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A review – Microparticulate drug delivery system

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ABSTRACT: The utilization of microparticles as innovative drug delivery systems has lately gained attention, particularly due to their adaptability for a larger range of applications. Microparticles have been a very successful drug delivery system as it has several advantages like improved bioavailability, reduced dosage frequency, limited fluctuation during therapeutic range, low toxic effect etc. This article provides a brief review of microparticle drug delivery system, different types of microparticles, drug release, materials, polymers used in these systems, and processes used to create these systems, treatment strategy and the microencapsulation techniques depending on polymeric microparticles.

Keywords: Microparticle, Microencapsulation, Matrix system, Reservoir system, Controlled drug delivery.

I. INTRODUCTION:

Microparticles are spherical particles with diameters from 10 μm to 1000 μm, [1] which have many different forms such as microcapsules, microspheres, micro-cages, microshell, micro rods, biosensor microparticles, and radioactive microparticles etc. The goal is to give the drug at the proper timing and dosage to minimize side effects and provide the greatest therapeutic advantages. Utilizing microparticles is one feasible method that satisfies the above objectives [2] Microparticles provide delivery of macromolecules and micro molecules via different routes and effectively control the release profile of such drugs. Microcapsules and microspheres are compatible with most natural and synthetic polymers and can be used for several routes of administration, including parenteral, oral, nasal, intraocular, topical, etc. Microspheres and microcapsules are favored over other colloidal drug delivery methods as drug carriers because of their greater stability and variety of manufacturing techniques [3]. Because of its unique and desirable qualities, such as biocompatibility, stability, target specificity, uniform encapsulation, better compliance, and controlled and sustained release patterns that are accountable for reducing toxicity and dosage frequency, Microparticle Drug Delivery System (MDDS) is a smart approach with a potent therapeutic impact that is in demanded globally in the medical technology industry. Microparticles encloses macromolecules, including vaccines, nucleic acids and proteins, and control their release by delivering them through multiple pathways.[4 , 2]. Microparticles offers protection to drug and provide local, controlled drug delivery. Microparticles can be made from a variety of natural and synthetic materials. The release rate can be increased by reducing the molecular weight of the polymer, the particle size and also by controlling the nature of the polymer [5]

Microparticles come in two different forms:

(1) Microcapsules, which function as micro reservoir systems, and

(2) Microspheres, which function as micro matrix systems.

Microspheres are basically spherical matrix systems, but microcapsules can have either a spherical or non-spherical shape. Microcapsules are small particles containing the active ingredient or core surrounded by a coating or shell [6]. Microparticles are widely applied to the development of controlled or extended-release dosage forms [7]. They play a very important role as drug delivery systems by improving the bioavailability of typical drugs and minimizing their side effects [8].

Microencapsulation technology protects drugs from the surrounding environment, stabilizes sensitive drugs, eliminates incompatibilities and masks unpleasant odors and/or tastes [9]. They are important for enhancing the bioavailability of typical drugs and reducing their side effects as drug delivery systems. The term microencapsulation refers to a number of technologies used to trap solids, liquids or gases within a polymer matrix or shell. [8]

Various core materials, including as adhesives, agrochemicals, live cells, active enzymes, flavors, fragrances, vitamins, water, and pharmaceuticals, have been encapsulated. This article provides a summary of the history, benefits, and applications, as well as information on

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preparation techniques, evaluation, and latest developments and applications [10]

Reasons for Microencapsulation

The microencapsulation technology ensures that the encapsulated material reaches the desired site of action without being affected by the environment. Here are the main reasons for microcapsules [8]:

- It is believed that supported or delayed drug release is the primary motivation for microencapsulation.
- This technique has typically been used to mask the taste and odor of various medications
- By using microencapsulation, drugs that are sensitive to oxygen, moisture, or light can be stabilized.
- Microencapsulation allows for the anticipation of drug incongruence.
- Microencapsulation can be used to anticipate the vaporization of several drugs, such as methyl salicylate and peppermint oil.
- Many drugs, including ferrous sulphate and KCl, have been microencapsulated to reduce their toxicity and GI discomfort.
- Microencapsulation can also be used to alter the site of assimilation.
- To reduce the possibility of factorial individual sharpening, hazardous substances like bug sprays could be microencapsulated.[11] [10]
- To disperse drugs that are water-insoluble in polymeric dispersion to increase their solubility.
- To improve the stability and activity of materials that are encapsulated (protection against oxidation or deactivation due to reaction in the environment).
- Minimize dose-related side effects, especially gastrointestinal irritation.
- To allow for the controlled release of active ingredients (sustained or delayed release).
- To allow targeted release of encapsulated materials to incorporate reasonably high drug concentrations.
- To control particle size and dispersibility in aqueous injectable media and improve the bioavailability of water-insoluble drugs.
- To increase patient compliance [8]

Advantages of microparticles:

MDDS offers many benefits due to their unique properties including size, shape, some of which are briefly explained as follows:

- They aid in the sustained and controlled release of the entrapped medication and offer protection to the drug from the gastrointestinal and other external environments.
- By improving the solubility profile of drugs that are poorly soluble, MDDS helps to enhance therapeutic benefit and decrease side effects.
- By avoiding repetitive drug administration and masking the taste and odor of drugs (such as fish oils and sulfa medicines), MDDS improves patient compliance and lowers toxicity concerns.
- MDDS also helps deliver incompatible agents by loading them into single shell by encapsulation [2].
- Encapsulation of live cells (resealed erythrocytes)
- Transforming a liquid into a free flowing solid
- Safe handling of toxic materials
- Facilitates the dispersion of water-insoluble compounds in aqueous media[12]
- The pH-trigged microparticles are utilized in gene therapy and immunization transition.
- Parenteral microparticles have the benefit of giving water soluble drugs in high concentrations without having severe osmotic reactions at the site of administration.[3]
- Improved process ability (improving solubility, dispersibility, flow ability)

Disadvantages of microparticles:

- It is governed by a number of variables, including the presence of food, residence time, and the type of polymer.
- When prepared at different doses, the release kinetics of the active ingredient change.
- Due to polymer degradation, drug may occasionally be delivered other than the targeted site
- In addition, formulating MDDS is much more expensive than producing equivalent standard preparations.
- To achieve reproducibility of the formulations, the process must be carried out with high standardization. [2]
- Process variables such as temperature change, pH change, solvent addition, evaporation, and agitation may have an impact on the stability of the core particles to be encapsulated.[12]

To overcome these drawbacks, the design of microparticle preparation can be changed, and alternative methods such as targeted delivery,

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inhalational delivery, intracranial local delivery, for neurological illnesses, and others can be used. [2]

Microparticles are of two types;

Microcapsules

Microcapsules are made up of a core material that is entirely enclosed in a polymeric or film. The coating of the microcapsules is a continuous polymer, porous and sometimes non-porous [5]. Microcapsules can be classifying into three categories on the basis of morphology such as

- **Monocored**:

Single hollow chamber is present in Monocored microcapsules.

- **Polycored**:

The shell of Polycored microcapsules has several chambers of various sizes.

- **Matrix Type**:

In matrix-like microcapsules, the active ingredient is incorporated into the matrix of the shell material

Microspheres

Microspheres are matrix-based systems. A rate-controlled polymer matrix contains the drug that is added to the microsphere [13, 3].

Polymers used for microparticle preparation:

It's important to understand the nature of the polymers used to create microparticles before learning about the various techniques used to create them.

Because they control how rapidly drugs are released from formulations, polymers are crucial. They even interact with the drug particles to change the flow characteristics [2].

Either synthetic or natural polymers are employed to prepare the microparticles. The polymer content ranged from 3% to 30% of the total weight, corresponding to a dry film thickness of 1-100 m. [5]

The encapsulation of drugs is determined by factors such molecular weight, biocompatibility, biodegradability, and polymer characteristics.

Ideal characteristics of the polymers include their stability, biocompatibility, biodegradability, effectiveness in loading drugs at higher concentrations, and capacity for controlled release of active ingredient. [2]

Localized drug delivery, sustained drug delivery, stability of drugs, release rate less dependent on drug characteristics, and steadier release rate with time are the five main benefits that polymeric drug delivery solutions can provide [12]

- Natural polymers are biodegradable, biocompatible and also bio-adhesive in nature. Because they have a high degree of swelling property in an aqueous medium and form gel, materials with biodegradable properties can extend the mean time when they come into contact with mucous membrane.
- Synthetic polymeric microspheres are widely used in a variety of fields, including clinical setup and as bulking agents, fillers, drug delivery vehicles, etc. They are considered to be safe and biocompatible, but they have the drawback of tending to move away from the injection site and causing side effects like embolism and organ damage[14] ,[3]

Table 1. Natural Polymers used in Micro particulate Drug Delivery Systems [3]

Natural Protein	Natural polysaccharides
Silk	Amylodextrin
Gelatin	Guar gum
Albumin	Agarose
Collagen	Starch
	Chitosan
	Poly – dextran
	Poly- starch
	Hyaluronic acid
	Pectin
	Chitin

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Table 2. Synthetic Polymers employed in Microparticulate Drug Delivery Systems; [14, 3]

Biodegradable	**Non-biodegradable**
Polyacetals	Hydroxypropyl methylcellulose (HPMC)
Poly amides	polydimethysiloxane
Polyalkonates	Polymethacrylates (PMMA),
polyurethanes	Polyvinyl pyrrolidine
Poly lactic-co-glycolic acid (PLGA)	Carboxymethyl cellulose (CMC)
Poly(glycolic acid)	Colloidal silica Poly (methyl methacrylate)
Poly lactic acid (PLA)	Ethyl vinyl acetate
Poly (Sebaic acid)	Cellulose acetate
Aminated polyphosphazenes	Cellulose acetate phthalate (CAP)
Poly phosphoesters	Poloxamines
Poly orthoesters	Poloxamers
Poly terphthalic acid	Poly hydro (ethyl methacrylate)
Poly(3 hydroxybutyrate) (PHB)	Acrolein

Drug Release Mechanisms

Controlled, sustained, or targeted release mechanisms are used for encapsulated compounds. The core material is often released from a microcapsule by one of three possible mechanisms: mechanical rupture of the wall, dissolving or melting of the wall, or diffusion through the wall. Ablation, which entails the gradual erosion of the microshell, and biodegradation are less frequent release processes [15, 16]. The following subsections cover the main processes of drug release from microcapsules.

a. Degradation-Controlled Monolithic System

In the degradation-controlled monolithic system, the drug dissolves in the matrix and is evenly distributed, becoming firmly attached to the matrix and only being released when the matrix degrades. The matrix's degradation occurs more slowly than the drug's diffusion.

b. Diffusion-Controlled Monolithic System

The active agent is released by diffusion in the diffusion-controlled monolithic system either before or at the same time as the degradation of the polymer matrix. Whether the polymer degrades through a homogeneous or heterogeneous mechanism affects the rate of release as well [8].

c. Diffusion-Controlled Reservoir System

The active material is encapsulated by a rate- controlling membrane in the diffusion-controlled reservoir system, through which it diffuses, with the membrane eroding until delivery is achieved. Drug release is unaffected by matrix degradation throughout this procedure [17].

d. Osmosis

In osmosis, the polymer coating of the microcapsule functions as a semipermeable membrane, resulting in a differential in osmotic pressure between the interior and exterior of the microcapsule. Thus, tiny pores in the coating allow the drug solution to be forced out of the microcapsule [18] [3].

e. Erosion

When some coating substances, including glyceryl mono stearate, beeswax, and steryl alcohol, experience coat erosion due to pH and enzymatic hydrolysis, drug release occurs. [19].

Factors affecting encapsulation efficiency:

- Polymer solubility in organic solvent
- The ability of organic solvents to dissolve in water
- Concentration of polymers.
- The proportion of dispersed phase with continuous phase (DP/CP ratio)

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- Rate of solvent removal
- Interactions in Drug and polymer
- Drug solubility in continuous phase
- Molecular weight of polymer [12]

The requirements to be considered to select the method for encapsulation are:

- There should be high yield and drug encapsulation efficiencies.
- The drug's biological activity and stability shouldn't be compromised throughout the microencapsulation process.
- Microspheres shouldn't show adherence or aggregation.
- The method should be feasible on an industrial scale.
- The primary factor used to choose the procedure is the type of polymer being employed. [12]

Method of preparation of microparticles:

A) Chemical methods:

- Emulsion polymerization
- Interfacial polymerization
- In situ polymerization

B) Physical methods:

- Suspension cross linking
- Solvent evaporation / solvent extraction
- Hot melt microencapsulation
- Coacervation / phase separation
- Spray drying
- Fluidized bed coating
- Encapsulation by Rapid expansion of Supercritical fluids

Single emulsion method:

This method is used to prepare microparticles based on natural polymers such as proteins and carbohydrates. Natural polymers are dissolved or dispersed in an aqueous medium, and then dispersed in a non-aqueous medium such as oil. The dispersed globules were then cross-linked. Heat and chemical cross linkers can both be used for cross linking.

The chemicals used for cross-linking include glutaraldehyde, formaldehyde, diacid chloride, and tetra phthalate chloride [5].

The type of surfactant favourably affects the MPs' bio performance in terms of particle size, particle charge, surface morphology, drug loading, and drug release [1].

Double emulsion method:

Double emulsion techniques include water in oil in water (W/O/W) or oil in water in oil (O/W/O) emulsion formulations. To prepare microparticles, both organic and synthetic polymers can be used. The double emulsion W/O/W is more suitable for water soluble drugs, peptides, proteins and vaccines. [1]. For water soluble drugs, peptides, proteins, and vaccines, the double emulsion W/O/W is more suitable To create the primary emulsion, also known as W/O emulsion, aqueous solutions of water-soluble drugs are added to polymers dissolved in oily solutions. The emulsification is carried out by a high-speed homogenizer. The primary emulsion is added to the excess water that contains emulsifiers while stirring continuously. The resulting mixture is known as a W/O/W emulsion. After that, the solvent is removed using an extraction or evaporation procedure [5]. Since the internal phase of a water-oil-water emulsion contains water, water-soluble medications can be easily encapsulated in it, which also allows hydrophilic drugs to be delivered over time. The external water phase of this technique, which makes it less viscous and easier to handle, making it advantageous for parentral administration. A two-step emulsification procedure is used to develop multiple emulsions. [6]

Normal emulsification method:

This is done by different methods such as bulk polymerization, suspension, precipitation, emulsion and micellar. Suspension polymerization is also known as bead polymerization. By heating the monomer or mixture of monomers as a droplet dispersion in a continuous aqueous phase, this is achieved. In order to start the polymerization, a mixture of monomers and an initiator or catalyst are heated. The resulting polymer can then be modified into microspheres [6].

Interfacial polymerization method:

Two monomers, one water soluble and the other oil soluble, are used in interfacial polymerization, which results in the formation of polymer on the droplet surface [20]. In interfacial polymerization, two reactants in a polymerization reaction meet at an interface and react rapidly [10]. In this technique, a capsule shell will be formed at or on the surface of the droplet or particle by polymerization of reactive monomers. The substances used are multifunctional monomers. Commonly used monomers include the

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multifunctional isocyanate and the multifunctional acid chloride. They will be used individually or in combination.

Aqueous phase containing a dispersing agent will be used to disperse the multifunctional monomer that is dissolved in liquid core material. The combination will be combined with a co-reactant multifunctional amine. This causes rapid polymerization at the interface to form the capsule shell [12]. Interfacial polymerization is used to produce both mono - core and matrix-type microcapsules depending on the solubility of polycondensate in the droplet phase. [8]

In situ polymerization method:

In situ polymerization adds polymerized monomers to an encapsulation reactor to form a capsule shell. No reactants are added to the core material in this process. Polymerization occurs by the formation of an interface between the dispersed core material and the continuous phase. A low molecular weight polymer is initially created, and as it expands, it deposits material on the surface of the core to form a solid capsule shell. The capsule shell is created by dispersion of the water-immiscible liquid and polymer at the acidic pH of urea with formaldehyde in an aqueous medium [3].

Suspension cross linking method:

Suspension crosslinking is suitable for the production of protein and polysaccharide microcapsules. Microcapsule formation by this method involves dispersing an aqueous solution of the polymer-containing core material in the form of small droplets in an immiscible organic solvent (suspension/dispersion medium). The suspending medium contains suitable stabilizers to maintain the individuality of the droplets/microcapsules. The droplets then harden by covalent cross-linking and converted directly into the corresponding microcapsules. Crosslinking occurs via heat (> 500 °C) or cross linkers (formaldehyde, terephthaloyl chloride, etc.). Suspension crosslinking is a versatile technique for microencapsulating soluble, insoluble, liquid, or solid materials to form both microcapsules and nanocapsules [8]. This is the best method for producing microcapsules of proteins and polysaccharides [12].

Solvent evaporation/ extraction method:

Solvent extraction is mainly used to encapsulate hydrophobic drugs by an oil-in-water (O/W) emulsification process. The main advantages of this method are the short hardening time and the direct incorporation of the active ingredient into the microparticles [1]. By dissolving the drug ingredient and polymer in an appropriate organic solvent, the solvent extraction or evaporation process is carried out. An emulsion is created by stirring the surfactant solution. The MPs are finally collected following solvent evaporation. The hollow inner core of the floating microparticle dosage form can be produced using solvent diffusion and evaporation techniques. Polymers like cellulose acetate, chitosan, Eudragit, Acrycoat, Methosyl, polyacrylate, polyvinyl acetate, carbopol, agar, polyethylene oxide, and polycarbonate have all been investigated for the development of such systems. By evaporating the solvent from the emulsion at a high temperature or by extracting it with a significant amount of water, compact microparticles are formed. Dichloromethane and chloroform are the two most common organic solvents used in emulsion solvent evaporation techniques [21].

Hot melt microencapsulation method:

It involves dispersion of the polymer in a suitable medium and then it is slowly cooled to form microparticles [5]. First, the polymer is melted and then mixed with finely sieved solid drug particles smaller than 50 µm. The mixture is then suspended in an immiscible solvent (such as silicone oil). Stir continuously and heat to 5°C above the melting point of the polymer. Once the emulsion is stable, it is cooled until the polymer particles solidify. The microspheres formed were washed by decantation with petroleum ether [6].

Coacervation or phase separation method:

This technique mainly prepares the reservoir system for encapsulated hydrophilic drugs such as peptides and proteins. The coacervate is a polymer-rich phase that is formed by its basic concept, which depends on the reduced solubility of polymers in the organic phase. A third component is then added to the system to separate the coacervate, forming two phases. Additionally, different methods, including the addition of salt, non-solvents, or incompatible polymers, temperature changes, and the induction of polymer-polymer interaction, can be used to separate polymers [8, 12]. Polylactic acid (PLA) microspheres were prepared using butadiene as an incompatible polymer [8]. It is widespread procedure to prepare gelatin and gelatin acacia microcapsules via coacervation or phase separation.

Phase separation can be simple or complex. A single polymer, such as gelatin or ethyl

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cellulose, is used in an organic or aqueous medium, respectively, in a process known as simple coacervation. Complex coacervation involves neutralization of charges on the colloid and is primarily pH dependent [20]. It involves two polymeric substances with opposing charges, such as gelatin and acacia, both of which are soluble in water. Microencapsulation by coacervation is performed by preparing an aqueous polymer solution (1-10%) in which the core material is dispersed at 40-50°C.To maintain the individuality of the finished microcapsules, a suitable stabilizer can be added to the mixture. In order to harden the microcapsule wall surrounding the core particles, a cross-linking agent is added after the coacervation mixture is cooled to about 5 -20˚ C [22, 3].

Spray drying and spray congealing method:

Spray drying and spray congealing are two techniques that differ depending on whether the solvent is removed or the solution is cooled [5].

The drug and the polymer are both dissolved in an organic volatile solvent and homogenized in a high-speed homogenizer. A hot air stream is then used to spray the resulting dispersion, causing the solvent to instantly evaporate and creating the microparticle. The cyclone separator is used to separate microparticles from the hot air, and vacuum drying is used to remove any remaining solvent [1]. High encapsulation efficiencies and the absence of any surfactant residue on the surface of the microparticles are important benefits of this approach [5].Temperature, pressure, nozzle diameter, mixture volume, polymer and drug concentration, rate of feed flow, and inlet temperature are factors that affect microparticle size and morphology [12, 5].

Generally, spray drying is a low-cost industrial process used to encapsulate flavors, oils, and perfumes [8].

The primary goal of this technique is to protect thermolabile active ingredients and prevent oxidation of sensitive drugs. It prevents product environmental damage and improves product quality through multiple drying stages [20].

Spray congealing, also known as spray chilling, is the dispersion of active moiety in melted coating material without the use of a solvent. The mixture is then sprayed into a stream of cold air to form solid droplets by cooling at temperatures below the melting point of the coating material [3].

Fluidized bed coating / Air suspension method:

Pharmaceuticals are frequently enclosed in fluidized-bed coating, which is utilized to encapsulate solid core materials, including liquids absorbed into porous solids. A spray of liquid coating material is applied to solid particles that need to be enclosed after they have been suspended in an air jet. Coating solution is sprayed on solid particles using a spray nozzle. A high pressure gas is used to apply the coating solution. At the gas-liquid interface, a strong shear force interaction creates waves that disperse the solution into droplets [3]. The capsule shell is then solidified by cooling or solvent evaporation. Suspending, spraying and cooling are continuously repeated until the capsule wall reaches the desired thickness. Drying rate is directly related to the bulk temperature of the supporting air stream [10].

Different types of fluid bed coaters include top spray, bottom spray and tangential spray [**3**].

A) Top spray: When granules are coated by top spray granulator system, granules usually have porous surface and interstices. Therefore, the bulk density of the granules produced is usually lower than that achievable with granulation techniques.

B) The rotating disc method (tangential spray coating method): which combines high-density centrifugal mixing and the efficiency of fluidized bed drying, results in a product with a higher bulk density but still with an interstitial void. It produces less friable and more spherical particles.

C) In the Wurster method (bottom spray): solid core particles are fluidized by air pressure and a wall material solution is sprayed on to the particles from the bottom of the fluidization chamber in a straight line with the air stream. When the nozzle is immersed in the air stream and simultaneously sprays the coating materials onto the fluidized bed particles, the coating solution droplets travel only a short distance before coming into contact with the solid particles. The result is a more even coating and a more uniform coating. As the coated particles are transported away from the nozzle by the air stream, the coating dries. The airborne particles rise up, settle, and then start a new cycle. The cycles continue until the desired film thickness is reached. It works effectively for covering particles uniformly with a polymeric membrane in a single process [12]. The particle size can be tuned by the well-controllable process parameters:

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properties of the core (density, hygroscopicity, surface area, particle size and shape, melting point, wettability, solubility, volatility, compressibility, crystallinity, hardness, cohesiveness, adsorption, friability and flowability of the core material).[23]

Application of air suspension

Using this technique, ascorbic acid has been microencapsulated in polymethacrylate and ethyl cellulose [8].

With the use of a Wurster air suspension mechanical assembly, Colette and Rubin illustrated coating headache medication gems of various work sizes with mixtures of ethyl cellulose and methylcellulose sprayed from an ethylene chloride: isopropyl alcohol (1: 1) solution. [10]

Encapsulation by Rapid Expansion of Supercritical Fluids:

Highly compressed gases with a combination of liquid and gas properties are known as supercritical fluids. The most often used substances are nitrous oxide (N2O), alkanes (C2 to C4), and supercritical carbon dioxide (CO2). Near the critical point, a minor change in temperature or pressure results in a significant change in the density of supercritical fluid. Supercritical CO2 is utilized extensively due to its low critical temperature value, nontoxic nature, and lack of flammability. It is also widely accessible, extraordinarily pure, and relatively inexpensive. Nanoparticles can also be produced using this approach. [12]

Supercritical-fluid expansion is used to incorporate core materials like insecticides, pigments, pharmaceutical ingredients, vitamins, flavors, and dyes. For the purpose of entrapping core components, a wide range of shell materials that either dissolve (paraffin wax, acrylates, polyethylene glycol) or do not dissolve (proteins, polysaccharides) in supercritical CO2 gas are utilized. A small nozzle is used to release supercritical fluid at atmospheric pressure after it has been kept under high pressure and contains the active component and the shell material. When the pressure suddenly drops, the shell material dissolves and deposits around the active ingredient (core), forming a coating layer.

This method has been used to encapsulate felodipine in poly (ethylene glycol). [8]

Evaluation of microparticles:

1. Particle shape & size determination:

Microscopy, sieve analysis, laser light scattering, the coulter counter method, and photon correlation spectroscopy are some methods that can be used.

Differential scanning calorimetry analysis can be used to determine crystallinity.

Freeze etch electron microscopy and freeze fracture microscopy can both be used to study shape and surface morphology.

The size range of the microparticles is also measured using a laser diffractometer and a light microscope.

A set of standard sieves with mesh sizes ranging from 10 to 100 can be used to analyze the sizes of all the batches of prepared microparticles. The amount of microparticles retained on each sieve is weighed after they have been passed through the set of sieves.

The average diameter is calculated by dividing the total weight by 100. [20]

2. The bulk and tap densities of the microparticles are also assessed. Mercury or helium intrusion potensiometry can also be used to assess a specific area and porosity. The angle of repose can be calculated using the fixed funnel and free-standing cone methods, and the compressibility index can be calculated using the tapped density method to assess the flow properties of microparticles **[**20**].**

3. Zeta Potential

Zeta potential levels greater than +25 mV or less than -25 mV indicate extremely stable microspheres

The electrophoretic mobility of microparticles dispersed in deionized water at a concentration of 1 mg/mL with folded capillary cells in the automatic mode of measurement duration can be used to calculate the zeta potential [24].

4. Surface Morphology

It gives important details regarding the microstructure and porosity of these drug delivery systems. Scanning electron microscopy is the method most frequently employed [12].

SEM analysis of surface morphology and microparticle shape yields crucial knowledge about porosity and microstructure. For the vacuum field required for image generation, samples prepared for this procedure must be dehydrated. They are covered in an electron-dense coating material before loading, such as gold, palladium, or a

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mixture of these. Sputtering or thermal vacuum evaporation can be used to apply the coating. When Tania M. et al. placed microsphere samples to aluminium stages and coated them with 10 m of gold/palladium using a Hummer sputter coater, then electronically captured the images [25].

5. Percentage Yield

Prepared microspheres were completely dried in an oven set at 37°C for 24 hours, and then weighed, as part of a study to determine the % yield of microparticles. Generally, percentage yield is calculated as follows:

% Yield = Yp / Yt × 100

Where Yp = practical yield and Yt = theoretical yield. [26]

6. Drug Content and Drug Loading

100 mg of microparticles are pulverized, and distilled water is then added to them in order to evaluate the drug content and loading. The resulting solution is allowed to stand for 12 hours before being sonicated for 30 minutes and filtered through Whatman no. 1 filter paper (GE Healthcare UK Limited, Little Chalfont, UK). Next, 2-100 mL of the clear filtrate are diluted with distilled water and their absorbances are measured on a spectrophotometer using distilled water as the blank. The calculations are as follows: [**8**]

Drug content (%) = Weight of drug in microspheres × 100
Weight of microspheres

Drug loading (%) = Weight of drug in microspheres × 100
Weight of drug initially added to microspheres

7. X-Ray Powder Diffractometry

X-ray powder diffractometry (XRD) is used to examine and record patterns in the drug, the polymer, and the blank and drug-loaded microspheres in order to determine how microencapsulation affects a drug's crystallinity[27] The scan rate used included 1 over the range of diffraction angles from 14 to 88 (02) and was 20 min [8].

8. The thermal properties: Thermal properties detected by differential scanning calorimetry and Thermo gravimetric analysis.

A. In differential scanning calorimetry or DSC: The amount of heat required to cause a change in the sample and reference is measured as a function of temperature. The sample and the reference were maintained at the same temperature throughout the test. The temperature was increased gradually to find a change in the samples. The reference sample should have a well-defined heat capacity within the temperature range being analyzed.
B. Thermogravimetric analysis (TGA), also known as thermal gravimetric analysis The TGA detected changes in weight and temperature on the samples. Raising the temperature gradually and plotting the weight against temperature is how the analysis is done. There are many ways to test temperatures that routinely reach 1000^{o}C or higher. The smooth curve is produced after the data. [28]

9. Entrapment Efficiency:

Drug loading and drug entrapment efficiency: The amount of drug required for administration is reduced by the high drug-loading capacity of micro particulates. There are two ways to load drugs:
- Incorporation method
- Absorption method.

Drug content and encapsulation efficiency depend on the solubility of the drug in the polymer composition, molecular weight, drug-polymer interactions. Because ionic interactions between drugs and polymers can be a very effective way to increase the drug load of small molecules.

Micro-particle capture efficiency or percent trap can be determined by allowing lysis of microparticles. The lysates are then determined for the active ingredients required by the monograph**.** The percent encapsulation efficiency is calculated using equation [29]:

% Entrapment = Actual content/Theoretical content x 100

10. Drug release studies were evaluated using USP Method II or Dissolution Test Method using PH 6.8 phosphate buffer solution with a release ambient temperature of 37 ± 0.5 and then checked with spectrophotometric measurements.

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In vitro release experiments can be performed by dialysis. In this method, a weighed amount of microparticles placed into a dialysis bag, which is immersed in a larger volume of continuous phase receiving fluid. The chamber is stirred and drugs with different uses that change from microspheres to continuous phase are sampled and analyzed periodically. H.Takahata et.al performed in vitro studies by incubating microparticles in PBS alone and PBS in dialysis tubes, internal media, and stomach [12]

Two different mathematical differential equations, namely (1) the first order equation and (2) Higuchi's square root of time equation, can be used with release kinetics to describe the dissolution profile from the microparticles system.

(1) First order model is given by $Mt / M\infty = 1- e-k1^t$

(2) Higuchi's square root of time model can be expressed as $Mt / M\infty = kH\ t1/2$

Where,

Mt is the amount of drug released at time t,

M∞ is the maximal amount of drug released at infinite time

k1 and kH are the rate constants for first order and Higuchi model, respectively.

11. Swelling:

Swelling studies of microparticles of different crosslinking densities can be determined separately by immersion in simulated gastric fluid (pH 1.2) without pepsin and in simulated intestinal fluid (pH 7.4) without pancreatin. In this process, a 9 cm dialysis membrane is activated by immersing in 50 ml of distilled water adjusted at 90°C for 1 h and then washing with distilled water. A known mass of microparticles is placed into an activated dialysis membrane, which is tied at both ends and immersed in a beaker placed in a thermostatic bath maintained at 37 ± 1ºC.The membrane is taken out of medium after 5 minutes interval, dried using filter paper, and weighed [24]. The degree of swelling is calculated according to the following formula:

% Swelling = M2 – M1 / M1× 100

Where M1 = initial weight of microparticles (g), and M2 = final weight of microparticles. [8]

12. Stability studies:

Studies on product stability were assessed in order to identify stable products for storage. For a period of 30 days, microparticles can be kept in glass bottles at temperatures as high as 4°C (freezing), 25°C (room temperature), and 50°C (hot temperature) and change in their drug content and morphology can be observed. [20]

13. In vivo Tissue Distribution Studies:

In vivo studies are an important part of any research because they provide solid evidence of the efficacy of microspheres and because the properties exhibited by microspheres are important for understanding. Functional characteristics of formulations in a biological system. To check the appropriate properties of the formulation in vivo, adult albino mice/rats/rabbits, etc. of a certain specified weight may be used. A calculated dose of the drug was given to each animal as a dispersion in saline with 1% tween 80. At predetermined intervals, the animals were injected with the microspheres administered via tail root vein and sacrificed by cervical dislocation. Organs such as lung, liver, kidney, heart and spleen are extracted and studied for targeted action. Tissue samples were stored for 24 h at -200°C. Then, drug concentration in each organ was determined quantitatively by HPLC method. In vivo tissue distribution studies in animal models were performed to demonstrate the hypothesis of targeting microspheres/formulations to the organ and to compare them with conventional dosage forms of the drug [12].

Applications of microparticles:

Biomedical Therapeutic:

- Microparticles are used in many areas of therapeutic/biomedical research: Delivering therapeutic siRNA (porous silicon microparticle)[30]
- Transport of drugs, biologicals and vaccines (chitosan-based nanocapsules/microcapsules)[31]
  Cell engineering with microparticles loaded with intracellular agents to manage cellular phenotype.[32]
- Alveolar macrophages for tuberculosis (inhalation of solid lipid microparticles)[33]
- Gentamicin/dextran's microparticles for treating wound bacterial infections [34]
- preparation of thiolated polydimethyl aminoethyl methacrylate (PDCy) and use of PDCy submicroparticles as oral insulin carriers in vitro.[35]

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Molecular Imaging:

Molecular imaging of disease conditions can enhance diagnosis, permitting correct and highly effective treatment. By specifically targeting molecules differentially expressed in disease states, researchers and clinicians can characterize disease at the cellular or tissue level. Targeted micron-sized particles of iron oxide (MPIO) are used as molecule specific contrast agents with magnetic resonance imaging (MRI), and early proof suggests their suitability for use with different imaging modalities [37].

Biosensors:

The use of core-shell particles as biosensors in biomedical applications such as medical diagnostics has been the subject of several recent studies. Due to the high demand for implantable biosensors for continuous monitoring and detection of analytes in vivo, various diseases can be diagnosed early and monitored in real time. Biosensors containing bio sensing agents and signaling factors can be used to detect biomarkers such as glucose, enzymes, ions, DNA and antibodies. Microfluidics has offered the opportunity to create smart microparticles with complex structures to fabricate biosensors with extended functions Xie et al. [38] created a hollow polyethylene glycol microcapsule to encase nanosensors in a liquid core. In vivo application of implantable biosensors used to detect biomolecules restricted by move or release from position. One approach to solve this problem is to encapsulate the nanosensors in a hydrogel scaffold. However, nanosensors in contact with the hydrogel wall can disrupt the sensor's function. Therefore, the team developed a microcapsule with a microfluidic liquid core to prevent contact of the nanosensors with the hydrogel. Nanosensors include glucose-sensitive quantum dots, heparin-sensitive gold nanorods and core-encapsulated gold nanorods. Biomolecules such as glucose and heparin propagate through the envelope and their interaction with nanosensors results in detectable optical signals [39].

Deep-Tissue Imaging:

Magnetic targeting of tumors with external magnets has been shown to be a promising technique to increase the delivery of cytotoxic agents to tumor cells and reduce their side effects. . However, it has many intrinsic limitations such as the inability to focus on areas within deep tissues, mainly because the size of the magnetic field is drastically reduced compared to that of magnets. Another clinically viable approach to focus on deep tissue is magnetic resonance navigation (MRN), which involves endovascular control of therapeutic micro carriers (TMMCs), performed with Advanced MRI scanner. A proof-of-concept study reported the preparation and testing of TMMCs designed keeping in mind the limitations of MRN and hepatic chemoembolization. TMMCs are biodegradable microparticles loaded with iron-cobalt and doxorubicin (DOX) nanoparticles. They show high saturation magnetization (Ms = 72 emu g-1), MRI tracking compatibility (high contrast on T2-weighted images), acceptable size for blood vessel embolization (50 um) and DOX release persists for several days. Pouponneau et al.[40] successfully piloted TMMC in vitro and in vivo in a rabbit model. They performed in vivo targeting of the right or left hepatic lobe using MRN through the hepatic artery 4 cm below the skin [8].

DNA Plasmid:

Controlled release of plasmid (pDNA) from biodegradable Polylactic-co-glycolic acid (PLGA) microparticles has the potential to enhance transgene expression. However, it has some limitations: limited packaging capacity, damage to pDNA during production, and confinement of microparticles in phagocytic compartments. The combination of PLGA with polyethylenenimine (PEI) can improve pDNA protection at the time of fabrication, increase encapsulation efficiency, and give PLGA microparticles the ability to escape from phagocytic compartments [8].

In Oral drug delivery:

Drugs for oral administration are generally dependent on their solubility and absorption. Those drugs have low water solubility and low bioavailability, the microscopic size of these drugs leads to increased oral absorption and bioavailability. Microparticles provide rapid action for drugs that are completely absorbed but slow [41]. Hai-feng Cheng et al. studied the oral microparticle delivery system of diltiazem, the microparticles were prepared with cellulose acetate and Eudragit R5100. Drug release from the microparticles was found to be 77.62 ± 2.12 to 97.50 ± 1.04 at the end of 12 h. The study concluded that the diltiazem microparticle floating oral drug delivery system could be an effective alternative to conventional oral tablets for cardiac delivery [42].

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Ocular Delivery:

MDDS is an attractive method for the preparation of ophthalmic products because, once the particles have penetrated the cornea, tear drainage can be delayed due to the particle size and thus achieving retention time. Longer, reducing drug elimination and increasing the effect. Using this approach, promising therapeutic benefits are obtained, but it should be borne in mind that the drug does not cause any kind of irritation or toxic effects. A study was performed in which CMC and polyvinyl alcohol (PVA) in their sodium salt form were used as polymers for the preparation of adrenaline loaded microparticles and this prepared formulation was able to swell with good interpenetrate network and can be used safely in ophthalmic delivery systems [43]

Microparticles in vaccines delivery:

Poly (ethylene glycol)-dextran (PEG-DEG) conjugates were used as combination stabilizers and surface modifiers to produce degradable poly (DL-lactide-co-glycolide) microparticles. By emulsification or solvent evaporation techniques. This approach offers the opportunity to attach hydrophilic species as target groups to biodegradable microparticles to enhance vaccine interaction with specific tissue sites [44]. Using thermoplastic polyesters of PLA and (glycolic acid) and their copolymers (lactides coglycolides), antigens such staphylococcus enterotoxin B, diphtheria toxoid, hepatitis surface antigen, and tetanus toxoid are formulated into microspheres [5].

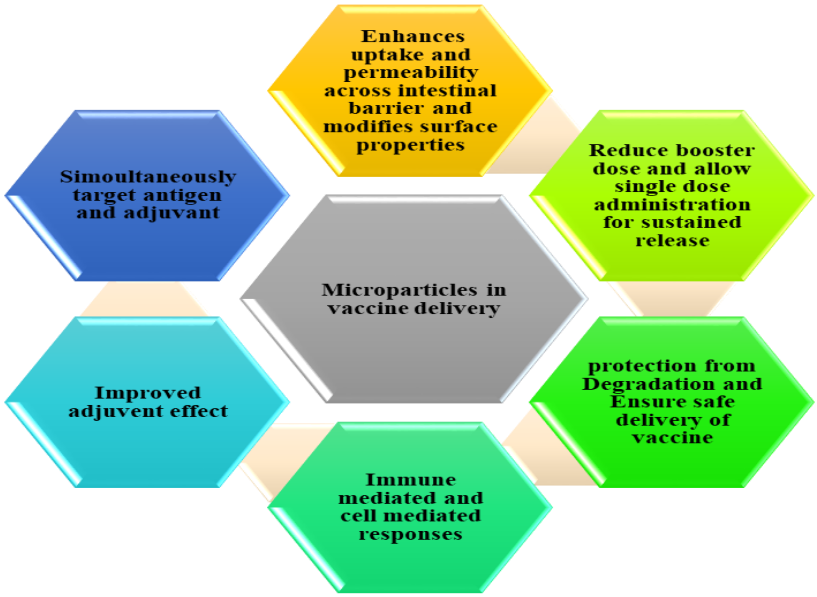

FIG: Therapeutic effects and advantages of MDDS in vaccine delivery

Role of MDDS in the Management of Diabetes Mellitus:

MDDS, especially in diabetes, has received considerable attention because it avoids repeated dosing, thereby preventing injury, pain, and injury associated with insulin; this method also supports drug release and improves treatment effectiveness. Effective therapy for diabetes in the clinical setting is delivered using insulin (INS), as subcutaneous injection or intravenous drip; however, administering INS by these routes could harm the patient and lead to injury. Furthermore, INS is a protein that can be easily digested by gastric enzymes, thereby limiting its bioavailability orally. Therefore, it makes practical sense to form an INS distribution system that avoids its degradation. For example, hydrogels have been extensively studied as carriers of excess protein. Such an approach has been reported using pH-sensitive hydrogel microparticles obtained by the polymerization of methacrylic acid dimethacrylate and polyethylene glycol (PEG), releasing only 25% of INS in acidic media (pH 2.5), followed by a long-lasting sustained effect up to 10 hours in alkaline media, with an INS encapsulation efficiency of 82%.[45]

Another interesting MDDS hydrogel was prepared using chitosan complexed with PEG and polymethylmethacrylate (PMMA) to form a matrix, which was then functionalized with thiol groups by

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incorporating cysteine on the carboxyl group of the polymer matrix. This system leads to slow release of INS due to activation of tyrosine kinases activated by carboxyl groups of matrix, promoting controlled and sustained release as well as preventing protein destruction of INS [46].

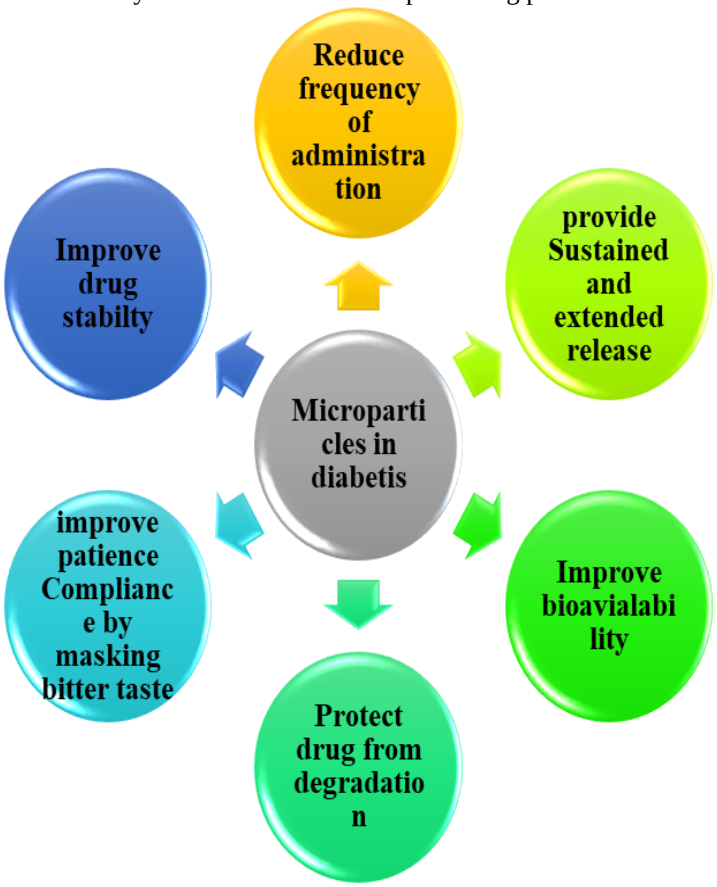

FIG: Therapeutic effects and advantages of MDDS in diabetes mellitus

Microparticles in Cancer therapy:

Micro particulate technology in cancer is the most useful today. Cancer is a disease in which growth or malignancy is the result of uncontrolled cell division. Anticancer drugs have the major disadvantage of being selective only for tumor tissues, leading to serious side effects and low cure rates. Conventional drug delivery methods fail to target only abnormal cells. Microparticle technology is perhaps the only method that can be used for site-specific actions without any significant adverse effects on normal cells [47].

A microparticle-based system has been developed to deliver therapeutic agents to brain tumors. Polymethylidene-malonate polymer is used to prepare biodegradable sustained-release microspheres loaded with 5-fluorouracil for the treatment of malignant brain tumors. The polymer degrades slowly and results in long-term local drug delivery, i.e. 5-Fluorouracil [48, 5].

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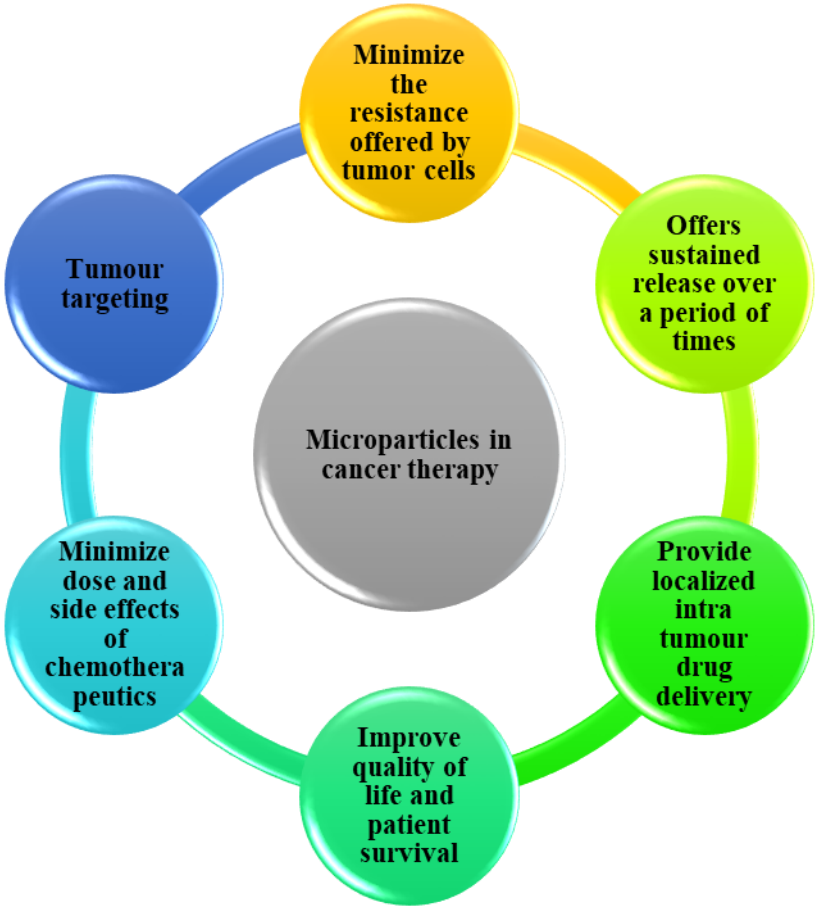

FIG: Therapeutic effects and advantages of MDDS in cancer

Pulmonary Delivery:

MDDS of 1 to 5 µm in size are suggested for lung accumulation. However, even 1–2 µm particles are eliminated by phagocytosis and thus the elimination half-life is further shortened. This led to the development of large porous MDDS with low density and improved aerosol efficiency. These particles are large and porous, so they interfere with the phagocytosis process and reduce the interaction between particles [49]. Porosity is achieved using substances called porogens. Although drug efficacy is increased in large porous MDDS, its release is not sustained in the long term. Therefore, to prepare a controlled extended release formulation, expandable MDDS was developed. These MDDS particles vary in size from 0.5 to 5 µm which are easily inhaled when dry, and when they accumulate in the lungs, their wet surface causes the particles to swell, thus solving two problems: reduced phagocytosis by macrophages and sustained drug release from swelling particles [2].

II. CONCLUSION:

Many microparticulate formulations have gained medicinal and diagnostic value over the last few decades. Many different polymers have been investigated, and a number of them have been shown to be effective.

The microparticles offer improved stability, increased bioavailability, taste masking, good handling properties, and controlled release of the active component. The methods for creating microparticles require fewer stages and less time. In a variety of drug delivery systems, microparticles are the ideal drug carriers. Researchers and academicians will gain a better understanding of the microparticle drug delivery for better management of life-threatening diseases. From various aspects of microparticle formulations, characterization, effect of their characteristics, and applications in cell specific delivery of drug molecules and therapeutic genes. For this reason, the majority of companies are

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currently focusing on the development of drug delivery systems using microparticles.

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