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MICROCAPSULES: AN APPROACH TO CURRENT DRUG DELIVERY - A REVIEW

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ABSTRACT

Microencapsulation is the expansion of all-encompassing one substance within another substance on a very small scale, yielding capsules ranging from less than 1-100µ in size. The encapsulation efficiency of the microcapsule depends upon different factors like concentration of the polymer, solubility of polymer in solvent, rate of solvent removal, solubility of organic solvent in water etc. Microencapsulation may be achieved by a innumerable of techniques. Microencapsulation of gear could also be with the aim that the core material be confined at intervals capsule walls for a particular amount of your time. On the opposite hand, core materials could also be encapsulated in order that the core material are discharged either bit by bit through the capsule walls, called controlled unleash or diffusion, or when exterior situation activate the capsule walls to rupture, melt, or dissolve.

KEYWORDS

Microencapsulation, Microcapsule, Encapsulation efficiency and Controlled release.

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INTRODUCTION

Conservative dosage forms are quickly absorbed, with the rising and downward portions of the concentrations versus time curve sparkly primarily the rate of absorption and elimination, respectively. In this oral dosage form, drug must be taken several times which results in fluctuating drug levels in plasma. This drawback can be overcome by formulation of sustained/controlled release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles sustained by the special technological construction and design of the system[1]. The objectives of sustained/ controlled release drug delivery include

two important aspects namely spatial placement and temporal delivery of drug. Spatial situation relates to targeting a drug to a specific organ or tissue, while sequential delivery refers to controlling the rate of drug delivery to the target tissue. A number of technical advancements have been made only just to sustain the duration of therapeutic activity and /or targeting the delivery of drug 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

Mono or multinuclear materials embedded in spherical coating matrix are called microspheres. Microcapsules developed for use in medicine consists of solid or liquid core material containing one or more drugs enclosed in coating material. The core may also be referred as nucleus and the coating as wall or sheet[6,7]. Microcapsules consist of free flowing powders of proteins or systemic polymers, which are biodegradable in nature and ideally having a particle size less than 200 µm. Microcapsules of biodegradable and non-biodegradable polymers have been investigated for sustained and controlled fashion[8-10]. The term "microcapsule" is defined, as a spherical particle with the size varying between 50 nanometres to 2 millimetres contain a central part material. Microspheres are in strict sense, spherically empty particles. Still, 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[11-13]. 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].

Types of microcapsules

The microcapsules are divided into three types:

1. Mononuclear / single core.

2. Polynuclear/ multiple core.
3. Matrix type.

Classification of Microcapsules

Micro/Nanocapsules

Microcapsules can be classified on the basis of their size or

Morphology

Microcapsules ranges in size from are one micron (one thousandth of mm) to few mm. Nanocapsules are also comes under microcapsules. The diameter of Nanocapsules are in the range of nanometre are referred to as to emphasize their smaller size.

Composition of microcapsules

Coating materials

There are so many coating materials are used for microencapsulation. Some reported coating polymers have also been used for some special applications particularly among the bioadhesives and mucoadhesives. On the other hand many traditional coating materials are useful in the gastrointestinal tract. Carboxylate and amino derivatives included in inert polymers and pH sensitive, which dissolve according to the degree of cross-linking. The selection of suitable coating material decides the physicochemical properties of the resultant microcapsules/ microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should have ability to form a film that is cohesive with the core material. It should have a property of nonreactive with the core material and chemically compatible, and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability. Normally hydrophilic polymers, hydrophobic polymers or a combination of both are applicable for the microencapsulation process. There are many coating materials are applicable in microencapsulation successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose, and cellulose acetate phthalate and styrene maleic anhydride. The thickness of film can be varried significantly depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules made up of a single particle or clusters of particles. When microcapsules are isolated from the liquid manufacturing vehicle, then after drying, the material appears as a free flowing powder. The compressed tablets can be prepared by these powders easily, hard gelatin capsules, suspensions, and other dosage forms.

Coating Material

Inert substance which coats on core with desired thickness

Compatible with the core material.

Stabilization of core material.

Inert toward active ingredients.

Controlled release under specific conditions.

The coating can be flexible, brittle, hard, thin etc.

Abundantly and cheaply available.

Composition of coating

- Inert polymer
- Plasticizer
- Colouring agent

Core materials

The coating is directly applied on core material to serve the exact purpose. Central part of microcapsule is made up of solids or droplets of liquids and dispersions are called as core material. The composition of core material can vary and thus furnish definite flexibility and allow effectual design and development of the desired microcapsule properties. There are many reasons for microencapsulation of a substance. It may include protection of reactive material from their environment, safe and convenient handling of the materials which are otherwise toxics noxious, taste masking, means for controlled or modified release properties means of handling liquids as solids, preparation of free flow powders and in modification of physical properties of the drug.

Core Material

The material to be coated.

It may be liquid or solid.

Liquid core may be dissolved or dispersed material.

Composition of coating material

Drug or active constituent.

Additive like diluents.
Stabilizers.
Release rate enhancers.

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 might allow one controlled unleash dose to substitute for many doses of non-encapsulated drug and additionally may decrease noxious facet effects for medication 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 within 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 state of affairs, a fixed amount of drug is in solution inside the microcapsule. The concentration distinction between the within and also the outside of the capsule decreases regularly because 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 can depend upon the composition of the capsule created and also the setting it's 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 polymerisation within the chosen agent ar embedded during a composite matrix. Rupture of associatey microcapsules by an approaching crack defect releases the healing agent into the crack plane by surface tension. When the free healing agent comes in reality with the catalyst, the ensuing polymerisation 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.

Morphology of microcapsule

The morphology of microcapsules depends mainly on the core material and the deposition process of the shell.

1. Mononuclear (core-shell) microcapsules contain the shell around the core.
2. Polynuclear capsules have many cores enclosed within the shell. 3- Matrix encapsulation in which the core material is distributed homogeneously into the shell material. - In addition to these three basic morphologies, microcapsules can also be mononuclear with multiple shells, or they may form clusters of microcapsules.

Purposes of microencapsulation

- Protection

- Heat, Oxygen,
- Controlled release
- Medicine delivery
- Immobilisation
- High cell density in bioreactors
- Capsular Perstraction
- In Situ Product Removal
- Structuration
- Liquid or gas to solid
- Dispersability
- Dust free
- Functionalisation
- Visual aspect
- Marketing

Advantages of microcapsule

Dispersions

Microcapsules are useful for handling solid or high-viscosity liquid epoxy compounds as low-viscosity aqueous emulsions. (VOC-free). Microcapsules allow you to maintain a stable liquid state over a long period of time, from days to months, when hardening agents are mixed in Microcapsules enable cross-linking reactions between encapsulated epoxy compounds and binder resins when heated to about 120°C. Substances hardened by chemical reactions should be able to achieve excellent adhesion, hardness, and water-resistance by taking advantage of the properties of epoxy compounds. Transparency can be maintained when dispersions, with each particle being one micrometer or smaller in diameter, are mixed in paints.

Particulates

Fluid particulates can be added to non-solvent-based or hydrophobic substances such as vinyl chloride and acrylic sols. Improved heat resistance and oil resistance should be achievable by a reaction with hardening agents when heated to about 120°C To increase of bioavailability to alter the drug release, To improve the patient's compliance, To produce a targeted drug delivery, To reduce the reactivity of the core in relation to the outside environment, To decrease evaporation rate of the core material, To convert liquid to solid form and To mask the core taste.

Other advantages

1. Micro-organism and enzyme immobilization, Enzymes have been encapsulated in cheeses to accelerate ripening and flavour development. The encapsulated enzymes are protected from low pH and high ionic strength in the cheese.
2. The encapsulation of microorganisms has been used to improve stability of starter cultures.
3. Protection against UV, heat, oxidation, acids, bases (e.g. colorant sand vitamins). E.g. Vitamin A / monosodium g.
4. Masking of taste or odours.
5. Improved processing, texture and less wastage of ingredients. Control of hygroscopy enhance flow ability and dispersibility dust free powder enhance solubility
6. Handling liquids as solids.
7. There is a growing demands for nutritious foods for children which provides them with much needed vitamins and minerals during the growing age. Microencapsulation could deliver the much needed ingredients in children friendly and tasty way.
8. Enhance visual aspect and marketing concept.
9. Today's textile industry makes use of microencapsulated materials to enhance the properties of finished goods. One application increasingly utilized is the incorporation of microencapsulated phase change materials (PCMs). Phase change materials absorb and release heat in response to changes in environmental temperatures. When temperatures rise, the phase change material melts, absorbing excess heat, and feels cool. Conversely, as temperatures fall, the PCM releases heat as it solidifies, and feels warm.
10. Pesticides are encapsulated to be released overtime, allowing farmers to apply the pesticides less amounts than requiring very

highly concentrated and toxic initial applications followed by repeated applications to combat the loss of efficacy due to leaching, evaporation, and degradation.

Method of preparation of microcapsules

The method of preparation and also the techniques utilized for microencapsulation overlap significantly. The varied microencapsulation processes may be divided into chemical, physiochemical, and electricity and mechanical processes. Chemical processes embody the surface and in place chemical change strategies. Physiochemical processes embody coacervation part separation, complicated emulsion, disintegrable dispersion and powder bed strategies. Mechanical processes embody the air-suspension technique, pan coating, and spray drying, spray congealing, micro-orifice system and rotary fluidization bed granulator technique. Additionally the spheronization is usually enclosed below the mechanical method of microencapsulation. Sustained unleash compounds microcapsules containing drug with numerous solubility characteristics were ready with mixture polymer dispersion in an exceedingly utterly binary compound atmosphere as another to the traditional microencapsulation technique[17-19]. The microencapsulation by coacervation-phase separation typically consists of 3 steps distributed below continuous agitation:

a. Formation of 3 unmixable chemical phases,
b. Deposition of coating, and
c. Rigidization of the coating. The coacervation-phase separation has been classified into 2 classes, easy coacervation and sophisticated coacervation.

The former implies addition of a powerfully hydrophilic substance to an answer of mixture. This accessorial substance causes 2 phases to be fashioned. The complicated coacervation is primarily a pH dependant method. The acidic or basic nature of the system is manipulated to supply microcapsules. On top of a particular important pH worth, the system relying upon its acidic or basic nature might turn out microcapsules. Below that pH worth they're going to not be fashioned. Sometimes complicated coacervation deals with the system containing over one mixture[20-22]. In surface chemical change, a chemical compound is formed to be polymerized at the interface of 2 incompatible substances. If the interior part could be a liquid, it's doable to disperse or solubilize the chemical compound during this part and emulsify the mixture within the external part till the specified particle size is reached. At this time a cross-linking agent is also accessorial to the external part. Since there's sometimes some migration of the chemical compound from the interior to external part, and since it's most well-liked that the cross-linking agent doesn't transfer to the interior part, the majority of any chemical change can surface at the interface[23-25]. The static strategies of microencapsulation involve trigging along the wall material and also the material to be encapsulated once each ar gaseous. The wall material should be liquid throughout encapsulation stage and should be capable of close the core material. The aerosols created should be oppositely charged. 3 chambers ar used for the method, 2 for atomization of the wall and core material and also the third for intermixture. Oppositely charged ions ar generated and deposited on the liquid drops whereas they're atomized[11,12,26]. The microcapsules were ready by a range of strategies. initial the primary} analysis resulting in development of microencapsulation procedures for prescribed drugs was first printed by Bungenburg de writer and Kaos in 1931, that proscribed the preparation of gelatin spheres and also the use of gelatin coacervation method for coating. The strategy of preparation and techniques utilized for microencapsulation overlap significantly. The assorted microencapsulation processes will be divided into chemical, physiochemical, and static and mechanical processes. Chemical processes embrace the surface and unmoved chemical change strategies. Physiochemical processes embrace coacervation part separation, complicated emulsion, soluble dispersion and powder bed strategies. Mechanical processes embrace the air-suspension methodology,

pan coating, and spray drying, spray congealing, micro-orifice system and rotary fluidization bed granulator methodology. Additionally the spheronization is usually enclosed below the mechanical method of microencapsulation. Additionally to classical spheronizing instrumentation, the Rotocoil from Aeromatic. Inc., instrumentation has been accustomed kind the spheres from extrudates of varied size that ar dried and coated with fluid bed unit (Kondo 1979)[27]. Kawashima, Niwa and Takeuchi (1992)[28] ready hollow microspheres [micro balloons] loaded with drug in enteric acrylic chemical compound shell by employing a novel emulsion solvent diffusion methodology. Sustained unharness chemical compounds microcapsules containing drug with numerous solubility characteristics were ready with mixture polymer dispersion during a fully liquid atmosphere as another to the standard microencapsulation technique. The microencapsulation techniques used for newer polymers ar, aside from some minor modifications, mostly the classical ones comprising chiefly the coacervation part separation, surface chemical change, static strategies, and mechanical strategies. The microencapsulation by coaservation-phase separation usually consists of 3 steps dole out below continuous agitation:

1. Formation of 3 incompatible chemical phases,
2. Deposition of coating, and
3. Rigidization of the coating. The coacervation-phase separation has been classified into 2 classes, straightforward coacervation and complicated coacervation (Feld *et al.* 1988)[29]. The former implies addition of a powerfully deliquescent substance to an answer of mixture. This adscititious substance causes 2 phases to be shaped. The complicated coacervation is in the main a pH scale dependant method. The acidic or basic nature of the system is manipulated to supply microcapsules. On top of an explicit crucial pH scale worth, the system relying upon its acidic or basic nature could manufacture microcapsules. Below that pH scale worth they're going to not kind. Typically complicated coacervation deals with the system containing quite one mixture. Physical methods: Pan coating: The pan coating method, wide employed in the pharmaceutical trade, is among the oldest industrial procedures for forming little, coated particles or tablets. The particles area unit tumbled in a very pan or different device whereas the coating material is applied slowly. Air-suspension coating: Air-suspension coating offers improved management and adaptability compared to pan coating. During this method the particulate core material that is solid, is spread into the supporting air stream and these suspended particles area unit coated with chemical compounds during a} volatile solvent departure a very skinny layer of polymer on them. This method is perennial many hundred times till the specified parameters like coating thickness, etc., area unit achieved. The air stream that supports the particles conjointly helps to dry them, and therefore the rate of drying is directly proportional to the temperature of the air stream which might be changed to more have an effect on the properties of the coating. The re-circulation of the particles within the coating zone portion is established by the look of the chamber and its in operation parameters. The coating chamber is organized specified the particles pass upwards through the coating zone, then disperse into slower moving air and sink back to the bottom of the coating chamber, creating perennial passes through the coating zone till the required thickness of coating is achieved.

Centrifugal extrusion

Liquids square measure encapsulated employing a rotating extrusion head containing coaxial nozzles. In this method, a jet of core liquid is encircled by a

sheath of wall answer or soften. 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 square measure on the wing, the molten wall may be hardened or a solvent may be evaporated from the wall solution. Since most of the droplets square measure among ± 100 percent of the mean diameter, they land in a narrow ring around the spray nozzle. Hence, if needed, the capsules is hardened when formation by catching them during a doughnut-shaped hardening bathtub. This method is superb for forming particles 400–2,000μm (16–79 mils) in diameter. Since the drops square measure shaped by the breakup of a liquid jet, the process is only suitable for liquid or slurries. A high production is achieved, up to 22.5 kg (50 lb) of microcapsules can be produced per nozzle per hour.

Vibrational nozzle

Core-shell encapsulation or small granulation (matrix-encapsulation) is done employing a streamline flow through a nozzle and a further vibration of the nozzle or the liquid. The vibration needs to be exhausted resonance with the Third Baron Rayleigh instability and ends up in terribly uniform droplets. The liquid can consist of any liquids with limited viscosities (0-10,000 m Pas have been shown to work), e.g. solutions, emulsions, suspensions, melts etc. The solidification can be done according to the used gelation system with an internal gelation (e.g. sol-gel process, melt) or Associate in Nursing external (additional binder system, e.g. in a slurry). The process works fine for generating droplets between 20–10,000μm (0.79–393.70 mils), applications for smaller and larger droplets are known. The units square measure deployed in industries and analysis principally with capacities of 1–20,000 kg per hour (2–44,000 lb/h) at working temperatures of 20–1,500 °C (68–2,732 °F) (room temperature up to molten silicon). Heads square measure accessible with from one up to many hundred thousand nozzles.

Spray-drying

Spray drying is a microencapsulation technique once a vigorous material is dissolved or suspended in an exceedingly soften or compound answer and becomes at bay within the dried particle. The main advantages are the ability to handle labile materials because of the short contact time in the dryer and the operation is economical. In fashionable spray dryers the consistence of the solutions to be sprayed is as high as three hundred mPa•s. Applying this system, at the side of the utilization of critical greenhouse emission, sensitive materials like proteins can be encapsulated.

Physicochemical methods

Ionotropic gelation happens once units of acid within the chains of the compound alginate, crosslink with multivalent cations. These may include calcium, zinc, iron and aluminium.

Coacervation-phase separation

Coacervation-phase separation consists of 3 steps administered beneath continuous agitation.

1. Formation of 3 unmixable chemical sections: liquid producing vehicle phase, core material section and coating material section.
2. Deposition of coating: core material is distributed within the coating compound answer. Coating polymer material coated around core. Deposition of liquid polymer coating around core by polymer adsorbed at the interface formed between core material and vehicle phase.
3. Rigidization of coating: coating material is immiscible in vehicle phase and is made rigid. This is done by thermal, cross-linking, or dissolution techniques.

Chemical methods

Interfacial polycondensation

In surface polycondensation, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this methodology is that the classical Schotten-Baumann reaction between ANd chloride and a compound containing a vigorous atom, such as an amine or alcohol, polyesters, polyurea, polyurethane.

Under the proper conditions, thin flexible walls form rapidly at the interface. A solution of the chemical ANd a diacid chloride ar blended in water ANd an solution containing an alkane series and a polyfunctional salt is another. An alkali is present to neutralize the acid formed during the reaction. At the interface of the emulsion droplets are formed by Condensed polymer walls.

Interfacial cross-linking

Interfacial cross-linking springs from surface polycondensation, and was developed to avoid the utilization of hepatotoxic diamines, for pharmaceutical or cosmetic applications. In this technique, the tiny bifunctional compound containing active element atoms is replaced by a biosourced chemical compound, sort of a macromolecule. When the reaction is performed at the interface of Associate in Nursing emulsion, the acid chloride reacts with the assorted useful teams of the macromolecule, resulting in the formation of a membrane. The method is extremely versatile, and also the properties of the microcapsules (size, porosity, degradability, mechanical resistance) will be bespoke. Flow of artificial microcapsules in microfluidic channels:

In situ polymerization

In a few microencapsulation processes, the direct chemical change of one compound is dole out on the particle surface. In one process, e.g. cellulose fibers area unit encapsulated in polythene whereas immersed in dry dissolvent. Usual deposition rates are about 0.5μm/min. Coating thickness ranges 0.2–75μm (0.0079–2.9528 mils). The coating is uniform, even over sharp projections. Protein microcapsules area unit biocompatible and perishable, and also the presence of the macromolecule backbone renders the membrane additional resistant and elastic than those obtained by surface polycondensation.

Matrix polymerization

In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple technique of this sort is spray-drying, in which the particle is formed by evaporation of the solvent from the matrix material. However, the solidifying of the matrix can also be caused by a chemical process.

Evaluation of Microcapsules[30,31]

A variety of analytical and physical methods is used to characterize particles and encapsulated ingredients.

- Particle size Payload
- Content uniformity and stability
- Active ingredient release profiles and activity Colloid stability
- Particle stability

Particles

Sizing down to 3 nm

Zeta potential

Particle Morphology

SEM/EDX (scanning electron microscope/energy-dispersive X-ray spectroscopy) Environmental SEM/STEM [scanning electron microscope (SEM)/scanning transmission electron microscope (STEM)]

Optical microscopy

Thermal Analysis

Differential scanning calorimetry

Thermal gravimetric analysis

Dynamic mechanical analysis

Rheology

Low viscosity fluids, gelation and curing profiles, reinforced solid mechanical properties Large dynamic shear range, sub-ambient to >600 °C temperature range

Multiple frequency waveform generation.

Payload/Content

HPLC (high performance liquid chromatography) IC, GC (gas chromatography), GC/MS (gas chromatography/mass spectrometry).

Fluorescent

Thermal gravimetric analysis

Release

Dissolution (pH, solvent)

Simulated body fluids

Cell culture

Tissue culture

Stability

Controlled environment such as:

Time
Temperature
Relative humidity
Ultraviolet
Simulated fluids
Thermal and pressure
By products

% Yield

The total amount of microcapsules obtained was weighed and the percentage yield calculated taking into consideration the weight of the drug and polymer.

%Yield = Practical yield/Theoretical yield x 100

Particle size analysis

For size distribution analysis, different sizes in a batch were separated by sieving; using a set of standard sieves (IP). The amounts retained on different sieves were weighed.

Encapsulation efficiency

Encapsulation efficiency was calculated using the formula:

Encapsulation efficiency= Estimated % drug content in microcapsules/ Theoretical % drug content in microcapsules x 100

Estimation of Drug Content

Microcapsules were calculated by UV spectrophotometric (Shimadzu 1700) method. The method was validated for linearity, accuracy and precision. A sample of microcapsules equivalent to 100 mg was dissolved in 25 ml ethanol and the volume was adjusted upto 100 ml using phosphate buffer of Ph.

The solution was filtered through Whatman No.1 filter paper. Then the filtrate was assayed for drug content by measuring the absorbance at 275 nm 13 after suitable dilution.

Wall thickness

Microcapsules were determined by the method of Luu *et al.*[32] 14 using equation:

$h = r (1-p) d1 / 3[pd2 + (1-p) d1]$

Whereas:

h = wall thickness of microcapsules
r = arithmetic mean radius
d1 = density of core material
d2 = density of coat material
p = proportion of medicament in microcapsules

Micro photographic Studies

The prepared microcapsules were characterized optically in terms of morphology, by using computer microscope (model Qx3).

In vitro Drug release Studies

Drug release was studied by using USP type II dissolution test apparatus (LABINDIA DISSO 2000) in Phosphate buffer of pH 6.8 (900ml). The paddle speed at 100 rpm and bath temperature at 37 ± 0.5°c were maintained throughout the experiment. A sample of microcapsules admire one hundred mg of aceclofenac was utilized in every take a look at. Aliquot adequate 5ml of dissolution medium was withdrawn at specific measure and replaced with recent medium to take care of sink condition. Sample was filtered through Whatman No. 1 filter paper and after suitable dilution with medium; the absorbance was determined by UV spectrophotometer (SHIMADZU 1700) at 275 nm. All studies were conducted in triplicate (n=3). The release of drug from marketed SR tablet was also studied to compare with release from microcapsules.

Data analysis

The data obtained from in vitro drug release study was fitted into models of data treatment as: zero order kinetics, first order kinetics, Higuchi square root model and Hixson-Crowell cube root model.

Applications of microcapsule

Some of the applications of microencapsulation are often represented well as given below:-

Prolonged release dosage forms. The microencapsulated drug are often administered, as microencapsulation is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms[33].

Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach[34].

It can be used to mask the taste of bitter drugs[12,35].

From the mechanical point of view, microencapsulation has been used to aid in the addition of oily medicines 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[36,37].

It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microencapsulation doesn't nonetheless offer an ideal 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[38,39].

The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case wherever direct contact of materials brings regarding liquid formation. The stability improvement of incompatible Aspirin-chlorpheniramine ester mixture was accomplished by micro-encapsulating each of them before mix[12].

Microencapsulation can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation[39].

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[40].

The hygroscopic properties of many core materials may be reduced by microencapsulation[41].

Many drugs have been microencapsulated to reduce gastric irritation[42].

Microencapsulation method has also been proposed to prepare intrauterine contraceptive device[42,43].

In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles[44-47].

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

Cell Immobilization: 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 employed to extend cell density, productivity and to avoid washout of the biological catalysts from the reactor. This has already been applied in fermentation alcohol and solvent production, sugar conversion or wastewater treatment.

Beverage Production: Today beer, wine, vinegar and other food drinks production are using immobilization technologies to boost yield, improve quality, change aromas, etc...

Protection of Molecules from Other Compounds: 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 several alternative molecule inactive or incompatible if mixed in any formulation. Moreover, microencapsulation additionally permits getting ready several formulations with lower chemical masses reducing considerably processes' value.

Drug Delivery: After designing the right biodegradable polymers, microencapsulation has permitted controlled release delivery systems. These revolutionary systems permit dominant the speed, 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 and 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 alternative coatings, and functionalized textiles.

Recent advances in microencapsulation

Several strategies and techniques square measure probably helpful for the preparation of chemical compound microparticles within the broad field of microencapsulation. The preparation method determines the type and the size of microparticle and influence the ability of the interaction among the components used in microparticle formulations. The term microparticle designates systems larger than one micrometer in diameter and is employed sometimes to explain each microcapsules and microspheres. Microparticles-containing medication square measure used for numerous functions together with -but not restricted to- controlled drug delivery, masking the taste and odour of drugs, protection of the drugs from degradation, and protection of 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[48]. Recently, numbers of publications and patents have been published. Hughes[49] 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 needs high general concentration of the prodrug. The organic compound prodrug is contained in perishable chemical compound microparticle system ready exploitation the o/w emulsion solvent evaporation strategies. Lee *et al.*[50,51] prepared a composition in the form of thin film or strip composed of microspheres containing antibiotic such as minocycline HCl. It was created employing a perishable compound, 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.*[46] 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[11]. 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.*[13] and Markland *et al.*[16] 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[52] 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 situformed matrix. Solidification methodology of the hydrophilic capsule materials like gelatin is through apace lowering the temperature and resulting dehydration. While such methodology achieved some vital industrial success, difficulties have generally been encountered in apace inducement natural process 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[53] 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[54] developed a way for getting ready enteric chemical compound microparticles containing a supermolecule matter in a very single or double emulsification method during which the enteric chemical compound 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.*[52,53] 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[54] 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 relative molecular mass of dairy product acid-glycolic acid chemical compound fraction (8,000 to about 15,000) is contained in a large amount, LHRH derivative readily interacts with these polymers of high reactivity[55] 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[56] Rickey *et al.*[57] 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 ensuing emulsion was then additional to associate binary compound 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.*[58,59]. Since evaporating the solvent from the dispersion isn't applicable for delicate and sensitive compounds and it's 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[49]. 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.*[60] 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 molecule wherever the outer surface of the microparticle is free from adsorbate molecules. Polysaccharides such as starch have been used as a matrix for encapsulation many active ingredients including proteins. Wen and Anderson[61] prepared double wall microspheres using two biodegradable polymers by the o/w emulsification solvent extraction process. Futo *et al.*[62] 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.[63] 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.*[64-66]. In addition, very little *et al.*[67] provided a high outturn technique of making ready multiple (at least 10) totally different microparticle formulations (containing promid DNA) in parallel supported 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.*[68]. Biodegradable microspheres ready victimization o/w emulsion technique and incorporating release-modifying agents and hydrogen ion concentration-stabilizing agents that resist changes in pH upon the addition of tiny amounts of acid or alkali such as basic amino acids, such as L-arginine were prepared[69]. 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.*[70] utilized starch to encapsulate vaccines using emulsification method. In process, associate immunologically active substance (vaccine) is suspended in associate liquid starch answer with associate amylopectin content exceptional eighty fifth by weight before being mixed with associate solution of a chemical compound having the flexibility of forming a 2 part liquid system. The starch droplets containing the vaccine are allowed to gel as the starch has capacity to gel naturally. Encapsulation of nucleotides and STH victimization easy or double emulsification ways was achieved by Johnson *et al.*[71] 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.*[72] produced surface changed microparticles that possess a completely unique supermolecule shell, and a surface coating. The supermolecule shell may incorporates cross-linked simple protein or alternative proteins with useful 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 one of the versatile drug delivery system of either oral or parenteral route of administration of a medication and should ideally produce the required plasma level and maintain a steady level for a chronic amount of your time and overcome issues related to the standard medical aid and enhance the therapeutic effectiveness of a given drug. The techniques of developing microacpsules through microencapsulation method pioneered the researchers to develop mixture and nano drug delivery system for uncounted medicine.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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