rickey et al.[65] provided a novel method for the preparation of biodegradable and biocompatible micro particles containing a biologically active agent such as risperidone, or testosterone dissolved in a blend of at least two substantially non-toxic solvents, free of halogenated hydrocarbons such as benzyl alcohol and ethyl acetate. The blend was dispersed in an aqueous solution to form droplets. The resulting emulsion was then added to an aqueous extraction medium. One of the solvents in the solvent blend would be extracted in the quench step (aqueous solution) more quickly than the other solvent. Owing to the high boiling point of the left solvent (benzyl alcohol) which is not easily removed by evaporation in air or other conventional evaporative means, some of the more rapidly extracted solvent can be added to the quench extraction medium prior to addition of the emulsion. Thus, when the emulsion is added to the quench liquid, extraction of the more rapidly extracted solvent is retarded and more of the second, more slowly extracted solvent is removed. A method for encapsulating vitamins, food supplements, oil soluble substances at high loading (70 wt%) by the solvent o/w emulsion extraction technique is provided by Kvitnitsky et al.[66,67]. Since evaporating the solvent from the dispersion is not applicable for delicate and sensitive compounds and it is not effective, because diffusion of solvent through a hard polymer wall is very slow, water at 10-30 times higher than the whole quantity of the organic solvent is added to the emulsion for extracting the solvent. Dawson and Koppenhagen [68].employed a relatively high non-ionic emulsifier concentration (5-15 wt%) in an emulsion-extraction method particularly applicable to those active agents that are susceptible to thermal degradation at temperatures above room temperature (i.e. 20 °C) such as enzymes, hormones and antigens. Eyles et al.[69] used the w/o/w and o/w/o emulsions to produce biodegradable microparticles that stimulate production of cytokines in a host cell, and contain single-stranded ribonucleic acid material, a stabilizing agent and a biologically active macromolecule where the outer surface of the microparticle is free from adsorbed molecules. Polysaccharides such as starch have been used as a matrix for encapsulation many active ingredients including proteins. Wen and Anderson [70] prepared double wall microspheres using two biodegradable polymers by the o/w emulsification solvent extraction process. Futo et al.[71]used a relatively large molecular weight (11,000 to about 27,000) lactic acid polymer or its salt to produce microspheres with prolonged release over a long period of time with a suppressed initial excessive release of a water soluble LHRH derivative via single or double emulsion. Ducrey et al.[72] incorporated LHRH in the form of a water insoluble peptide salt (The LHRH agonist triptorelinpamoate) to provides slow release microparticles made of a copolymer of the PLGA type (at least 75 % of lactic acid) by the emulsion method. A method of encapsulating DNA retaining its ability to induce expression of its coding sequence in a microparticle for oral administration prepared using the w/o/w emulsion and using biodegradable polymers under reduced shear is produced by Jones et al.[73-75]. In addition, Little et al. [76] provided a high throughput method of preparing multiple (at least 10) different microparticle formulations (containing promid DNA) in parallel based on the double emulsion/solvent evaporation technique. The encapsulation of hormones such as calcitonin for the sustained release delivery has been achieved by Woo et al.[77]. Biodegradable microspheres prepared using o/w emulsion technique and incorporating release-modifying agents and pH-stabilizing agents that resist changes in pH upon the addition of small amounts of acid or alkali such as basic amino acids, such as L-arginine were prepared [78]. According to the disclosure of the invention, sustained release is affected by the unique interplay of the components of the novel microsphere delivery system. Reslow et al. [79] utilized starch to encapsulate vaccines using emulsification method. In process, an immunologically active substance (vaccine) is suspended in an aqueous starch solution with an amylopectin content exceeding 85% by weight before being mixed with an aqueous solution of a polymer having the ability of forming a two phase aqueous system. The starch droplets containing the vaccine are allowed to gel as the starch has capacity to gel naturally. Encapsulation of nucleotides and growth hormone using simple or double emulsification methods was achieved by Johnson et al.[80]respectively. Similar to synthetic polymers, such as poly (lactic acid) or polyorthoesters, proteins have also been used to form microparticles or microspheres for drug delivery. Most are cross-linked in solution using glutaraldehyde, or hardened at elevated temperatures. Unfortunately, there are problems with

significant loss of biological activity of incorporated materials and lack of controlled size and *in vivo* degradation rates. Suslick et al. produced surface modified microparticles that possess a novel protein shell, and a surface coating. The protein shell might consist of cross-linked albumin or other proteins with functional moieties for cross-linking, while the surface coating comprises polyethylene glycol, a second protein or an antibody. Microparticles are prepared via emulsification followed by protein agglomeration and cross-linking. The surface coating may be covalently-bonded to the cross-linked protein shell or it may be electrostatically adsorbed to the cross-linked protein shell. The surface of the microparticles can be altered to vary the *in vivo* pharmacokinetics and bio distribution.

CONCLUSION

Microcapsule is a versatile drug delivery system of either oral or parenteral route of administration of a medication that should ideally produce the required plasma level and maintain a steady level for a prolonged period of time, overcome problems associated with conventional therapy, and improve the therapeutic efficacy of a given drug. The techniques for creating microacpsules via the microencapsulation process paved the way for researchers to create colloidal and nano drug delivery systems for a variety of medications.

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