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ADVANCED APPROCHES TO FORMULATE MUCOADHESIVE MICROSPHERE

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ABSTRACT

Carrier technology provides an interesting as well as an intelligent approach for the delivery of drug. It offers delivery of drug by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. Microspheres constitute an important part of this particulate drug delivery system because of their small size and other efficient properties. Microsphere are free flowing powder, consist of spherical particle of size ideally less than 1 to 1000 µm. Each particle of microspheres is basically a matrix of drug dispersed in a polymer from which release obtained by a first order kinetic process. In the microsphere, the polymers used are biodegradable and biocompatible. Internal structure of microspheres is a matrix of drug and polymeric excipient. The microspheres are meant to reduce the dosing frequency and improve patient compliance by designing and evaluating sustained release mucoadhesive microspheres for effective control of disease over a longer period of time. Mucoadhesive microsphere exhibit a prolonged residence time at the site of application and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved or better therapeutic performance of drug. Mucoadhesive drug delivery systems promises several advantages that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient. Hence, uptake and consequently bioavailability of the drug is increased and frequency of dosing reduced with the result that patient compliance is improved. In recent years such Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local

effects. Microspheres received much attention for prolonged release and targeting of anticancer drugs. In future by combining various other strategies, microspheres will find the central place in novel gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS: Polymer, Natural Mucoadhesive Substance.

INTRODUCTION

Microsphere are small spherical particle, with diameter in the micro merit range (typically 1um to 1000 um (1mm)). Microspheres are sometime referred to as micro particle. Microsphere can be manufactured from various natural or synthetic materials. Glass microsphere, polymer microsphere and ceramic microsphere are commercially available. Solid and hollow microspheres are widely in density and, therefore, are used for different application. Hollow microspheres are typically used as additive to lower the density of materials. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene, polystyrene and expandable microsphere are the most common type of polymer microsphere.[1]

Microsphere should flexibility in design and development, attractive in appearance, better, improves the safety and efficiency of bio-active agents, desired release pattern can be engineered.[2] Microsphere are characteristically free flowing powder consisting of protein and synthetic polymer which are biodegradable in nature and ideally having a particle size less than 200 um. A well design controlled drug delivery system can overcome some of the problem of conventional therapy and enhance the efficacy of a given drug.[3]

Microsphere carrier systems, made from natural polymer are attracting considerable attentions for several years, for sustained drug delivery. Today, those dosage forms which can controlled the release rate and which are target specific have a great impact in development of novel drug delivery system. Microspheres are part of such novel drug delivery system. Microspheres are potential candidate for such drug delivery system. The success of these microspheres is limited because short resident time at the site of absorption therefore, it would be advantageous to provide an intimate contact of the drug delivery system with absorbing membrane this can be achieved by coupling bio-adhesion to microsphere and formulating bioadhesive microsphere. These microspheres provide advantages such as efficient absorption and increased bioavailability of drug owing to high surface-to-volume

ratio, a much more intimate contact with the mucus layer and specific targeting of drug to the absorption site.[4]

TYPE OF MICROSPHERE

1. POLYMERIC MICROSPHERE

The different type of polymeric microsphere can be classified as follows and they are biodegradable polymeric microsphere and synthetic polymeric microsphere.

a. Biodegradable Polymeric Microsphere

b. Synthetic Polymeric Microsphere

a. Biodegradable Polymeric Microsphere

Natural polymer such as starch is used with the concept that they are biodegradable, biocompatible and also bio-adhesive in nature. Biodegradable polymer prolong the residence time when contact with mucus membrane due to its high degree of swelling property with aqueous medium, resulting gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in sustained manner.

b. Synthetic Polymeric Microsphere

The interest of synthetic polymeric microsphere are widely used in clinical application, moreover that also used as bulking agents, fillers, embolic particles, drug delivery vehicle etc and prove to be safe and biocompatible.

2. MAGNETIC MICROSPHERE

This kind of delivery system is very important which localized the drug to the desease site. In this large amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carrier receive magnetic responses to the magnetic field from incorporated materials that are used for magnetic microsphere such as chitosan, dextran etc. The different types are therapeutic magnetic microsphere which is used to deliver chemotherapeutic agent to liver tumour. Drugs like protein and peptide can also be targeted through these systems.

Diagnostic microsphere can be used for imaging liver metastases and also can be used for distinguish to bowel loops from other abdominal structure by forming nano sized particle super magnetic iron oxide.

3. FLOATING MICROSPHERE

In floating type the bulk density is less than gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increase gastric residence and increased fluctuation in plasma concentration. Moreover it reduces chances of striking and dose dumping. Another way it produces prolongs therapeutic effect and therefore reduces dose frequency.

4. RADIOACTIVE MICROSPHERE

Radio immobilized therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumor of interest. So all these condition radioactive microsphere deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues.[5]

5. BIO ADHESIVE MICROSPHERE

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of water soluble polymer (5). The term bioadhesion describes materials that bind to biological substrate, such as mucosal membrane and this offer the possibility of creating an intimate and prolong contact at the site of administration resulting in prolong residence time can expand absorption.

ADVANTAGES OF MICROSPHERES OVER CONVENTIONAL DOSAGE FORM

- Microspheres can be encapsulated many type of drugs like small molecules, protein and nucleic acid.
- Microspheres can easily administer through a syringe needle.
- They are generally biocompatible, can provide high bioavailability.
- They capable of sustained release for long period of time. Several commercial products are based on polymeric microspheres including Lupron Deport and Nutropin.
- Improve patient compliance and convenience due to less frequent dosing of drug.
- Reduction In fluctuation of steady state plasma level and therefore helps in better control of disease condition.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care cost through improved therapy, shorter treatment period and less dose frequency.[6]

IDEAL CHARACTERISTICS OF MICROSPHERE[4]

The preparation of microspheres should satisfy following criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controllable particle size and dispersability in aqueous vehicles for injection
- Release of active agent with good control over a wide time scale
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.
- Should be stable at room temperature.

CRITERIA FOR THE DRUG TO PREPARE MICROSPHERES

The drug

- Should be low in molecular weight
- Should Have high water solubility
- Its chemical structure can be modified
- Should be chemically and physically compatible with other excipients.
- Should have good bioavailability.
- Should be compatible with polymer used.
- Should be non-toxic or less toxic.
- Should have log p value 1-3.

MUCOADHESIVE MICROSPHERE

Microspheres are frequently used drug delivery system and may also possess mucoadhesive properties. Microspheres form an important part of such novel drug delivery systems. They have varied applications and are prepared using assorted polymer. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes.[7] This can be achieved by coupling mucoadhesion characteristics to microsphere and developing mucoadhesive microsphere. Mucoahesive microsphere have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to absorption site.

MECHANISM OF MUCOADHESION

Several theories have been proposed to explain the fundamental mechanism of adhesion.[8] A general mechanism of mucoadhesion drug delivery system is shown in figure.

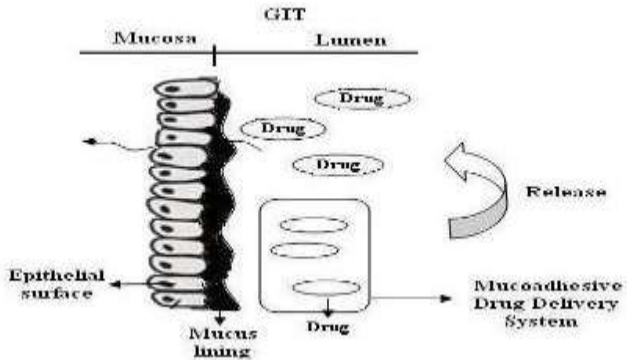

Figure 1 Mechanism of Mucoadhesion

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucosal layer. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

Mucoadhesion has the following Mechanism

1. Intimate contact between a mucoadhesive delivery system and mucosal membrane (wetting or swelling phenomenon)
2. Formation of chemical bonds between the entangled chains (adsorption)
3. Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration)

Electron Theory

According to this theory, electron transfer occurs upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structure.[19] This result in the formation of electrical double layer at the interface e.g. interaction between positively charged polymer chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provide an intimate contact between a dosage form and absorbing tissue.[20]

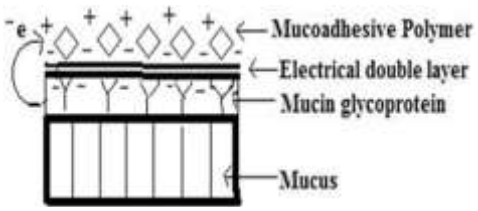

Figure 2 Diagrammatic Representation of Electron Theory

Absorption Theory

According to this theory, after an initial contact between two surfaces.[21] the material adheres because of surface force acting between the atom in two surfaces.[22] two type of chemical

bonds resulting from these forces can be distinguished as primary chemical bond of covalent nature and secondary chemical bonds having many different forces of attraction, including electrostatic forces, vanderwall forces, hydrogen and hydrophobic bond.[23, 24]

Diffusion Theory

According to this theory, the polymer chain and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.[25] The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.[26, 27]

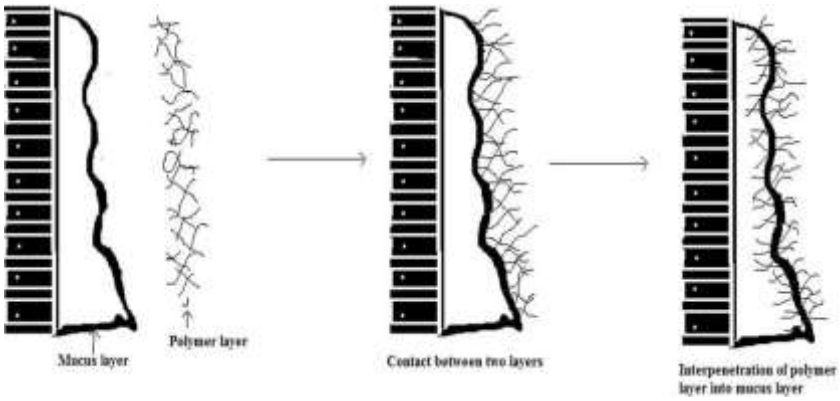

Figure 3 Representation of Diffusion Theory

a. Polymer layer and mucus layer before contact.
b. Polymer layer and mucus layer immediately after contact.
c. Polymer layer and mucus layer after contact for a period of time.

Wetting Theory

The wetting theory postulate that if the contact angle of liquid on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of liquid, the liquid may act as an adhesive among the substrate surface.

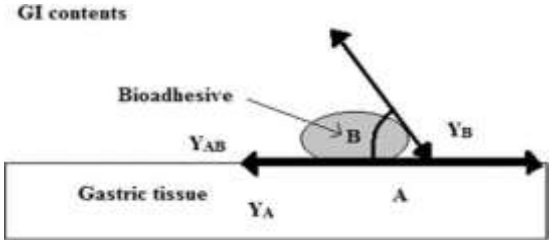

Figure:4 Representation of the Interfacial Forces Involved in Wetting Theory

Cohesive Theory

The cohesive theory proposed that the phenomenon of bioahesion is mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting diffusion and cohesive theory).

POLYMER USED FOR MUCOADHESIVE MICROSPHERE

Mucoadhesive polymers are water soluble and water insoluble polymer, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

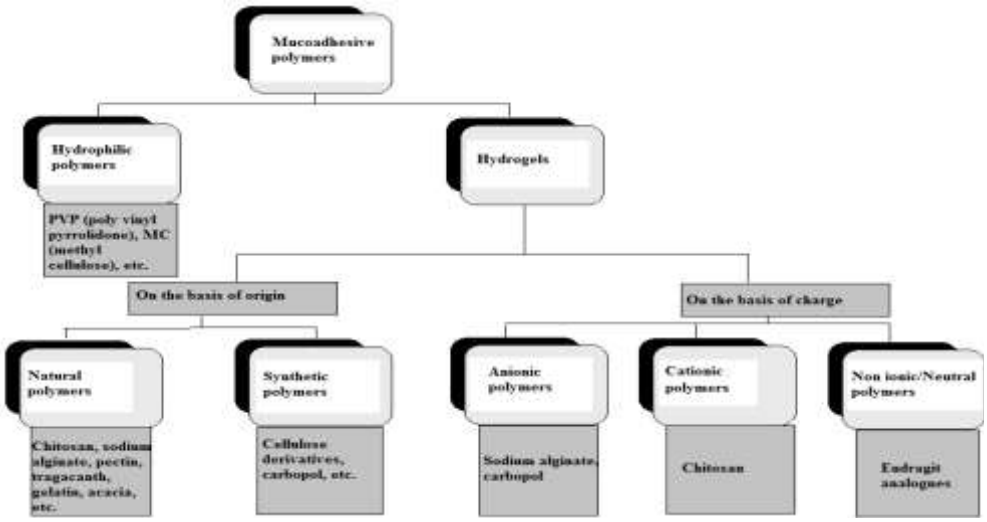

Figure 5 Classification and Example of Mucoadhesive Polymer[28]

Hydrophilic Polymer

The polymer within this category is soluble in water. Matrices developed with these polymer swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolyte extends greater mucoadhesive property when compared with neutral polymer.[9]

Hydrogels

Hydrogels can be defined as three dimensionally cross linked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and

sucrose indicated an increase in the Mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid) chain density per unit area.[10]

Thiolated Polymer

The presence of free thiol group in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub- domains present in mucin which can substantially improve the Mucoadhesive properties of the polymers eg-poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents.[11,12,13,14,15]

Lactin-Based Polymer

Lactins are proteins which have ability to reversibly bind with specific sugar carbohydrate residues and are found in both animal and plant kingdom.[16,17,18] The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery system.

Table 1 List of Natural and Synthetic Polymer

Synthetic polymer	Natural polymer
Cellulose derivative	Tragacanth
Polycarbophil	Sodium alginate
Poly(ethylene oxide)	Karaya gum
Poly(vinyl pyrrolidone)	Guar gum
Poly(vinyl alcohol)	Gelatin
Poly(hydroxy ethyl methylacrylate)	Chitosan
Hydroxyl propyl cellulose	Soluble starch

IDEAL CHARACTERISTICS OF AN MUCOADHESIVE POLYMER

1. The polymer and its degradation products should be non-toxic and nonabsorable from the GIT.
2. It should be non-irritant to the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow daily incorporation to the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

APPLICATION OF MICROSPHERES IN DRUG DELIVERY

There are several applications of microspheres some of which are stated as follows.[29]

Targeting of Active Agents[30]

• Inactive: Here the term inactive means that the microsphere surface is not modified in any means. These unmodified microspheres gather in specific tissue reticuloendothelial system

• Active: The term active indicates to alter microsphere surface with ligand (antibodies, enzymes, protein A, polysaccharides)

• Physical: Temperature or pH sensitive microspheres

• Directly to diseased site

Increasing Efficacy and Decreasing Toxicity[31]

• Changes the absorbance and bio distribution

• Delivers drug in desired form

• In case of multidrug resistance helps to prevent drug interactions

Protection of Active Agent[32]

• Decreases harmful side effects

• Protects drug that undergoes metabolism in gastrointestinal environment

Providing Desired Release Profile[32]

• Affects the time in which the drug is released

• Prolong time -increases duration of action and decreases frequency of administration

• Dependent on drug and polymer properties

Medical application[33]

 Release of proteins, hormones and peptides overextended period of time.

 Gene therapy with DNA plasmids and also delivery of insulin.

 Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricin toxoid, diphtheria, birth control.

 Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial/intravenous application.

 Tumour targeting with doxorubicin and also treatments of leishmaniasis.

 Magnetic microspheres can be used for stem cell extraction and bone marrow purging.

 Used in isolation of antibodies, cell separation, and toxin extraction by affinity chromatography.

 Used for various diagnostic tests for infectious diseases like bacterial, viral, and fungal.

Radioactive microsphere's application[34]

 can be used for radioembolisation of liver and spleen tumours.

Imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep veinthrombosis can be done.

Other applications

 Fluorescent microspheres can be used for membrane based technologies for flowcytomettry, cell biology, microbiology,

Fluorescent Linked Immune-Sorbent Assay

 Yttrium 90 can be used for primary treatment of hepatocellular carcinoma and also used for pretransplantmanagement of HCC with promising results.

 Used for radiosynvectomy of arthritis joint, local radiotherapy, interactivity treatment.[34]

METHOD OF PREPARATION

SINGLE EMULSION TECHNIQUE

In this method a dispersion or solution of natural polymers is prepared in aqueous medium. This mixture is then dispersed in the non-aqueous medium such as oil followed by cross linking of dispersed globules either by means of heat or chemical cross linking agents as shown in Fig. (6).[35] Based on the type of cross linking the method is classified as:

Preparation of Microsphere by Thermal Cross-Linking

Citric acid , as a cross-linking agent was added to 30 ml of an aqueous acetic acid solution of polymer (2.5 % wt./vol) maintaining a constant molar ratio between polymer and citric acid. The polymer cross-linker solution was cooled to 0c and then added to 25 ml of corn oil previously maintain at 0^0c, with stirring for 2 minutes. This emulsion was added to 175 ml of corn oil maintains at 120^0 c, and a cross-linking was performed in a glass beaker under vigorous stirring (1000 rpm) for 40 minutes. The microspheres obtained were filtered and then washed with diethyl ether, dried, and sieved.[36]

Preparation of Microsphere by Glutaraldehyde Cross Linking 2.5% (wt. /vol) polymer solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous

phase (125 ml) consisting of light liquid paraffin and heavy liquid 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 continuing at 2000 rpm using a 3-blade propeller stirrer. A drop by drop solution of a measured quantity of aqueous glutaraldehyde was added at 15, 30, 45 and 60 minute. Stirring was continue for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were finally dried in vacuum desiccators. [57]

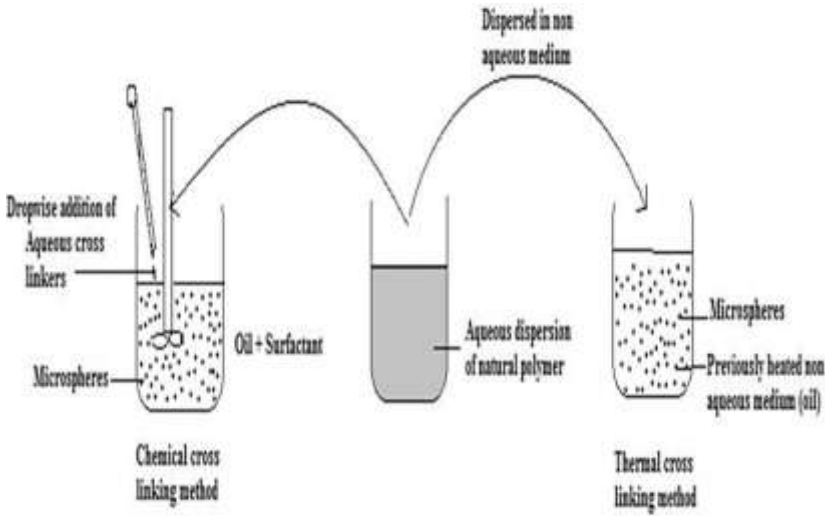

Figure 6: Single Emulsion Technique

DOUBLE EMULSION METHOD (A Hydrous Technique)

This method involves the formation of multiple emulsions or double emulsion of type water in oil in water (w/o/w) and is best suited for water soluble drugs. It involves both natural as well as synthetic polymers in formulation. First an aqueous drug polymer solution is dispersed in a lipophilic organic continuous phase under vigorous stirring to form a homogeneous mixture [37]. The continuous phase consists of polymer solution that eventually encapsulates the drug present in dispersed aqueous phase as shown in Fig. (**8**). This primary emulsion is then subjected to sonication before addition to aqueous solution of polyvinyl alcohol (PVA) that results in the formation of double emulsion.[38] The later double emulsion formed is subjected to solvent evaporation or solvent extraction process by maintaining emulsion at reduced pressure or stirring so that volatile organic phase evaporates out. The emulsion is added to the large amount of water (with or without surfactant) into organic phase diffuse out and the solid microspheres are separated out by filtration and washing.[39]

POLYMERIZATION TECHNIQUES

This technique is further classified into two types:

- Normal polymerization method
- Interfacial polymerization method

Normal polymerization method: This method uses different techniques such as bulk, suspension precipitation, and emulsion and miceller polymerization process.

- **Bulk polymerization:** A monomer or a mixture of monomer containing an initiator is first heated to initiate the polymerization reaction and carry out the process. The initiator or catalyst facilitates or accelerates the rate of reaction. The polymer thus obtained is molded or fragmented as microspheres. Drug must be either adsorbed or added during the process of polymerization for better encapsulation efficiency. This method leads to the formation of purepolymer but suffers a difficulty in dissipating heat of reaction which adversely affects the thermolabileactive ingredients.[40]

- **Suspension polymerization:** Also known as bead or pearl polymerization, this method involves the heating of monomer or mixture of monomers along with drugs as droplets dispersion in a continuous aqueous phase containing an initiator and other additives. This method can be carried out at low temperature since continuous external phase is normally water through which heat can easily dissipate [(41)]. Suspension polymerization leads to the formation of high molecular weight polymer at relatively faster rate. However it leads to the association of polymer with unreacted monomer other additives thus creating a major disadvantage.[42]

- **Emulsion polymerization:** This method is similar to suspension polymerization but differs in one step. In this method, the initiator present in the aqueous phase later on diffuse to the surface of the micelles or emulsion globules.[43]

Interfacial polymerization method: As the term denotes, it involves reaction of monomers at the interface between the two immiscible liquid phases to form a polymer film enveloping the dispersed phase. Two reaction monomers employed involve one which is soluble in continuous phase and the other being dispersed in continuous phase. The continuous phase is generally aqueous in nature throughout which the second monomer is emulsified. Monomers in either phase diffuse and polymerize rapidly at the interface.[44]

PREPARATION OF MICROSPHERES BY TRIPOLYPHOSPHATE

Chitosan solution of 2.5% wt. /vol concentration was prepared. Microspheres were formed by dropping the Bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic Stirrer) 5% or 10% wt. /vol TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, then they were air dried.[45,46]

PREPARATION OF MICROSPHERE BY EMULSIFICATION AND IONOTROPIC GELATION

Dispersed phase consisting of 40 ml of 2 % vol/vol aqueous acetic acid containing 2.5 % wt./vol polymer was added to the continuous phase of hexane (250 ml) and span 85 (0.5 % wt./vol) to form a w/o emulsion . After 20 minute of mechanical stirring, 15 ml of 1N sodium hydroxide solution was added at the rate of 5 ml per min at 15-minute intervals. Stirring speed of 2200 rpm was continue for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried.[47,48]

SPRAY DRYING

In spray drying 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 homogenisation. This dispersion is then atomised in a stream of hot air. The atomisation leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading to the formation of microsphere in a size range of 1-100 um. Micro particle are separated from the hot air by means of the cyclone separator while the trace of the solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic condition.[49]

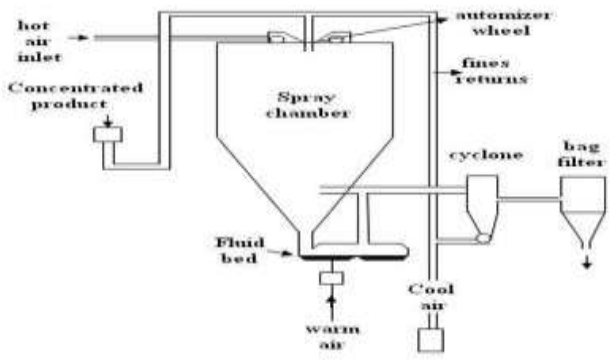

Figure 7: Spray Drying Method for Preparation of Microsphere

SOLVENT EVAPORATION

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 to core material mixture is dispersed in liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for 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 core materials may be either water soluble or insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous or non aqueous.[50]

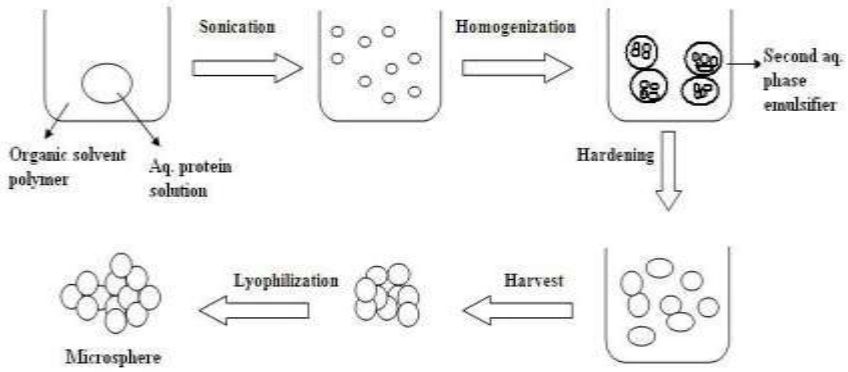

Figure 8: Solvent Evaporation Method For Preparation of Microsphere

WET INVERSION TECHNIQUE

Polymer solution of acetic acid was dropped into an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microsphere formed were allowed to stand for 1 hour and cross-linked with 5 % ethylene glycol diglysidyl ether. Microspheres were then washed and freeze dried. Changing the pH of coagulation medium could modify the pore structure of microsphere.[51]

PHASE INVERSION MICROENCAPSULATION

This is another method of preparation of microspheres which involves the addition of drug to a diluted polymeric solution (usually 1-5% w/v in methylene chloride). This mixture is then poured into an unstirred bath of strong non-solvent (petroleum ether) in a solvent to non-solvent ratio of 1:100, resulting in the spontaneous production of microspheres of specific size range which can then be filtered, washed with petroleum ether and dried with air. It is the

simplest and fast process of microencapsulation involving negligible loss of drug and polymer.[55,56]

COMPLEX COACERVATION

Microparticle can also prepared by complex coacervation. Sodium alginate, sodium cmc, and sodium polyacrylic acid can also be used for complex coacervation with chitosan to form microsphere. These micro particle are formed by interionic interaction between oppositely charged polymer solution and kcl and cacl2 solutions. The obtained capsules were hardened in the counter ion solution before washing and drying.[52,53]

HOT MELT MICROENCAPSULATION

The polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 um. The mixture is suspended in a non-miscible solvent (like silicon oil), continuously stirred, and heated to 5c 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 for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. Polyanhydrides. Microspheres with diameter of 1-100 um 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.[54]

Table 2 List of Marketed Formulation of Microsphere

Commercial name	Drug	company	Method of preparation	Indication	polymer	Delivery route
Vivitrol	Naltrexon	alkemes	Double emulsion(oil in water)	Alcohol dependence	-	i.m.
Risperidol consta	Risperidone	Janssen/alkemes	Double emulsion(oil in water)	Schizophrenia, bipolar I disorder	PLGA	i.m.
Sandostatin LAR	Octreotide	Novartis	Phase separation	Acromegaly	PLGA-glucose	i.v. or s.c.
Lupron depot Enantone depot Trenantone Enantone gyn	Leuprolide	TAP TAKEDA	Double emulsion(water in oil in water)	Prostate cancer/ Endometrios	PLGA OR PLA	i.m.
Nutropin depot	Somatropin	Genentech/alkemes	Cryogenic spray-drying	Growth deficiencies	PLGA	s.c.
Somatulin LA	Lanreotide	Ipsen-beafour	Phase-separation	Acromegaly	PLGA	i.m.
Suprecur MP	Buserelin	Sanofi-aventis	-	Endometriosis	PLGA	i.m
Trelstar depot Decapeptyl SR	Triptorelin	Pfizer ferring	Phase-separation	Prostate cancer	PLGA OR PLA	i.m.
Parlodel LAR	Bromocriptine	Novartis	Spray-drying	Parkinsonism	PLGA-Glu	s.c. or i.m.
Arestin	Minocyclin	orapharma	-	Periodontitis	PLGA	subgingival
Zoladex	Goserelin aceteate	I.C.I.	-	Prostate cancer	-	s.c.
Posilac	Recombinant Bovine separation	Monsanto	-	To increase milk production in cattle	-	i.m. or s.c.

CONCLUSION

The microsphere prepared by glutaraldehyde and thermal cross-linking showed good stability in HCl. Microsphere have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres has additional advantages such as efficient absorption, 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 drugs to the absorption site. Mucoadhesive microsphere 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.

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