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MICROPARTICLES: A NOVEL APPROACH TO CONTROLLED DRUG DELIEVERY SYSTEM

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ABSTRACT

The controlled release is to deliver a constant supply of the active ingredient, usually at a zero order rate; by continuously releasing for a certain period time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drug at a predetermined rates locally or systematically, for a specific period of time. microparticles are small particles of solids or small droplets of liquids surrounded by walls of natural and synthetic polymer films of varying thickness and have a diameter upto range of 0.1 µm - 200µm. They provide the sustained and controlled delivery of drug to long period of time. The microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities or masking of unpleasant taste. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for the drugs. The present review highlights several carriers used in the preparation of microparticles, preparation methods of microparticles, their release mechanisms, evaluation parameters, their advantages and applications. Therefore microparticles open up new vistas of research in the development of novel drug delivery systems.

KEYWORDS: Microparticles, Controlled drug delivery, Polymers, Microencapsulation techniques.

INTRODUCTION

The controlled drug delivery system is to deliver a constant supply of the active ingredient, usually at a zero order rate, by continuously releasing, for a certain period of time, an amount

of the drug equivalent to the eliminated by the body. Controlled release system means any drug delivery system that maintains adequate and desired release of drug over an extended period of time. Hydrophillic polymer matrix is widely used for formulating a controlled dosage form·controlled release drug delivery employs drug – encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months. Microparticulate drug delivery system is one of the processes to provide the sustained & controlled delivery of drug to long periods of time. They are small particles of solids or small droplets of liquids surrounded by walls of natural & synthetic polymer films of varying thickness & degree of permeability acting as a release rate controlling substance & have a diameter upto the range of 0.1µm-200µm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. One such approach is using microspheres a cariers for drugs. There are two types of microparticulate drug delivery system microspheres and microcapsules. Microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non spherical in shape. Microcapsules are those in which entrapped substances is distinctly surrounded by distinct capsule wall and micrometrics in which entrapped substance is dispersing throughout the microspheres matrix.

Microparticle are of two types

a) Microsphere is a term used for small spherical particles, with diameters in the micrometer range(typically $1\mu m$ to $1000\mu m(1mm)$. Due to their small particle size, microspheres are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.

b) Microcapsules are small particles, which contain an active agent or core material surrounded by a coating or shell. Micro spherical for oral use has been employed to controlled the drug release, and to reduce or eliminate gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Micro capsulation is used to modify and drug release.

Controlled drug delivery systems could be extremely useful in providing the optimal therapy for a given drug molecule.

Polymers Used in Microspheres

A number of different substances both biodegradable as well as nonbiodegradable have been investigated for the preparation of microspheres; these materials include polymers of natural origin or synthetic origin and also semisynthetic substances. Microspheres can be prepared by using both hydrophilic and hydrophobic polymers.

Hydrophilic polymers

These are includes gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.

Hydrophobic polymers

These are include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

Biodegradable polymers

These materials also slowly disappear from the site of administration; however it occurs in response to a chemical reaction such as hydrolysis. Example: Polylactic acid (PLA), poly glycolic acid (PGA), Polycaprolactone (PCL) and several generic classes such as the poly anhydrides and polyorthoesters.

Non-Biodegradable

Hydrophobic Polymers

These materials are inert in the environment of use, are eliminated or extracted intact from the site of administration. Example:Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyether urethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) and Polyvinyl chloride (PVC), Acrycoat, Eudragit S etc.

Hydrogels

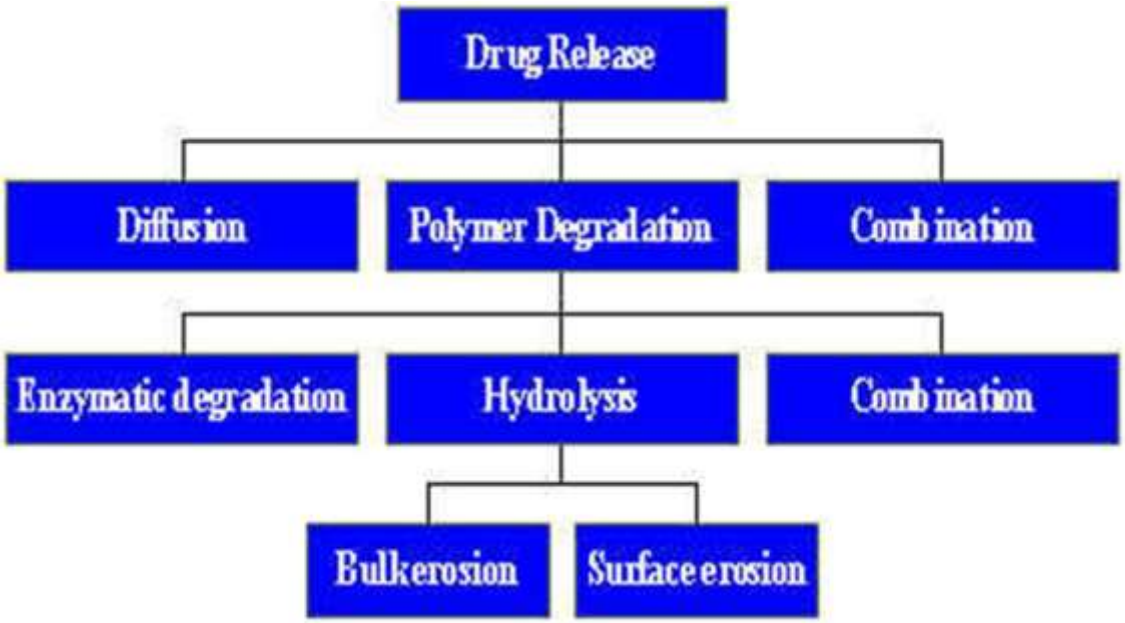
These polymers swell but do not dissolve when brought in contact with water. As with the hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrier to the transport and release of drugs.

ADVANTAGES

1. Better Bio-availability of the drug.
2. Decreased local and systemic side effects, Ex GI irritation etc of drugs on oral ingestion.
3. Taste and odor masking and Protection from environment.
4. Prevents fluctuation of plasma drug concentration.

5. Improvement of flow of powder.
6. Improved efficiency in treatment and patient compliance.
7. There is chemical and physical storage stability (for both drug and carrier system).
8. Use of biodegradable lipids.
9. Allow hydrophilic and hydrophobic drugs to be incorporate.
10. Safe handling of toxic substances.
11. Particle size reduction for enhancing solubility of the poorly soluble drug.
12. Targeted release of encapsulated material.
13. Separation of incompatible components Ex: Excipients, buffers and other drugs.
14. Aid in dispersion of water insoluble substance in aqueous media.
15. Effective delivery of agents which are insoluble or sparingly soluble in water and smaller microparticles need to be prepared for application to other sites such as the eye, lung, and joints.
16. Microparticles in the form of microcapsules can also be used as carrier for drugs & vaccines as diagnostic agents & in surgical procedures.
17. They are useful in administration of effervescent dosage form of medicaments to individual unable to chew, Ex: Debilitated patients having difficulty in swallowing solids & the elderly.
18. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

Release mechanism of microparticles



REASONS OF MICROENCAPSULATION

- To develop modified release dosage forms for targeted or sustained release purpose.
- To mask the taste of bitter or noxious drugs for their convenient handling.
- For converting volatile and oily substances or extracts to tabulated dosage forms to avoid tacky granulations and improve flow properties.
- To protect drugs from environmental hazards such as humidity, light, oxygen or heat and gastrointestinal biodegradation.
- To enhance compatibility between various drugs and excipients formulated together.
- For easy handling of hygroscopic and toxic substances such as fumigants, herbicides, insecticides and pesticides.
- To prepare immobilized cells or enzymes.

Method of preparation: The methods of preparation and its choice are equivocally determined by some formulation and technology related factor as mentioned below.[15]

1. The particle size requirement
2. The drug or protein should not adversely affected by the process.
3. Reproducibilty of release profiles and methods
4. No stability problem
5. There should be no toxic products associated with the final product.

Preparation of microspheres can be done by suitable methods like (vyas et al.,2002b):

1. Single Emulsification Technique
2. Double emulsion technique
3. Emulsion solvent evaporation technique
4. Emulsion cross linking method
5. Co-acervation method

a) Co-acervation thermal change:
b) Co-acervation non solvent addition:

6. Spray drying technique
7. Emulsion-solvent diffusion technique
8. Multiple emulsion method
9. Hot Melt Microencapsulation
10. Ionic gelation method

1. Single Emulsification Technique

Generally, by this technique carriers of natural polymers like proteins and carbohydrates are prepared. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, diacid chloride, tetra phthalate chloride etc.

2. Double emulsion technique

Double emulsion method of microsphere preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophillic organic continous phase. This protein solution may contain the active constituents. The continous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained dispersed aqueous phase.The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol(PVA). This results in the formulationof a double emulsion . The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.

1. Emulsion solvent evaporation technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2% sodium of PVP as Emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hours. Diclofenac microspheres are prepared by this method.

2. Emulsion cross linking method

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hour at 40oC. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35oC, results in w/o emulsion then further stirring is done for 10 min at 15^0C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5 mL of aqueous

glutaraldehyde saturated toluene solution at room temperature for 3 hours for cross linking and then was treated with 100 mL of 10 mm glycerine solution containing 0.1% w/v of tween 80 at 37^0C for 10 min to block unreacted glutaraldehyde. Examples for this technique is Gelatin microspheres.

1. Co-acervation method

a. Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product is washed with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

b. Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl isobutylene in closed beaker with magnetic stirring for 6 hours at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hours and then in oven at 50^0C for 4 hours.

2. Spray drying technique

It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly (epsilon-caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental conditio achieving drug loaded microspheres.

3. Emulsion-solvent diffusion technique

The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1hour. Thus the formed floating microspheres were washed and dried in a dessiccator at room temperature. The following micro particles were sieved and collected.

4. Multiple emulsion method

In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then re emulsified in aqueous medium. Under optimised condition discrete microspheres were formed during this phase.

5. Hot melt evaporation

The polymer is first melted and then mixed acid soil drug particle or liquid drugs. This mixture is suspended in an immscible solvent and heated to 50℃ above the melting point of the polymer under continuous stirring. The emulsion is then cooled below the melting point until the droplets solidify.

6. Ionic gelation method

This is a specific embodiment of a more general approach in which the polymer filaments or monomer subunits used in forming the microparticles are mixed with a suspension of proteins, such as agar, gelatin, or albumin. One method employs alginate plus Ca +2in producing the particles. The mixture is then dispersed under conditions effective to produce desired sized particles containing the mixture components. In the case of gelatin gelled particles having a desired size. The particles are then treated under polymerization and/or cross linking conditions, preferably under conditions that do not also lead to cross linking of gelatin molecules to the polymer structure. After microparticle formation, the gelatin molecules may be removed from the structure, with such in a decondensed form, e.g., by heating the material or enzymatic digestion.

EVALUATION OF MICROPARTICLES

The parameters and methods used to evaluate microparticles are: The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microparticles have different microstructures. These microstructures determine the release and the stability of the carrier.

➢ **Microparticles yield:** These studies involve determination of the amount of microparticles obtained at the end of preparation and polymer and drug that are consumed in its preparation. It can be calculated as follow

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

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

➢ **Drug Entrapment Efficiency**: It is determined by calculating the amount of drug that is entrapped in the microparticles and the drug which is adsorbed on the surface or interior of the polymer. The amount of free, adsorbed and entrapped drug should be capable of being determined separately and this determination indicated the efficacy of the microparticles produced in terms of its active ingredients.

Determination of free drug in microparticles (unentrapped drug): Accurately weighed microparticles are taken in a beaker. Saline is added to the mixture and shaken well to liberate the free drug present in the polymeric matrix. The free drug is quantified by suitable analytical method. It is calculated by.

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

The amount of drug present at the surface is measured by digesting the microparticles with saline (0.9%w/v) at room temperature, sonicating the solution in an ultrasonic bath for 5 min and centrifuging it at 3000vpm for 2 min. The supernatant is filtered through 0.45µm filter and the drug is quantified by a suitable analytical method.

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

➢ **Entrapped drug in microparticles:** The residue left over from the extraction of the free and adsorbed drug is mixed with 5ml of 0.1m glacial acetic acid. The sample is centrifuged at 5000rpm for 10 minutes. The supernatant is filtered through 0.45µm filter and the amount of drug entrapped is quantified by suitable analytical method.

$$\text{Percentage of the encapsulated drug} = \frac{\text{Quantity of drug encapsulated}}{\text{Quantity of drug added for encapsulated}}$$

➢ **Particle size and shape:** The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microparticles. The microparticles structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microparticles surfaces and after particles are cross-sectioned, it can also be used for the

investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microparticles. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microparticles.

➢ **Infrared spectroscopy:** FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microparticles is investigated measuring Alternated Total Reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microparticles depending upon manufacturing procedures and conditions.

Density determination

➢ **Bulk & tap density:** Bulk density and tapped density of microparticles is also evaluated. Weighed amounts of microparticles were taken in a 10ml measuring cylinder after shaking lightly to break any agglomerates. After observing the initial volume of microparticles the cylinder was allowed to fall under its own weight on a hard surface from the height of 2-5 cm. The tapping was continued at a rate of 100taps/min until no further change in volume was noted. Bulk density refers to a measure used to describe a packing of particles or granules.

$$\text{Bulk density} = \frac{\text{mass of powder}}{\text{volume of packing}}$$

$$\text{Tapped bulk density} = \frac{\text{mass of powder}}{\text{tapped volume of packing}}$$

➢ **Compressibility:** This is the value useful in prediction of flowability. The % compressibility of microparticles can be calculated using the following formula:

$$C = \frac{\rho b - \rho u}{\rho u} \times 100$$

Where, ρb = tapped density ρu = bulk density

➢ **Angle of Repose:** Flow properties of microparticles can be evaluated by determining the angle of repose by fixed funnel & free standing cone method. Angle of repose is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microparticles in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The advancing and

receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microparticles.

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

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose.

➢ **Determination of drug content**: To determine the yield and efficiency of drug loading, microparticles were analyzed for drug content. 100 mg Microparticles were crushed to give fine powder, distilled water was added, and the solution kept for 12 hr. After 12 hr, the solution was sonicated for 30 min. The solution was then filtered through whatman filter paper No. 1. Two milliliters of clear filtrate was diluted to 100ml with distilled water. The absorbance of the solution was measured on a Shimadzu UV-1700 at respective absorbance using distilled water as blank.

➢ **Entrapment efficiency:** The capture efficiency of the microparticles or the percent entrapment can be determined by allowing washed microparticles to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation.

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

➢ **The Drug release studies** was evaluated by USP method II or dissolution test method using phosphate buffer PH 6.8 with the temperature of release medium at 37 ±0.5 & then assaying spectrophotometrically.

➢ **Release kinetics** to model the dissolution profile from the microparticles system two different mathematical differential equation can be used i.e.

(1) First order equation;

(2) Higuchi's square root of time equation.

(1) First order model can be expressed as

$Mt / M\square = 1 - e^{-k1t}$

(2) Higuchi's square root of time model is given by

Mt / M□ = 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. Stability studies were evaluated to find out stable product under storage. Micro particles can be stored in Blass bottles at elevated temperature i.e. 4±1ºC freezing temperature, 25±1º C room temperature, 50±1ºC hot temperature for a period of 30 days & observed for change in drug content & morphology.

APPLICATIONS OF MICROPARTICLES

- Microparticulate drug delivery offers several applications for drugs having poor bioavailability. A number of pharmaceutical encapsulated products are currently on the market, Such as aspirin, theophylline and its derivatives, vitamins, antihypertensive, potassium chloride, progesterone and contraceptive hormone combinations.
- Application areas of microcapsules include pharmaceutical and biotechnology products, cosmetics, diagnostic aids, biological filtration devices, veterinary and zoo technical. products, foods and food additives, flavors, fragrances, detergents, paints, agricultural chemicals, adhesives, industrial chemicals, household products, packaging, textiles, photographic and graphic arts materials.
- These microcapsules are important in providing sustained and controlled release, improving drug stability, reducing vaporization of volatile oils, protecting moisture/light/oxidation sensitive drugs, masking unpleasant taste and odor, converting liquids to powders and Sepa- rating incompatible substances within a single system.
- Anti-inflammatory drugs are another group in which microencapsulation is employed. Diclofenac sodium, Flufenamic acid, Glaphenine, Hydrocortisone, Ibuprofen, Indometha-cin, Naproxen, Oxyphenbutasone, and Prednisone are examples of encapsulated drugs in this group.
- Vitamins A, B1, B2, B6, B12, C, D, were encapsulated to provide formation of smooth and thick-walled microcapsules largely prevented the aggregation of microcapsules and showed low dissolution rate.
- Converting Liquids to Free-Flowing Powders Citrus essential oil, cod liver oil, benzaldehyde, carbon tetrachloride, and oil droplets were coated and recovered as fine powders. The authors have stated that the bulk droplet size of the encapsulated material appeared to be a factor in the strong capsule wall, which protects against vaporization and oxidation.

- There are many reasons why drugs and related chemicals have been microparticles. The technology has been used widely in the design of controlled release and sustained release dosage forms.
- To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin etc.
- Many drugs have been microparticles to reduce gastric and other G.I. Tract irritations. Sustained release aspirin preparations have been reported to cause significantly less G.I. Bleeding than conventional preparations.
- A liquid can be converted to a pseudo-solid for easy handling and storage. Eg. Eprazinone. Hygroscopic properties of core materials may be reduced by microparticle eg. Sodium chloride.
- Microparticles have been employed to provide protection to the core materials against atmospheric effects, e.g. Vitamin A, Palmitate.
- Separation of incompatible substance has been achieved by encapsulation.

CONCLUSION

The microparticles drug delivery system is a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. The microparticles offers a variety of opportunities such as protection and masking, better process ability, improve bioavailability, decreasing dosing frequency, improve stability, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action.

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