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MICROPARTICLE: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

A well designed controlled drug delivery system can overcome some of the problems of conventional drug delivery system and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One of such approach is using microspheres as carriers for drug delivery. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. It is the reliable means to deliver the drug to the target site with specificity and to maintain the desired concentration at the site of interest without untoward effects.

KEY WORDS

Microsphere, Target action, Polymer microsphere and marketed microsphere.

INTRODUCTION

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are sphericalfree flowing particles consisting of proteins or synthetic polymers which are biodegradable innature. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and are used fordifferent applications. Hollow microspheres are typically used as additives to lower thedensity of a material. Solid microspheres have numerous applications depending on whatmaterial they are constructed of and what size they are.[1]

There are two types of microparticles;

- Microcapsules.
- Micromatrices

Microcapsules are those in which entrapped substance is distinctly surrounded by distinctcapsule wall.

Micromatricesare those in which entrapped substance is dispersed throughout the microspheres matrix. [2]

Fig.1: structure of microspheres

TYPES OF MICROSPHERES

I. Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as Bioadhesion.The term "Bioadhesion" describes materials that bind to

biological substrates, such as mucosal membranes. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Bioadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary, colon and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[3]

II. Magnetic microspheres

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different type is therapeutic magnetic microspheres which are used to deliver chemotherapeutic agent to liver tumour.[4]Diagnostic microspheres can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides. The aim of the specific targeting is to enhance the efficiency of drug delivery and at the same time to reduce the toxicity & side effects. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. When the magnetic carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied & often augmented by magnetic agglomeration. The accumulation of the carrier at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters example particle size, surface characteristic, field strength, & blood flow rate etc. The magnetic field helps to extravagate the magnetic carrier into the targeted area. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body. It is possible to replace large amounts of drug targeted magnetically to localized disease site, reaching effective and up to several fold increased drug levels. This technique which requires only a simple injection is far less invasive than surgical methods of targeted drug delivery. Another advantage is that particles in the magnetic fluid interact strongly with each other, which facilitates the delivery of high concentrations of drug to targeted areas.[5] Magnetic microspheres can be filled with drugs or radioactive materials to treat a variety of illnesses. Magnets applied outside the body attract the spheres to the disease site where they deliver therapeutics in a targeted way. The magnets attract the microspheres to the immediate area of the wound site and stop them there. The spheres gradually break down and release growth factors over a period of weeks, allowing blood vessels and damaged tissues to regrow and repair. Small amounts of drug targeted magnetically to localized sites can replace large doses of drug that using traditional administration methods freely circulate in the blood and hit the target site in a generalized way only.[6]

III. Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant instomach without affecting gastric emptying rate. The drug is released slowly at a desiredrate, if the system is floating on gastric content and increases gastric residence and it increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drugs like ranitidine, famotidine, ketoprofen etc. given through this form.[7]

IV. Radioactive microspheres

Radio emobilisation therapy microspheres sized 10-30nm is of larger than capillaries and gets trapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these conditions radioactive microspheres deliver high radiation dose to the

targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radioactivity is not released from microspheres but acts within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters. It offer new solutions for patients who need drugs delivered directly to tumours, diabetic ulcers and other disease sites.[8]

V. Mucoadhesive microspheres

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting eitherentirely of a mucoadhesive polymer or having an outer coating of it.Microspheres in general, have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, *etc.* on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[9]

Advantages

1. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix forthe controlled release of drug.
3. Microspheres received much attention not only for prolonged release, but also fortargeting of anticancer drugs to the tumour.[10]
4. The size, surface charge and surface hydrophilicity of microspheres have been found tobe important in determining the fate of particles in vivo.
5. Studies on the macrophage uptake of microspheres have demonstrated their potential intargeting drugs to pathogens residing intracellularly.
6. Blood flow determination: This study has been carried out using radiolabelledmicrospheres.[11]

Ideal properties [12]

- Longer duration of action
- Control of content release
- Increase of therapeutic efficiency
- Protection of drug
- Reduction of toxicity
- Biocompatibility**,** Sterilizability
- Relative stability
- Water solubility and dispersibility
- Bioresorbability**,** Target ability
- Polyvalent

Criteria for the Preparation of Microspheres[13]

- The ability to incorporate reasonably high concentration of drug.
- Stability of the preparation with a clinically acceptable shelf life.
- Controllable particle size.
- Dispersability in aqueous vehicle for injection.
- Release of active agent with good control over wide time scale.
- Biocompatibility with biodegradability.
- Susceptible to chemical modification.

Characteristics

1) Microspheres are spherical, empty particles.
2) Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. They have a particle size less than 200 µm.
3) Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout a particle matrix have the potential for the controlled release of drug.
4) These carriers received attention not only for prolonged release but also for the targeting of the anti-cancer drug to the tumour.[11]

Polymers used in the preparation of Microspheres[14]

1. *Synthetic polymers*

- Non-biodegradable
  - Polymethyl methacrylate(PMMA)
  - Acrolein
  - Glycidyl methacrylate

- Epoxy polymer
- Biodegradable
  - Lactides and glycolides and their copolymers, Poly alkyl cyano acrylates
  - Poly anhydrides

2. *Natural polymers*

- Proteins:
  - Albumin
  - Gelatin
  - Collagen
- Carbohydrates:
  - Starch
  - Agarose
  - Carrageenan
  - Chitosan
- Chemically modified carbohydrates:
  - Diethylaminoethyl cellulose
  - Poly (acryl) dextran
  - Poly (acryl) starch

Types of polymeric Microspheres[15]

1) Albumin microspheres
2) Gelatin microspheres
3) Starch microspheres
4) Dextran microspheres
5) PLGA microspheres
6) Polyphosphazene microspheres
7) Polyanhydried microspheres
8) Chitosan microspheres
9) Carrageenan microspheres
10) Alginate microspheres
11) Poly (alkyl cyanoacrylate) microsphere
12) Polyacrolein microspheres

MECHANISM OF DRUG RELEASE[16]

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspensions have been recently introduced.

The classifications of such systems are as follows:

1. Diffusion controlled system
2. Dissolution controlled systems
3. Dissolution and diffusion controlled systems
4. Osmotically controlled systems
5. Ion exchange systems

1. Diffusion controlled systems

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. In general two types of sub classes of diffusion systems are recognised they are,

a) Reservoir devices
b) Matrix devices

a. Reservoir devices

Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane. The nature of membrane determines the rate of release of drug from the system.

The process of diffusion is generally described by Fick's equations,

$$J = -D\, dc/dx$$

Where,

J -- Flux (amount/area-time)

D -- Diffusion co-efficient of drug in the membrane (area/time)

dc/dx -- rate of exchange in concentration C, with respect to a distance X in the membrane.

Advantages

1. Zero order delivery is possible
2. Release rate variable with polymer type

Disadvantages

1. Potential toxicity if system fails
2. System must be physically removed from implant sites
3. Difficult to deliver high molecular weight compounds
4. Generally increased cost per dosage unit

b. Matrix devices

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi.

$$Dm/dh = C_o d_h - Cs/2$$

Where, dm = Change in the amount of drug released per unit area

d_h= Change in the thickness of zero of matrix that have been depleted of drug

Co = total amount of drug in unit volume of matrix

Cs = saturated concentration of drug within the matrix

Advantages

1. Can deliver high molecular weight compounds.
2. Easier to produce than reservoir devices.

Disadvantages

1. Removal of remaining matrix is necessary for implanted systems
2. Cannot obtain zero order release

The reason for the attenuation of drug release rate in Higuchi profile that when a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablets superficial layers and consequently, the release rate in is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by water and drug molecules into and out of the tablet respectively. Therefore any mechanism that lessens the time dependent increase in the diffusion path length would reduce the attenuation of dissolution rate.

Diffusion rate modifications

a) Thickness of the separating layer,
b) Porosity
c) Partition coefficient
d) Modification of the diffusion co-efficient
   i. Modification of efficient molecular size
   ii. Modification of viscosity
e) Modification of concentration

2. Dissolution – controlled systems

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution. This being the case, SR preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

The dissolution process at steady state, is described by Noyes - Whitney equation,

$$dc/dt = KDA (C_S-C) = D/h\ A (C_S-C)$$

Where, dc/dt = Dissolution rate

KD = Diffusion coefficient

Cs = Saturation solubility of the solid

C = Concentration of solute in bulk solution

H = Thickness of diffusion layer

Principles of dissolution rate modification

Modification of (a) solubility, (b) specific area, (c) particle shape and surface structure, (d) dissolution conditions (contact of solid particles with the solvent and (e) crystallographic modification.

3. Dissolution and Diffusion – controlled release system

Strictly speaking, therapeutic systems will never be dependent on dissolution only or diffusion only. In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

The mechanism of release from simple erodible slabs, cylinders and spheres has been described by Hopenberg are described as

$$Mt/M = 1 - (1- K_0t/C_0a)^n$$

Where, n = 2 for cylinder and

n = one for a slab

Mt = mass of drug release at time t

M = mass released infinite time.

Advantages

a. Easier to produce than reservoir devices
b. Can deliver high – molecular weight compounds

c. Removal from implant sites is not necessary

Disadvantages

a. Difficult to control kinetics owning to multiple process of release
b. Potential toxicity of degraded polymer must be considered

4. Osmotically controlled systems

This device is fabricated as tablet that contains water soluble osmotically active drug, of that was blended with osmotically active diluents by coating the tablet with a cellulose triacetate barrier which functions as semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane, when this was kept in water.

5. Ion exchange systems

These are salts of cationic or anionic exchange resins or insoluble complexes in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

METHODS OF PREPERATION

1. Spray drying and spray congealing technique
2. Solvent evaporation technique
3. Solvent extraction technique
4. Wet Inversion Technique
5. Complex coacervation method
6. Hot Melt Microencapsulation
7. Single emulsion method
8. Multiple emulsion method
9. Ionic gelation
10. Polymerization techniques
    a) Normal polymerization
    b) Interfacial polymerization
11. Coacervation phase separation method
12. Crosslinking method
    a) Thermal crosslinking
    b) Chemical crosslinking
13. Hydroxyl appetite (HAP) microspheres in sphere morphology

1. Single emulsion technique[17]

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. 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, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.

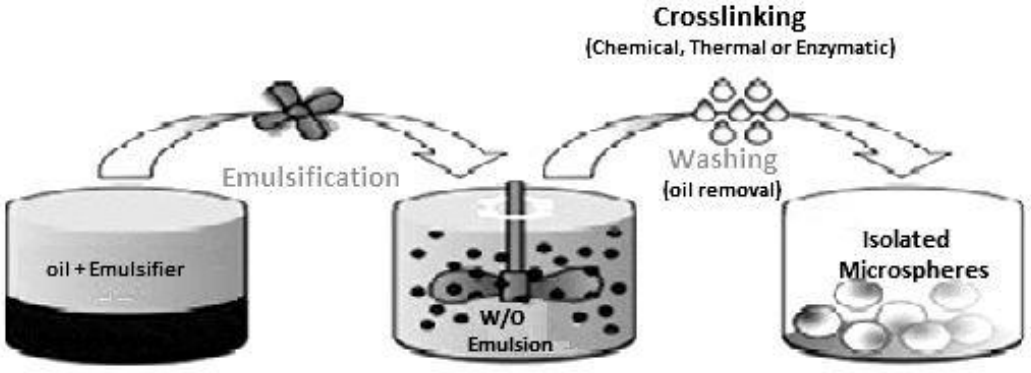

Fig. 2: Processing scheme for microspheres-preparation by single emulsion technique.

2. Double emulsion technique[18]

Double emulsion method of microspheres preparation involves the formation of the multiple emulsion or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used

with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in 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 formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction a number of hydrophilic drugs like leutinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.

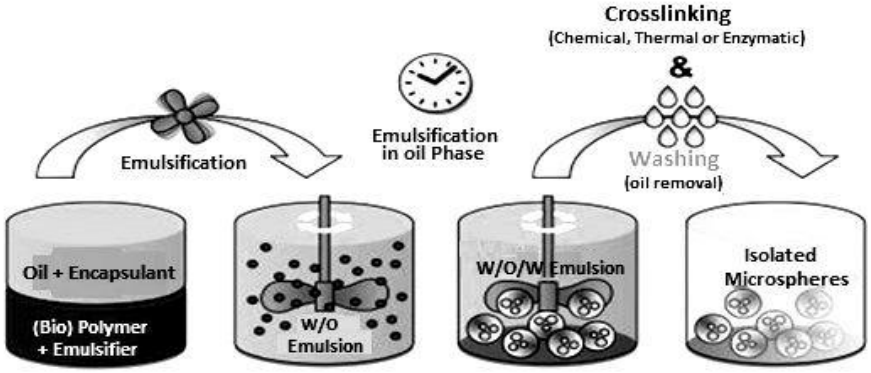

Fig.3: Processing scheme for microspheres-preparation by double emulsion technique

i. Water-oil-water(W/O/W) multiple emulsion system[19]

The preparation and characterization of the drug loading, encapsulation efficiency and morphology of biodegradable polyester microspheres containing somatostatin acetate and poly(D,L- lactide), poly(D,L-lactide/glycolide), or poly(L-lactide) prepared by a modified solvent evaporation method based on the formation of multiple W/O/W emulsions were reported by Hermann and Bodmeier. An increase in the volume fraction of the internal aqueous phase in the primary W/O emulsion resulted in lower encapsulation efficiencies. Replacement of methylene chloride as an organic solvent with ethyl acetate reduced the encapsulation efficiency and increased the porous nature of the microspheres. Except for microspheres prepared with very low molecular weight polymers, the encapsulation efficiency was not affected by the polymer type and molecular weight. The preparation substantially affected the morphology and porosity of the microspheres. Stability of the primary emulsion is a perquisite for the successful encapsulation of multiple emulsions.

ii. W/O/O method

O'Donnell and co-workers prepared multiphase microspheres of poly (DL- lactic-co-glycolic acid) by a multiple emulsion potentiometric dispersion technique. Water soluble compounds were dissolved in the aqueous phase (W) and emulsified in soyabean oil (O) to form a stable emulsion. This primary emulsion was dispersed in a solution of PLGA and acetonitrile (O) to form a W/O/O emulsion. The W/O/O emulsion was then dispersed in a hardening solution of light mineral oil (O) using a potentiometric dispersion technique as illustrated in Fig. 8 to produce microspheres of the W/O/O/O type with a very narrow and selective size distribution. The size of the microspheres was controlled by varying the internal diameter of the conductive infusion tube or by the variation of voltage applied to the conductive tube. Particle size analysis revealed a narrow particle size distribution with 80% of the microspheres made by this method in the 20 to 40μm range as compared to a wide distribution of 50 to 500μm for microspheres made by conventional agitation methods.

Chlorpheniramine maleate was encapsulated with a loading efficiency of 88.9% with the potentiometric method as compared to a loading efficiency of 74.3% for the agitation method.

3. Polymerization techniques[20]

The polymerization techniques conventionally used for the preparation of the microspheres
are mainly classified as:
I. Normal polymerization
II. Interfacial polymerization. Both are carried out in liquid phase.

Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization.

Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. Bulk polymerization has an advantage of formation of pure polymers.

Interfacial polymerization

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

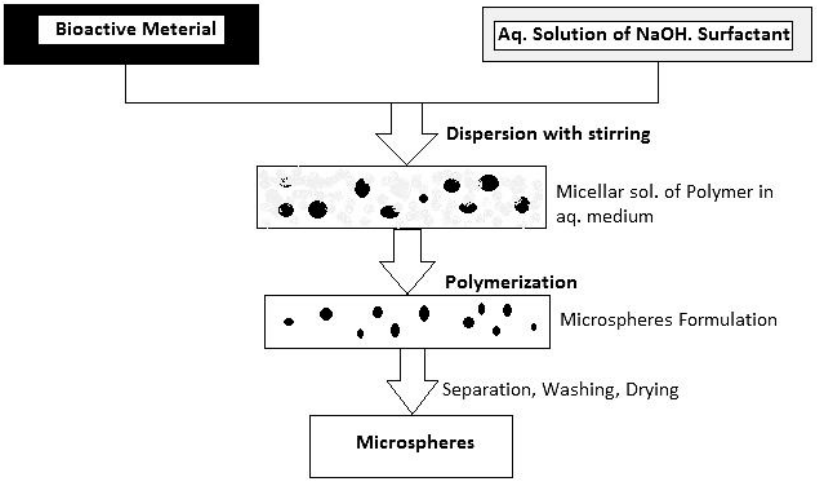

Fig. 4: Polymerization method

4. Phase separation coacervation technique[21]

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the

agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

5. Spray drying and spray congealing[22]

These methods are based on the drying of the mist of the polymer and drug in the air.Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmitic acid using spray congealing. Very rapid solvent evaporation, however leads to the formation of porous microparticles.

6. Solvent extraction[23]

Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

7. Solvent Evaporation[24]

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The solvent Evaporation technique is shown in Figure:10. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

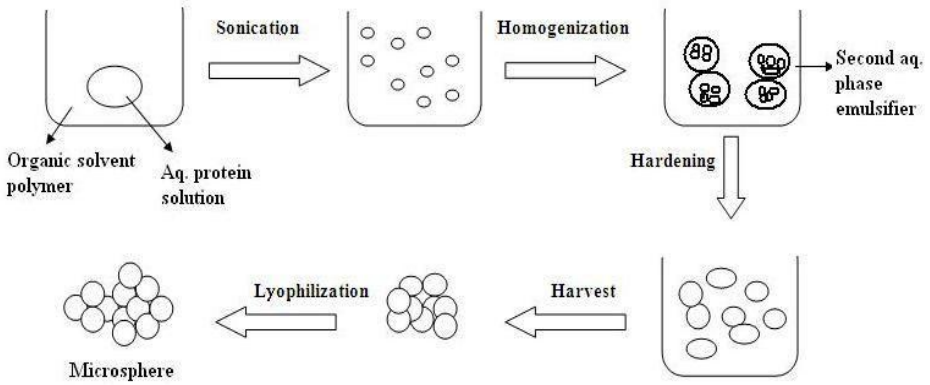

Fig. 5: Solvent evaporation method for preparation of microsphere.

8. Wet Inversion Technique[24]

Chitosan solution in acetic acid was dropped into an aqueous solution of counter ion sodium tripoly posphate through a nozzle. Microspheres formed were allowed to stand for 1hr and cross linked with 5% ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of the coagulation medium could modify the pore structure of CS microspheres.

9. Complex Coacervation[24]

CS microparticles can also prepare by complex coacervation, Sodium alginate, sodium CMC and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl & $CaCl_2$ solutions. The obtained capsules were hardened in the counter ion solution before washing and drying.

10. Hot Melt Microencapsulation[24]

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50µm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, *e.g.* polyanhydrides. Microspheres with diameter of 1-1000µm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

11. Ionic gelation technique[25]

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

12. Quasi-emulsion solvent diffusion[26]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi-emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase is consisting of drug, ethanol and polymer is added at an amount of 20% of the polymer in order to enhance plasticity. At first, the internal phase is manufactured at 60°C and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40°C for a day.

13. Crosslinking methods

i. Thermalcross-linking

Citric acid, as a cross-linking agent was added to 30 mL of an aqueous acetic acid solution of chitosan (2.5% wt/vol) maintaining a constant molar ratio between chitosan and citric acid(6.90 × 10−3 mol chitosan: 1 mol citric acid). The chitosan cross-linker solution was cooled to 0°C and then added to 25 mL of corn oil previously maintained at 0°C, with stirring for2 minutes. This emulsion was then added to 175 mL of corn oil maintained at 120°C, and cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40minutes. The microspheres obtained were filtered and then washed with diethyl ether,dried, and sieved.[27]

ii. chemical cross linking

A 2.5% (w/v) chitosan solution in aqueous acetic acid was prepared. This dispersed phasewas added to continuous phase (125 mL) consisting of light liquid paraffin and heavyliquid paraffin in the ratio of 1:1

containing 0.5% (wt/vol) Span 85 to form a water in oil(w/o) emulsion. Stirring was continued at 2000 rpm using a 3- blade propeller stirrer). Adrop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25%v/v) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C-80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in vacuum desiccators .[28]

14. Hydroxyl appetite (HAP) microspheres in sphere morphology[29]

This was used to prepare microspheres with peculiar spheres in sphere morphologymicrospheres were prepared by o/w emulsion followed by solvent evaporation. At first o/wemulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5%w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organicphase was dispersed in the form of tiny droplets which were surrounded by surfactantmolecules this prevented the droplets from co-solvencing and helped them to stay individualdroplets .While stirring the DCM was slowly evaporated and the droplets solidify individualto become microspheres.

2.8 DRUG LOADING AND RELEASE KINETICS[30]

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug/protein. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence ofadditives (e.g.cross linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micromorphology of the carrier and the properties of the polymer itself. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients. In order to study the exact mechanism of drug release from the microspheres, drug release data was analysed according to Zero-order, First-order, Higuchi square root, Hixson Crowell and Peppas equation. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. 11The zero-order kinetic (equation1) describes the systems in which the drug release rate is independent of its concentration. The first order kinetic describes the systems in which the drug release rate is concentration dependent. [12] Higuchi described the release of drug from an insoluble matrix as a square root of the time-dependent process on the basis of Fickian diffusion. [33] The Hixson Crowell cube root law describes the drug release from systems in which there is a change in the surface area and the diameter of particles present in the tablet. Peppas equation describes the release when more than one type of release phenomena could be involved or when the release mechanism is not well known. [34]

$R = k_0 t$ .....(1)

$\text{Log UR} = k_1 t\ 2.303$ .....(2)

$R = k_2 t_{1/2}$..... (3)

$(UR)_{1/3} = k_3 t$ .....(4)

$\log R = \log k_4 + n \log t$ .....(5)

Where R and UR are the released and unreleased percentages, respectively, at time t.

And K_O, K_1, K_2, K_3 and K_4 are release rate constants for Zero order, First order, Higuchi,Hixson-Crowell and Peppas-Korsmeyer rate equations, respectively.

EVALUATION PARAMETERS

Physicochemical Evaluation Characterization

The characterization of the micro particulate carrier is an important phenomenon, whichhelps to design a suitable carrier for the proteins, drug or antigen delivery. Thesemicrospheres have different microstructures. These microstructures determine the releaseand the stability of the carrier.

1. 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 todetermine the shape and outer structure of microparticles. LM provides a control overcoating parameters in case of double walled microspheres. The microspheres structures canbe visualized before and after coating and the change can be measured microscopically. SEMprovides higher resolution in contrast to the LM. SEM allows investigations of themicrospheres surfaces and after particles are cross-sectioned, it can also be used for theinvestigation of double walled systems. Confocal fluorescence microscopy is used forthe structure characterization of multiple walled microspheres. Laser light scatteringand multi size coulter counter other than instrumental methods, which can be used forthe characterization of size, shape and morphology of the microspheres.[31]

2. Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheres can be determined using the electron spectroscopyfor chemical analysis (ESCA). ESCA is used for the determination of the atomiccomposition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

3. Attenuated total reflectance-Fourier Transfom-Infrared Spectroscopy:

FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. Thesurface of the microspheres is investigated measuring alternated total reflectance (ATR).The IR beam passing through the ATR cell reflected many times through the sample toprovide IR spectra mainly of surface material. The ATR-FTIR provides information about thesurface composition of the microspheres depending upon manufacturing procedures.

4. Density determination:

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and hence the density of the microsphere carrier is determined.

5. Isoelectric point:

The micro electrophoresis is an apparatus used to measure the electrophoretic mobilityof microspheres from which the isoelectric point can be determined. The mean velocity atdifferent pH values ranging from 3-10 is calculated by measuring the time of particlemovement over a distance of 1 mm. By using this data the electrical mobility of the particlecan be determined. The electrophoretic mobility can be related to surface containedcharge, ionisable behaviour or ion absorption nature of the microspheres.

6. Angle of contact:

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mount above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microspheres.[32]

7. *In vitro* methods

There is a need for experimental methods which allow the release characteristics and permeability of a

drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies havebeen employed as a quality control procedure in pharmaceutical production, in productdevelopment etc. Sensitive and reproducible release data derived from physico chemicallyand hydro dynamically defined conditions are necessary. The influence of technologicallydefined conditions and difficulty in simulating *in vivo* conditions has led to development of anumber of *in vitro* release methods for buccal formulations; however no standard *in vitro*method has yet been developed. Different workers have used apparatus of varyingdesigns and under varying conditions, depending on the shape and application of thedosage form developed. The dosage form in this method is made to adhere at the bottom ofthe beaker containing the medium and stirred uniformly using overhead stirrer. Volume ofthe medium used in the literature for the studies varies from 50-500 ml and the stirrerspeed form 60-300 rpm.

Interface diffusion system

This method is developed by Dearden& Tomlinson. It consists of four compartments.The compartment A represents the oral cavity, and initially contained an appropriateconcentration of drug in a buffer. The compartment B representing the buccalmembrane, contained 1-octanol, and compartment C representing body fluids,contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1- octanol were saturated with each other.Samples were withdrawn and returned to compartment A with a syringe.

Modified KesharyChien Cell:

A specialized apparatus was designed in the laboratory. It comprised of a KesharyChiencell containing distilled water (50ml) at 370 C as dissolution medium. TMDDS (TransMembrane Drug Delivery System) was placed in a glass tube fitted with a 10# sieve at thebottom which reciprocated in the medium at 30 strokes per min.

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* releaseprofiles using both rotating elements, paddle25, 26, 27 and basket 28, 29. Dissolutionmedium used for the study varied from 100- 500 ml and speed of rotation from 50-100 rpm.[33]

8. *In vivo* methods

Methods for studying the permeability of intact mucosa comprise of techniques thatexploit the biological response of the organism locally or systemically and those that involvedirect local measurement of uptake or accumulation of penetrants at the surface.Some of the earliest and simple studies of mucosal permeability utilized the systemicpharmacological effects produced by drugs after application to the oral mucosa. Howeverthe most widely used methods include *in vivo* studies using animal models, buccalabsorption tests, and perfusion chambers forstudying drug permeability.

In vitro-In vivo correlations

Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites arereferred to as "*in vitro-in vivo* correlations". Such correlations allow one to developproduct specifications with bioavailability.

Percent of Drug Dissolved *In Vitro* Vs Peak Plasma Concentration

One of the ways of checking the in vitro and in vivo correlation is to measure the percent of the drug released from different dosage forms and also to estimate the peak plasmaconcentrations achieved by them and then to check the correlation between them. It isexpected that a poorly formulated dosage form releases amount of drug than a wellformulated dosage form, and, hence the amount of drug available for absorption is lessfor poorly formulated dosage form than from a well formulated dosage form.

Percent of Drug Dissolved VsPercent of Drug Absorbed

If the dissolution rate is the limiting step in the absorption of the drug, and is absorbedcompletely after dissolution, a linear correlation may be obtained

by comparing thepercent of the drug absorbed to the percent of the drug dissolved. If the rate limiting step inthe bioavailability of the drug is the rate of absorption of the drug, a change in thedissolution rate may not be reflected in a change in the rate and the extent of drugabsorption from the dosage form.

Dissolution Rate Vs Absorption Rate

The absorption rate is usually more difficult to determine than the absorption time. Since theabsorption rate and absorption time of a drug are inversely correlated, the absorption timemay be used in correlating the dissolution data to the absorption data. In the analysis ofin vitro and in vivo drug correlation, rapid drug absorption may be distinguished fromthe slower drug absorption by observation of the absorption time for the dosage form. Thequicker the absorption of the drug the less is the absorption time required for the absorption of the certain amount of the drug. The time required for the absorption of thesame amount of drug from the dosage form is correlated.[34]

9. Swelling Index

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount ofmicrospheres were allowed to swell in given buffer. The excess surface adhered liquiddrops were removed by blotting and the swollen microspheres were weighed by usingmicrobalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there wasno change in the dried mass of sample.

The swelling index of the microsphere was calculated by using the formula;

Swelling index =

(mass of swollen microspheres – mass of dry microspheres/mass of dried microspheres) x 100.[20]

Table: 1. Drugs and methods used as microspheres

Sl. No:	Drugs	Methods used	Reference
1	5-fluoro uracil	Solvent evaporation	22
2	Ranitidine floating microsphere	Ionic gelation method	23
3	albendazole	Spray drying technique	24
4	Atenolol Mucoadhesive microsphere	Spray drying technique	25
5	Candesartan and captopril matrix microsphere	Emulsion-solvent evaporation	26
6	Cefpodoximeproxetil	Emulsion-solvent diffusion	27
7	Chlorpherniramine maleate	o/o Emulsion solvent evaporation	28
8	ciprofloxacin	Coacervation phase separation	29
9	Clarithromycin hollow microsphere	Emulsion-solvent diffusion	30
10	Diltiazem hydrochloride	Emulsion-solvent evaporation	31
11	Diltiazem hydrochloride hollow microsphere	Emulsion-solvent evaporation	32
12	Fexofenadine HCl microsphere	Spray drying technique	33
13	glipizide	Emulsion-solvent evaporation	34

MARKETED PRODUCTS OF MICROSPHERES:

Drug	Commercial name	Company	Technology	Indication
Risperidone	RISPERDAL® CONSTA®	Janssen®/ Alkermes, Inc	Double emulsion (oil in water)	Schizophrenia; bipolar I disorder
Naltrexone	Vivitrol®	Alkermes	Double emulsion (oil in water)	Alcohol dependence
Leuprolide	Lupron Depot®	TAP	Double emulsion (water in oil inwater)	Prostate cancer/endometriosis
	Enantone Depot®	Takeda		
	Trenantone®	Takeda		
	EnantoneGyn	Takeda		
Octreotide	Sandostatin® LAR	Novartis	Phase separation	Acromegaly
Somatropin	Nutropin® Depot[a]	Genentech/ Alkermes	AlkermesProLease® Technology (Cryogenic spray-drying)	Growth deficiencies
Triptorelin	Trelstar™ depot	Pfizer		
	Decapeptyl® SR	Ferring	Phase separation	Prostate cancer
Buserelin	Suprecur® MP	Sanofi-Aventis	N/A	Endometriosis
Lanreotide	Somatuline® LA	Ipsen-Beafour	Phase separation	Acromegaly
Bromocriptine	Parlodel LAR ™	Novartis	Spray dry	Parkinsonism
Minocycline	Arestin®	Orapharma	N/A	Periodontitis

Other marketed microspheres:

1. *Therasphere* – contains millions of tiny radioactive glass beads filled with Y-90 – emit beta particles that penetrate a mean of 2.5 min into the surrounding tissue.
2. *SIR-spheres* – composed of millions of tiny polymer beads filled with Y-90 - emit beta particles that penetrate a mean of 2.5 min into the surrounding tissue.
3. *Embosphere microspheres* (contains trisacrylcrosslinked with gelatin) – for the treatment of uterine fibroids, hypervascular tumours (or) arteriovenous malfunctions.
4. *Embogold microsphere* – to treat proximal and distal embolization – acrylic copolymer crosslinked with gelatin.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. It has been observed that microspheres are better choice of drug delivery system than many other types of drug delivery system because it is having the advantage of target specificity and betterpatient compliance. Its applications are enormous as they are not only used for delivering drugs but also for imaging tumours, detecting bio molecular interaction etc. So in future microspheres will have an important role to play in the advancement of medicinal field.

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