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A Review on Microparticles Drug Delivery System

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Abstract: Multiparticulate drug delivery methods frequently include microparticles, microspheres, and microcapsules, which have both medical and technological advantages. Microparticles are employed as multiunit drug delivery systems with well-defined physiological and pharmacokinetic benefits to increase efficacy, tolerance, and patient compliance. Their sizes range from 1 to 1000 m. In the creation of microparticles for drug delivery research, a variety of polymers have been used to increase therapeutic effectiveness while lowering side effects. Microparticles today are made of polymers, ceramic, and glass. Microparticles are more stable in the biological milieu than liposomes are. Surface-linked targeting moiety can be built into microparticles. In order to administer drugs to specific areas, this technique is employed. For controlled and long-term release, microparticles are also utilised. To treat many sick states such ophthalmic disorders, cancer, cardiac diseases, and inflammation, macromolecules are encapsulated inside microparticles. This review covers the pros, cons, types of microparticles, preparation method, evaluation of microparticles, and applications.

Keyword: Microparticle, Microsphere, Emulsion, Encapsulated

I. INTRODUCTION

"Microparticulate drug delivery system is one of the ways for delivering drugs over lengthy periods of time in a regulated and sustained manner. They are small solid particles or liquid droplets surrounded by walls of natural and synthetic polymer films of different thickness and degree of permeability that operate as a release rate controlling substance and have a diameter ranging from 0.1m to 200m." [1] "Kramer proposed the use of albumin micro particles in medication delivery systems in 1974. Microparticles as continuous release carriers were proposed by Java Krishna and Catha in 1997. Haemoglobin has also been reported to be used as a natural biodegradable carrier for medications in Microparticulate delivery." [2]

"Microparticles allow for the delivery of macromolecules via a multitude of pathways while also allowing for effective drug release control. They could also be utilised to deliver vaccines and materials like DNA for gene therapy purposes. Microparticles provide effective protection against degradation (e.g., enzymatic), the ability to administer the drug in a regulated and localised manner throughout time periods ranging from a few hours to months, and ease of administration (compared to alternative forms of controlled release parenteral dosages, such as macro sized implants). Controlled drug delivery systems have the potential to provide the best treatment for a specific drug molecule." [3]

"Microparticles, or microparticles, as they are often known, are small spheres with a diameter mostly less than 1000 um. Well-established manufacturing procedures can be used to create microparticles. A drug can be distributed uniformly throughout the polymer matrix (microparticles) or encapsulated into the polymer matrix to produce a drug reservoir (microcapsules)". [4]

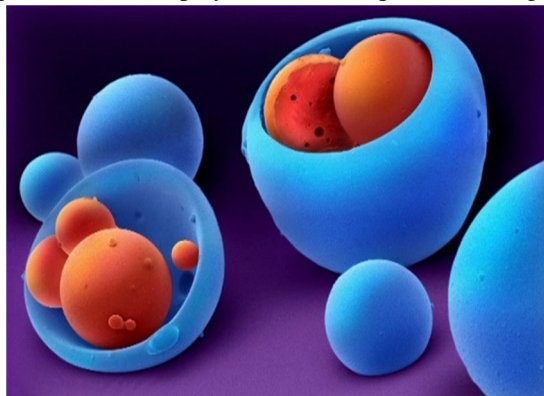


Fig. No. 1: Microparticle [44]

A. Advantages of Microparticles

- 1) "It protects the encapsulated medication from enzymatic breakdown.
- 2) It is simple to implement.
- 3) This method aids in the hiding of unpleasant tastes.
- 4) They aid in the improvement of medication relative bioavailability.
- 5) This approach allows for precise drug administration to specific locations.
- 6) Drug toxicity is minimised thanks to the tiny particles.
- 7) Amorphous drugs are also made with micro particles (desirable physical properties).
- 8) Drugs' local side effects on oral intake, such as GI discomfort, are also reduced.
- 9) This approach produces a sustained-release formulation with a reduced drug dose, which aids in plasma concentration maintenance and increases patient compliance.
- 10) pH-activated microparticles are employed in vaccines, gene therapy, and transfection.
- 11) Parenteral micro particles can be used to provide high concentrations of water soluble medicines without causing severe osmotic effects at the injection site.
- 12) They can also be preserved in the form of dry particles or suspension for a longer period of time.
- 13) These micro particles come in the form of a tablet with an effervescent disintegration agent which is useful for a person who is unable to chew." [5]

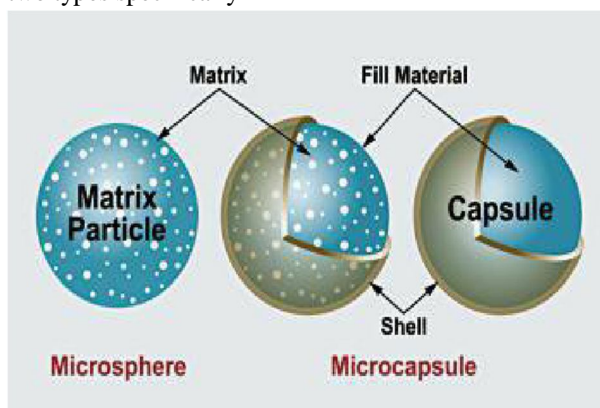
B. Disadvantages

Although the tiny particles are impressive, they do have several drawbacks, including the following:

- 1) "Controlled release formulations have greater material and processing costs than normal formulations.
- 2) The fate of polymer matrix and its environmental impact
- 3) Plasticizers, stabilisers, antioxidants, and fillers are examples of polymer additives.
- 4) There is a lack of repeatability.
- 5) Changes in temperature, pH, and the addition of solvents can all affect the drug's stability.
- 6) Aggregation of particles occurs as a result of their tiny size and huge surface area, making physical handling of micro particles in liquid and dry forms problematic.
- 7) These issues must be resolved before micro particles can be employed in clinical settings." [6]

II. TYPES OF MICROPARTICLE

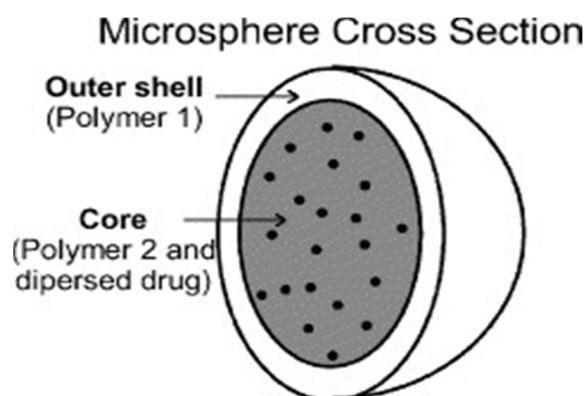
Microparticle are mainly divided into two types specifically-



"Fig. no. 2: Types of Microparticle" [42]

III. MICROSPHERE

"Microspheres are free flowing powder which is made up of spherical particles having diameter < 200 diameter. It can be injected with a needle with a number of 18 or 20. They are made up of biodegradable proteins or synthetic polymers found in nature. A well-designed controlled drug delivery system can address some of the drawbacks of traditional therapy while also improving a medicine's therapeutic efficacy." [7]



“Fig. no.3: Microsphere”^[45]

A. Types of Microsphere

- Bioadhesive Microsphere
- Floating Microsphere
- Radioactive Microsphere
- Magnetic Microsphere
- Polymer Microsphere

- 1) *Bioadhesive*: “Adhesion is defined as the adhesion of a medication to a membrane using the adhesive properties of water-soluble polymers.”^[8] “In which some polymers' bioadhesive properties are used to route medication to a specific target. These polymers become adherent upon hydration and can be used for a long period.
- 2) *Floating Microsphere*: The majority density of floating types is substantially lower than that of gastric fluid, therefore they stay buoyant within the stomach without impacting gastric emptying rate.”^[9]
- 3) *“Radioactive Microspheres*: Radioactive microspheres are a subclass of microspheres that interact radioactively and are normally treated similarly to non-radioactive microspheres. In addition to the matrix material, radioactive microspheres always contain one or more radionuclides that define the microsphere and demonstrate its targeting ability in a specific target region.
- 4) *Magnetic Microsphere*: Type of sphere that is made up of magnetic particles. This mechanism is critical because it permit the drug to be delivered to the illness site. A larger amount of freely circulating medicine can be substituted with a smaller amount of magnetically focused drug in this way. Magnetic carriers receive magnetic responses to a magnetic field from integrated components such as chitosan, dextran, and other materials utilised in magnetic microspheres. Therapeutic magnetic microspheres and diagnostic magnetic microspheres are the two types.
 - a) Therapeutic Magnetic Microspheres, for example, are utilised to deliver chemotherapy agents to liver tumours. This method is also target drugs such as protein, peptides.
 - b) Diagnostic Microspheres: By producing Nano size particles supramagnetic iron oxides, it can be used to image liver metastases as well as identify bowel loops from other abdominal structures”.^[10]
- 5) *Polymer Microsphere*
 - a) *Biodegradable Polymeric Microsphere*: “Natural polymers like starch are employed since they are biodegradable, biocompatible, and bioadhesive in nature. Due to its high degree of swelling property with aqueous medium, biodegradable polymers lengthen the residence period when in contact with mucous membranes, resulting in gel formation. The rate and amount of medication release are controlled by the polymer concentration and the release pattern throughout time. The fundamental disadvantage is that drug loading efficiency of biodegradable microspheres in clinical application is complex, making drug release difficult to control.
 - b) *Synthetic Polymeric Microspheres*: Synthetic polymeric microspheres are widely employed in clinical applications as bulking agents, fillers, embolic particles, drug delivery vehicles, and other applications, and have been shown to be safe and biocompatible. However, the fundamental disadvantage of these microspheres is that they tend to move away from the injection site, posing a risk of embolism and further organ injury.”^[11]

B. "Material used in Microsphere

Microspheres used usually are polymers. They are classified into two types:

1) Synthetic Polymers

There are two types of synthetic polymers.

- a) *Polymers that are not Biodegradable:* Polymethylmethacrylate (PMMA), acrolein, glycidyl methacrylate, and epoxy polymers are only a few examples.
 - b) *Biodegradable Polymer:* Biodegradable polymers are a type of biodegradable polymer that can be used in a variety of Lactides, Glycolides, and their copolymers, for example. Poly anhydrides, Poly alkyl cyanoacrylates
- 2) *Nature Polymer:* Proteins, carbohydrates, and chemically modified carbohydrates are all examples of natural polymers. Albumin, Gelatin, and Collagen are all proteins. Agarose, Carrageenan, Chitosan, and Starch are all carbohydrate sources. Poly dextran and Poly search are two examples of chemically modified polysaccharides'' [12, 13].

IV. MICROCAPSULE

"This method of encapsulation a substance inside a small capsule is called as microencapsulation. Microcapsules are little spheres surrounded by a homogeneous wall. The core/internal phase of the microcapsule is referred to as the core/internal phase, while the shell/coating is referred to as the shell/coating. Microcapsules range in size from 1 to 7mm. Solids, liquids, and gases can all be encapsulated, which can change the size and structure of capsules." [14]

V. REASONS FOR MICROENCAPSULATION

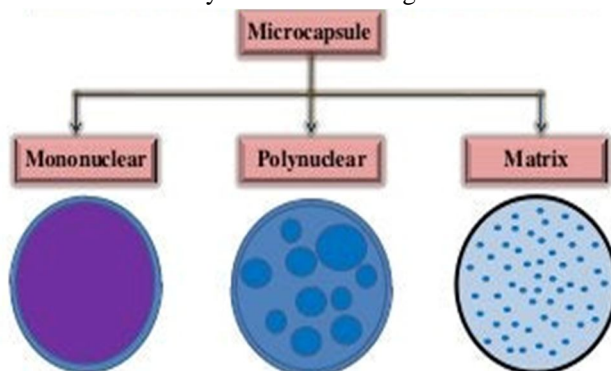
- 1) "This technique has been widely utilised to conceal the taste and odour of various pharmaceuticals in order to increase patient compliance.
- 2) This technology can be used to turn liquid drugs into a free-flowing powder.
- 3) Microencapsulation can be used to stabilise medications that are susceptible to oxygen, moisture, or light.
- 4) Microencapsulation can be used to prevent drug incompatibility.
- 5) Microencapsulation can prevent the vaporisation of several volatile medications, such as methyl salicylate and peppermint oil.
- 6) Many medications, including ferrous sulphate and KCl, have been microencapsulated to minimise toxicity and GI irritation.
- 7) Microencapsulation can also be used to change the absorption site.
- 8) Toxic substances, like as pesticides, can be microencapsulated to limit the risk of factorial person sensitization.
- 9) Microencapsulated vitamin A palmitate has improved stability, according to Bakan and Anderson." [15]

A. Classification

"Microcapsules can be classified into three categories;

- Mononuclear/Single core.
- Poly nuclear/Multiple core.
- Matrix type.

Mononuclear microcapsules have a shell surrounding the core, whereas poly nuclear microcapsules have many cores encased in the shell. In the case of matrix, the core material is uniformly distributed throughout the shell." [16,17]



"Fig. no.5: classification of microcapsule" [47]

VI. PREPARATION OF MICROPARTICLE-

A. Single Emulsion Process

“Oil-in-water (o/w) emulsification is used in this procedure. The organic phase of the O/W emulsion system is made up of a volatile solvent containing dissolved polymer and the medication to be encapsulated, as well as a dissolved surfactant.

The aqueous phase contains a surfactant that prevents the organic droplets from coalescing once they have formed. To make an o/w emulsion, the polymer – solvent medication solution is emulsified (with the right amount of agitation and temperature). The emulsion is made by mixing the organic and aqueous phases using a propeller or magnetic bar.

Surfactants are employed to prevent coalescence and stabilise the dispersed phase droplets generated during emulsification. Surfactants are amphipathic in nature and will align themselves at the droplet surface, lowering the free energy at the interface between the two phases and increasing stability.

Resistance to coalescence and microsphere flocculation is also provided by the surfactant. PVA is a commonly utilised surfactant in the production of microparticles.”^[18]

B. Double Emulsion Process

“Double emulsion process is regularly used for medication which are not soluble in organic solvent. If the drug's form is tiny enough, a solid-in-oil-in-water emulsion(s/o/w) method could be employed to encapsulate it. To avoid massive bursts associated with the dissolution of bigger crystals, the size of the drug crystal should be at least an order of magnitude less than the target microparticle diameter.

Smaller crystals will be uniformly dispersed throughout the emulsion's organic droplet. This approach has been used to encapsulate hydrophilic medicines (cisplatin, doxorubicin).

The issue with encapsulating hydrophilic drugs is that if the drug is lost to the external aqueous phase during the encapsulation process, the remaining drug may migrate to the droplet's surface before solidifying.

To reduce the likelihood of these issues, the organic droplet should be consolidated into microparticles as soon as feasible after creation.

This is accomplished by combining a viscous organic polymer and drug solution with a large secondary volume of water, which draws the organic solvent into the aqueous phase quickly, leaving the encapsulated medication in the microparticle. The viscous dispersion phase reduces the volume of organic solvent in the droplet, allowing it to be removed more quickly. It also makes it more difficult for the solid drug particle/crystal to migrate to its surface, resulting in more uniform drug distribution within the particle.”^[19]

C. Phase Separation

“A third component is mixed to the polymer solution to decrease the polymer solution to decrease the solubility of the encapsulating polymer. The technique produces two liquid phases: a polymer-containing coacervate phase and a polymer-depleted supernatant phase.

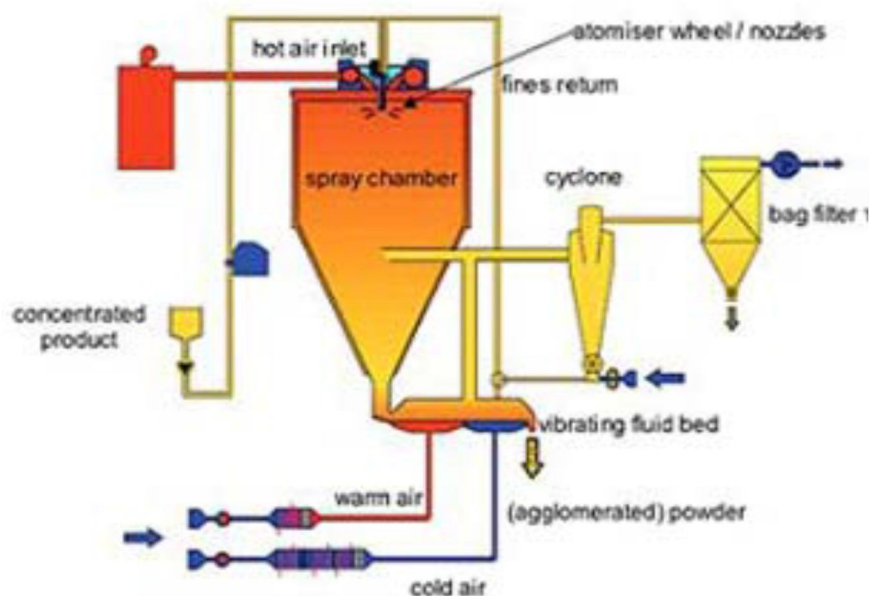
The coacervate coats the medication that is dispersed/dissolved in the polymer solution. coacervation process having the following three steps:

- 1) Phase separation of the polymer solution,
- 2) Coacervate adsorption around the drug particle.
- 3) Solidification of the microspheres.”^[20]

D. Spray Drying

“Spray drying is a common procedure in the pharmaceutical industry, and various researchers have looked at it as a way to make biodegradable microparticles. It is quick, simple, and easy to scale up, requires only mild conditions, and is less reliant on drug and polymer solubility factors.

The medication is usually dissolved or suspended in a polymer solution in this approach. The solution/suspension is then delivered into the spray drying device via the nozzle, where the polymer/drug solution is quickly combined with air and driven through a small diameter opening. The polymer/drug solution is nebulized at nozzle 25, and the resulting droplet is immediately dried by evaporation before being collected.”^[21]

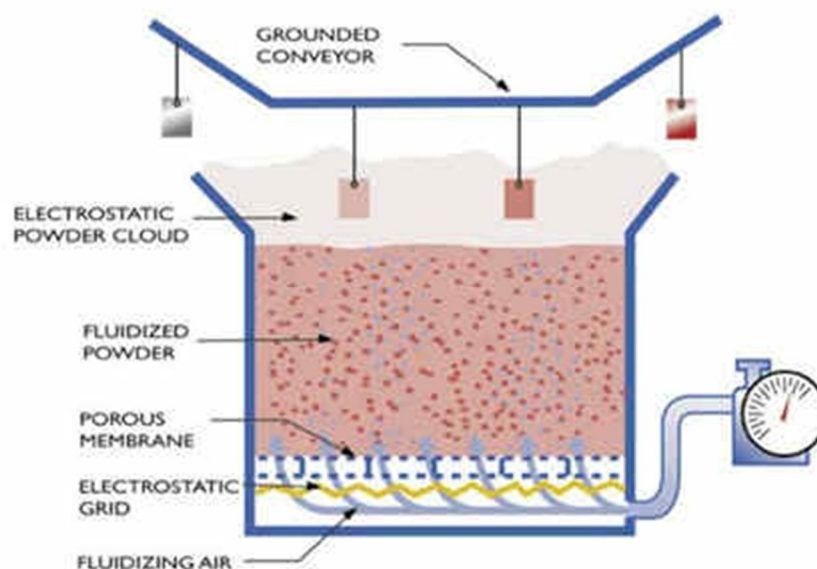


“Fig. No.6: Spray Drying”^[43]

E. Fluidized Bed Coating

“Fluidized bed coating method in which top, bottom and tangential are three popular methods. Because granules often have a porous surface and an interstitial void area, the bulk density of the granules formed is typically low. The tangential-spray coating process uses a combination of centrifugal, high-density mixing and fluid bed drying efficiency to produce a product with a high bulk density but some interstitial void space. It results in particles that are less friable and have a more spherical form. The solid core particles are fluidized by air pressure in the bottom spray method, and a solution is sprayed to the particles from the bottom of the fluidization chamber (which is similar to the air stream).”^[22]

“The coating materials are sprayed into the fluidized particles by the spraying nozzle, which is suspended in the air. Because the coating solution droplets only travel a short distance before colliding with the solid particles, the film is more evenly distributed. After that, the coated particles are hoisted into the air stream, which dries the coating. The particles that have been raised into the air stream are then settled, and a new cycle begins.”^[23]



“Fig. no.7: Fluidized Bed Coating”^[46]

F. Solvent / Emulsion Extraction Process

“The organic phase is removed by extraction of the organic solvent in this procedure for the manufacturing of micro particles. Water miscible organic solvents, such as isopropanol, are used in this procedure. Extraction with water as a solvent removes the organic phase. The hardening time of the microspheres is reduced as a result of this process. The dissolving of polymer in a solvent is required for the preparation of micro particles. The solution is then emulsified in a vegetable oil, and an amphiphilic agent is added to the emulsion to aid in solvent extraction, resulting in the formation of micro particles.”^[24]

VII. EVALUATION OF MICROPARTICLE

“Microparticles are evaluated by using the parameters and methods: The microparticle carrier’s characteristic is a significant phenomenon that contributes in the development of a suitable carrier for protein, drugs, or antigens. The microstructures of these microparticles vary. The release and stability of the carrier are determined by these microstructures.”^[25]

A. Microparticles Yield

“These studies entail determining the amount of microparticles obtained at the end of the preparation process, as well as the amount of polymer and medication consumed during the process.”^[26]

It can be calculated as follow:

$$\text{Percentage Yield} = \frac{\text{Practical Yield} \times 100}{\text{Theoretical Yield}}$$

$$\text{Practical yield of microparticle} = \frac{\text{Amount of encapsulated drug}}{\text{Amount of added drug}}$$

VIII. DRUG ENTRAPMENT EFFICIENCY-

“The amount of drug entrapped in microparticles and the amount of drug adsorbed on the surface or inside of the polymer are calculated to estimate drug entrapment efficiency. The amount of free, adsorbed, and entrapped medication should all be able to be assessed individually, and this measurement revealed the microparticles' efficacy in terms of active components.

Determination of free drug in microparticles (unentrapped drug): Microparticles are accurately weighed and placed in a beaker. To liberate the free drug included in the polymeric matrix, saline is added to the mixture and well mixed. A suitable analytical approach is used to quantify the free drug. It is determined by.

$$\text{Percentage loading of microparticle} = \frac{\text{Quantity of free drug present}}{\text{Weight of microsphere}}$$

By digesting the microparticles with saline (0.9 percent w/v) at room temperature, sonicating the solution in an ultrasonic bath for 5 minutes, then centrifuging it at 3000vpm for 2 minutes, the amount of drug present at the surface can be determined. The medication is measured using an appropriate analytical method after the supernatant is filtered through a 0.45m filter.

$$\text{Percentage loading of microsphere} = \frac{\text{Quantity of drug present}}{\text{Weight of the microsphere}}$$

- 1) *Entrapped Drug in Microparticles*: 5ml of 0.1m glacial acetic acid is combined with the residue left over following the extraction of the free and adsorbed drug. The sample is centrifuged for 10 minutes at 5000rpm. The supernatant is filtered with a 0.45m filter, and the amount of drug entrapped is determined using an appropriate analytical method.”^[26]

Percentage of the encapsulated drug =

Quantity of the drug encapsulation

Quantity of the drug added for encapsulation

- 2) *Particle Size and Shape*: “Traditional light microscopy (LM) and scanning electron microscopy (SEM) are the two most used methods for visualising microparticles (SEM). Microparticles' shape and exterior structure can be determined using both methods. In the case of double-walled microparticles, LM allows you to modify the coating parameters. The structure of the microparticles may be seen before and after coating, and the difference can be assessed microscopically. In comparison to the LM, the SEM has a better resolution. SEM can be used to investigate the surfaces of microparticles and, when the particles have been cross-sectioned, it can also be used to investigate double-walled systems. The structure of multiple walled microparticles is characterised using confocal fluorescence microscopy. Other than experimental approaches, laser light scattering and multi size coulter counter can be used to characterise the size, shape, and morphology of microparticles.
- 3) *Infrared Spectroscopy*: The degradation of the carrier system's polymeric matrix is measured using FT-IR. The surface of the microparticles is studied using a technique called Alternated Total Reflectance (ATR) (ATR). The IR beam travelling through the ATR cell reflected numerous times through the sample, yielding mostly surface material IR spectra. Depending on the manufacturing techniques and conditions, the ATRFTIR can provide information regarding the surface composition of microparticles.”^[27]

IX. DENSITY DETERMINATION

- 1) *Bulk & tap Density*: “Microparticles bulk and tapped densities are also evaluated. After lightly shaking to break up any agglomerates, weighed amounts of microparticles were placed in a 10ml measuring cylinder. After measuring the initial volume of microparticles, the cylinder was allowed to fall from a height of 2-5 cm on a hard surface under its own weight. The tapping was repeated at a rate of 100 taps per minute until there was no more change in volume. Bulk density is a metric that describes how tightly particles or granules are packed together.”^[28]

Bulk Density - $\frac{\text{Mass of Powder}}{\text{Volume of packing}}$

Tapped bulk Density - $\frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$

- 2) *Compressibility*: Compressibility is the value can be used to see flowability. The percentage compressibility of microparticle can be calculated by using formula:

$$C = \frac{P_b - p_u}{p_b} \times 100$$

Where, p_b = tapped density,

P_u = bulk density.

- 3) *Angle of Repose*: The angle of repose of microparticles can be determined using the fixed funnel and free standing cone methods. The wetting property of a micro particle carrier is determined by measuring the angle of repose. It decides whether microparticles are hydrophilic or hydrophobic in nature. This thermodynamic feature is unique to solids and is influenced by the adsorbed component's existence. A droplet is placed in a circular cell set above the objective of an inverted microscope to measure the advancing and receding angle of contact. Within a minute of microparticle deposition, the contact angle is measured at 200°C.

$$\Theta = \tan^{-1} (h/r)$$

Where, h = height of pile

r = radius of the base

θ = angle of repose

- 4) *Determination of Drug Content*: Microparticles were tested for drug content to measure the yield and efficiency of drug loading. 100 mg of microparticles were crushed to a fine powder, distilled water was added, and the solution was left to sit for 12 hours. The solution was sonicated for 30 minutes after 12 hours. After that, the solution was utilized by whatman filter paper no.1. With distilled water, two millilitres of clear filtrate were diluted to 100 millilitres. The solution's absorbance was determined using a Shimadzu UV-1700 at the appropriate absorbance and distilled water as a blank.” [30, 29]
- 5) *Capture Efficiency*: “Allowing washed microparticles to lyse can be used to measure the capture efficiency of the microparticles or the percent entrapment. The active ingredients in the lysate are then determined according to the monograph's requirements. The following equation is used to compute the percent encapsulation efficiency.

$$\% \text{ Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$$

X. PEPTIDE ENTRAPMENT & ENTRAPMENT EFFICACY

HPLC analysis is possible.

- 1) *Differential Scanning Calorimetry (DSC) Analysis*: The DSC method can offer both qualitative and quantitative data on the drug's physicochemical condition in the microsphere. Melting, recrystallization, and decomposition, as well as outgassing or a change in the heat capacity of the listed material, are all examples of endothermic or exothermic processes. DSC is used to compare and contrast multiple samples of the same material in order to determine their similarities and differences, as well as the effects of additives on the material's thermal properties.” [31]
- 2) *Application*
- a) “Microcapsule application include pharmaceutical and biotechnology products, cosmetics, diagnostic aids, biological filtration device, veterinary and zoological technics products, foods and food additives, flavours, fragrance, detergents, paints, agricultural chemicals, adhesives, industrial chemicals, household products, packaging, textiles, and photographic and graphic arts materials.
- b) These microcapsules are useful for achieving sustained and controlled release, reducing vaporisation of volatile oils, protecting moisture/light/oxidation-sensitive drugs, masking unpleasant taste and odour, converting liquids to powders, and separating incompatible substances within a single system.
- c) Encapsulated antibiotics include amoxicillin, ampicillin, bacampicillin, cephalexin, cephadrine, chloramphenicol, clarithromycin, erythromycin, potassium pheneticillin, ofloxacin, and ciprofloxacin.” [32,33,34,35,36]
- d) “Furosemide, chlorothiazide, and sulphonamide were encapsulated to create sustained-release formulations with the benefit of avoiding the short periods of peak diuresis seen with conventional formulations.” [37,38]
- e) “Antihypertensives include isosorbide-5-mononitrate (IS-5-MN), dihydralazine sulphate, piritanide and propranolol HCl, captopril, nicardipin, and dipyridamole. IS-5-MN microcapsules were adjusted and prepared to keep the effect going and overcome the tolerance that developed in previous preparations” [39, 40]
- f) “Echocardiography and other ultrasonic imaging techniques use air-filled tiny particles. They're also utilised in cosmetics as opacifiers or reflectivity enhancers.

- g) Solid microspheres are employed in the nasal delivery of medications such as polypeptides, insulin, somatostatin, and metoclopramide, among others.
- h) PH-activated micro particles have been utilised to administer pharmaceuticals via IV injection, intradermal injection, rectally, orally, intravaginal, inhalational administration, and mursal delivery, among other methods.
- i) They're also utilised to give medication. A pathogen's or tumour's antigenic epitope.
- j) The tiny particles can help with cell transfection and gene therapy. 11. Condensed phase micro particles are used as stable strong kit for enzymes, antibodies, dye.”^[41]

XI. CONCLUSION

A physical technique to altering and improving the pharmacokinetic and pharmacodynamic features of numerous types of pharmacological molecules is the microparticles drug delivery system. Microparticles provide a number of benefits, including protection and masking, as well as improved process efficiency. capabilities, increased bioavailability, reduced dose frequency, improved stability, lower dissolution rate, easier handling, and spatial targeting of the active ingredient This method allows for precise distribution of small doses of powerful medications; drug costs are lowered concentrations in locations other than the target organ or tissue and labile.

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