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MICROSPHERES- A PROGNOSTICATES NOVELIZE DRUG DELIVERY SYSTEM

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Abstract

The requisite intention in the drug therapy besides disease is to accomplish the craved therapeutic assiduity of the drug in plasma or at the place of action and assert it for the intact continuance of treatment. A drug on being consumed in conventional dosage forms contribute to ineluctable variation in the drug assiduity preeminent to nether medication or overmedication and augmented frequency of dosage distribution also poor patient compliance. To denigrate drug abjection and deprivation, to preclude inauspicious fallout and to enhance drug bioavailability assorted drug deliverance and drug targeting systems are presently under development. Handling the cure of grievous disease stipulations has postulated the evolution of forward-looking thoughts to alter drug delivery techniques.

Drug targeting means deliverance of the drug-loaded system to the place of concern. Drug carrier systems embrace polymers, micelles, microcapsules, liposomes, and lipoproteins to name some. Distinct polymer bearer maintains dissimilar effects on drug delivery. Synthetic polymers are ordinarily non-biocompatible, non-biodegradable and extravagant. Polymers such as Eudragit RS100 and Eudragit RL100 are destitute of such problems. Eudragit is a biocompatible and nontoxic polymer with fantabulous film-forming potency. Being of cationic character, Eudragit RS100 and Eudragit RL100 are able to oppose with polyanions giving ascent to polyelectrolyte complexes. Hence Eudragit RS100 and Eudragit RL100 have transformed as an encouraging polymer for the formulation of microspheres/nanospheres and microcapsules. The proficiency employed to microencapsulate with Eudragit RS and Eudragit RL comprises solvent evaporation, ionotropic gelation, spray drying, emulsion phase separation, simple and complex coacervation. This review focuses on the preparation,

characterization of Eudragit RS100 and Eudragit RL100 microspheres and their purpose in modern drug delivery systems.

Key Words: Bio-compatible, ionotropic, nanospheres, microspheres, solvent evaporation.

Introduction

Drug delivery concenters on utmost bioavailability at peculiar sites in the body and over a revolution of time. Nanomedical advances to drug delivery centralize on the evolution of nanostructure devices alike the microcapsules microspheres, or nanospheres to meliorate the bioavailability of the drug and place it to the peculiar site of concern **[1]**. Nowadays, science and technology are liberating their utmost emphasis on the evolution of sustained-release pharmaceuticals. Different types of drug delivery systems for oral administration such as drug release rate-controlled delivery systems, time-controlled delivery systems, and site-specific delivery systems have been extensively developed **[1,2].** This matter persists to be the concenter of an enceinte deal of aid in both industrial and academic laboratories**.** There presently subsist multiple products in the market explicated for both oral and injectable routes of administration that claim sustained or controlled drug delivery. The potency of the drug delivery system is its efficiency to modify the pharmacokinetics and biodistribution of the drugs **[3]**. Nanotechnology seems to hold the capability to ameliorate drug delivery and drug targeting preeminent to augmented competency and decreased toxicity, which would result not only in a avid welfare to patients but also to pharmaceutical and drug delivery companies by producing new market opportunities **[4].** Drug delivery sometimes is targeted at crossing specific barriers such as the blood-brain barrier, in ordain to extend the drug concentration at the site of action to meliorate potency; or to obtain alternative and agreeable route of delivery for protein drugs that cannot be extradited through gastrointestinal tract owed to abjection**[5]**. A novel drug delivery system (NDDS) is a system that provides multiple drug delivery solutions such as:Topical Drug Delivery, Transmucosal Drug Delivery, Oral Drug Delivery Systems and Materials, Parenteral and Implant Drug Delivery Systems, Pulmonary and Nasal Drug Delivery, Transdermal and Delivery of Proteins and Peptides, Drug Delivery Pipelines, Drug Delivery Deals. The utility of lipid or polymer-based nanoparticles have demonstrated meliorate pharmacological and therapeutic actions and stimulate overall welfare in the novel drug delivery systems. In the innovation of controlled release dosage formulations selection

of polymer is of essential importance since it works as drug carrier **[6]**. Eudragit RS100 and Eudragit RL100 is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts make the polymers permeable.**[7]**Being biocompatible, possessing wrinkle free anti tacking features, Eudragit offers valuable advantages such as pH-dependent drug release, increase in drug effectiveness, good storage stability as well as unique drug release functionality. Microspheres are tiny orbicular particles, with diameters 1 μm to 1000 μm and are extensively employed as drug carriers for controlled release **[8]**. It is used to modify or retard the drug release. **[9]** Microspheres have the potential to deliver the drug in a controlled fashion **[10].** They are globular free streaming particles comprising of proteins or synthetic polymers which are biodegradable in nature. Microspheres (<10 μm) encourage their entry into lymph nodes and afford a high-level concentration of antigen over an extended time-period**.[11]**There are two types of microspheres; microcapsules and micromatrices, which are delineated as Microcapsules are those in which ensnared substance is clearly encircled by discrete capsule wall and micromatrices in which ensnared substance is spread throughout the matrix. Microspheres at times referred to as microparticles. The microparticulate delivery systems include mainly pellets, microcapsules, microspheres, lipospheres, emulsions, and multiple emulsions**.[12]**Microspheres can be fabricated from assorted natural and synthetic materials. Microspheres play a significant role to meliorate bioavailability of conventional drugs and denigrating side effects. **[13, 14, 15, 16, 17]**

Ideal Characteristics of Microspheres: [18, 19]

- The potency to integrate moderately mellow assiduity of the drug.
- The constancy of the formulation after synthesis with a clinically satisfactory shelf life.
- Controlled particle size and dispersibility in aqueous vehicles for injection.
- Exemption of participating reagent with a good control over a large time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

Advantages of Microspheres: [20]

- Particle size diminution for aggravating solubility of the poorly soluble drug.

- Provide continuant and extended therapeutic effect.
- Provide continuant drug assiduity in the blood thereby accessing patent compliance
- Diminish dose and toxicity.
- Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
- Decrease the dosing frequency and thereby ameliorate the patient compliance.
- Wagerer drug usage will meliorate the bioavailability and decrease the incidence or intensity of adverse effects.
- Microsphere morphology permits a controllable variance in abjection and drug release.
- Convert liquid to solid form and to disassemble the bitter taste.
- Protects the GIT from irritant effects of the drug.
- Biodegradable microspheres have the advantage over wide polymer implants in that they do not expect surgical procedures for implantation and remotion.
- Controlled release delivery biodegradable microspheres are used to restraint drug release rates thereby reducing toxic side effects, and eradicating the inconvenience of repeated injections.

Limitation: [21]

Some of the disadvantages were found to be as follows:

- The costs of the materials and processing of the controlled release formulation are substantially superior to those of standard preparations.
- The designate of the polymer matrix and its outcome on the environment.
- The designate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers.
- Reproducibility is up to a lesser extent.
- Process stipulations alike alteration in temperature, pH, solvent addition, and evaporation/agitation may regulate the stability of core particles to be encapsulated.
- The environmental encroachment of the abjection products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.

Novel Approaches of Microspheres Drug Delivery System

The word novel is searching something out of necessity. An ideal controlled drug delivery system is the one which renders the drug at a predetermined rate, locally or systemically, for a particular period of time. The first research preeminent to the evolution of microencapsulation procedures for pharmaceuticals was published by Bunge burg de Jong and Kass in 1931 and dealt with the formulation of gelatin spheres and the usage of gelatin coacervation process for coating. In the late 1930s, Green and co-workers of National cash register co. Dayton, Ohio, formulated the gelatin coacervation process. Since then various other coating materials and processes of application have been formulated by the pharmaceutical industry for the microsphere of medicines. The microsphere is a speedily expanding technology. As a process, it is a means of employing relatively lean coating to small particles of solid or droplets of liquids and dispersions.**[22]**Microspheres are defined as solid orbicular microscopic particles embracing dispersed drug in either solution or microcrystalline form. They are ranging in size from 1 to 1000 micrometer**[23].** They were first reported in 1959 by Sidney Fox, K. Harada, and J. Kendrick. Microspheres as a carrier for the drug are one such access which can be consumed in a sustained controlled release fashion. This access allows the precise delivery of a diminutive quantity of the potent drugs, decreased drug assiduity at the site other than the target site and the protection of the amenable compound before and after the dispensation and anterior to the site of action. Presently, they are used as bulking agents, embolic- or drug delivery particles, carrier materials for purification purposes in the biochemical sciences**[24]** and also to use as flow indicators.**[25]**Microspheres provides the means of converting liquids to solids, of altering colloidal and surface properties, of allowing environmental protection and of controlling the release characteristics or availability of coated materials.**[26]**

Therapeutical Agents Utilized for Microspheres Drug Delivery System

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 µm. Microsphere because of their size and shape offers a ball bearing effect. Recently, dosage forms that precisely control the release rates and targets to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems **[27].** 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. Several drugs which have been utilized in microspheres drug delivery system are enlisted below**. [28]**

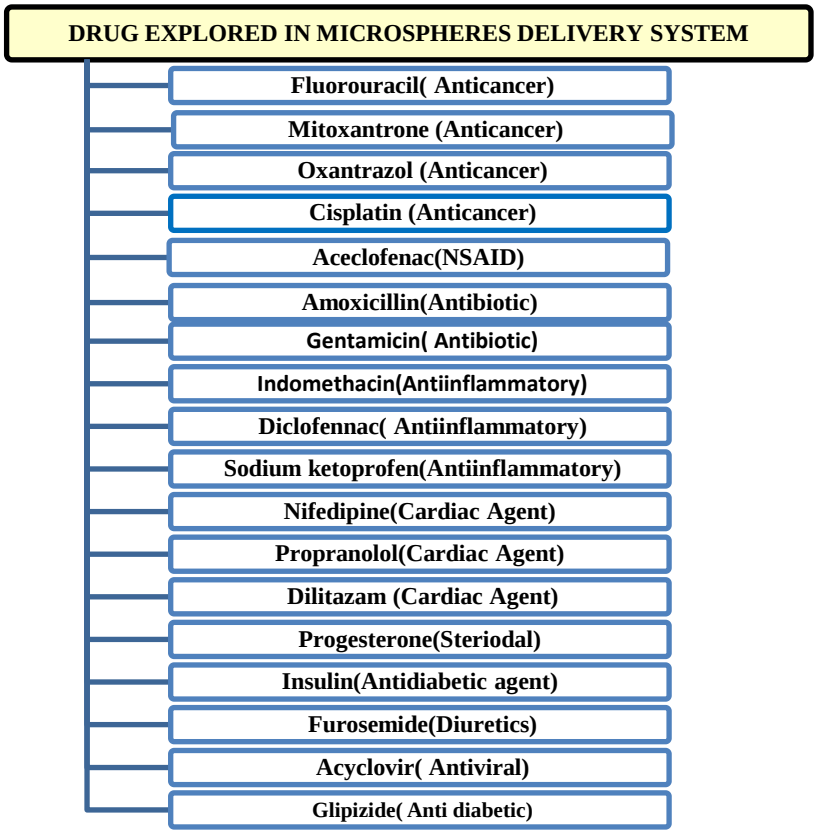


Fig. 1. Therapeutical agents utilized for microspheres drug delivery system.

Types of Microspheres:

- Bioadhesive microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Polymeric microspheres i) Biodegradable polymeric microspheres ii) Synthetic polymeric microspheres

1. Bioadhesive microspheres: [29, 30]

Adhesion can be defined as sticking of the 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 ocular, buccal, nasal, rectal etc. can be termed as bio-adhesion. These kinds of microspheres display an extended residence time at the site of application and cause intimate contact with the absorption site and produce better therapeutic action.

2. Magnetic microspheres: [31, 32]

This kind of delivery system is very much significant which localizes the drug to the disease site. In this larger quantity of freely circulating drug can be substituted by a smaller quantity of the magnetically targeted drug. Magnetic carriers acquire magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types of magnetic microspheres are:

A. Therapeutic magnetic microspheres used to deliver the chemotherapeutic agent to a liver tumor. Drugs like proteins and peptides can also be targeted through this system.

B. Diagnostic microspheres, 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.

3. Floating microspheres: [33, 34, 35]

In floating types, the bulk density is smaller than the gastric fluid and so remains buoyant in the stomach without poignant gastric emptying rate.

The drug is discharged slowly at the craved rate, and the system is found to be floating on gastric content and enhances gastric residence and boost fluctuation in plasma engrossment. Moreover, it also represses chances of dose dumping. It evolves elongated therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres.

4. Radioactive microspheres: [35, 36]

Radioembolization therapy microspheres sized 10-30 nm are of bigger than the diameter of the capillaries and gets broached in the first capillary bed when they come across. They are injected in the arteries that precede them to a tumor of interest so all these conditions radioactive microspheres render high radiation dose to the targeted areas without damaging the normal surrounding tissues. It dissents from drug delivery system, as radioactivity is not released from microspheres but acts from within a radioisotope typical distance and the dissimilar kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

5. Polymeric microspheres: [36]

The distinct types of polymeric microspheres can be classified as follows and they are Biodegradable polymeric microspheres and Synthetic polymeric microspheres.

Biodegradable polymeric microspheres: [37]

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers protract the residence time when contact with mucous membrane due to its eminent degree of swelling property with an aqueous medium, results in gel formation. Biodegradable polymers, particularly in the form of injectable microparticles, have been inspected comprehensively for their competence of releasing therapeutically helpful proteins in the controlled way **[38].** The rate and extent of drug release are controlled by the concentration of polymer and the release pattern in a sustained manner. The main disadvantage is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. However, they render a spacious range of application in microsphere-based treatment.

For example, Lactides and Glycolides and their copolymers, Poly alkyl cyanoacrylates, Polyanhydrides.

ii) Synthetic polymeric microspheres: [39]

Synthetic polymeric microspheres are extensively used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc. and proved to be safe and biocompatible but the main drawback of this kind of microspheres, are lean to migrate away from the injection site and lead to potential risk, embolism, and further organ damage.

For example Polymethyl methacrylate acrolein (PMMA), Glycidyl methacrylate, Epoxy polymers

Approaches for Formulation of Microspheres

- Spray Drying
- Solvent Evaporation
- Single emulsion technique
- Double emulsion technique
- Phase separation coacervation technique
- Spray drying and spray congealing
- Solvent extraction
- Quasi-emulsion solvent diffusion using

- Polymerization technique

Spray Drying: [40]

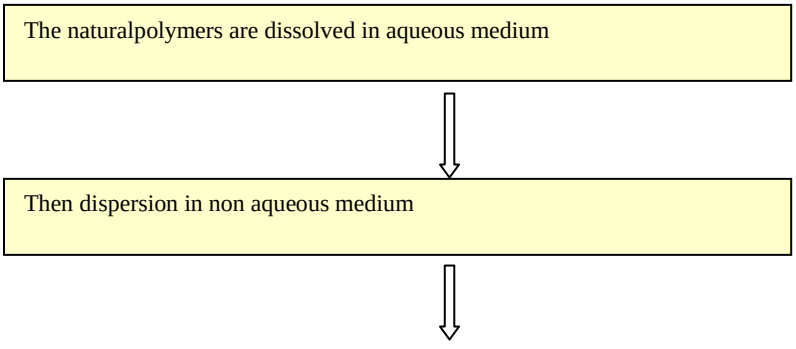
In Spray Drying technique, the polymer is first dissolved in an appropriate volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then spread in the polymer solution with eminent-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading to 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 trace of solvent is abstracted by vacuum drying. One of the major advantages of this process is the feasibility of operation under aseptic conditions.

Solvent Evaporation Method: [40, 41]

The microspheres prepared by a solvent evaporation method **[42]** according to this technique the drug is dissolved, in polymer which is antecedently dissolved in chloroform and the resulting solution on is added dropwise to aqueous phase containing 0.2% PVA as emulsifying agent and agitated at 500 rpm, then the drug and polymer solution transformed into a fine the droplet which solidifies into rigid microspheres and then collected by filtration, washed with demineralized water.

Single Emulsion Technique: [43] The microparticulate carriers of natural polymers i.e. those of carbohydrates and proteins carbohydrates are prepared by a single emulsion technique. The chemical cross-linking agents used are as follows:

- Glutaraldehyde
- Formaldehyde
- Diacid chloride etc.



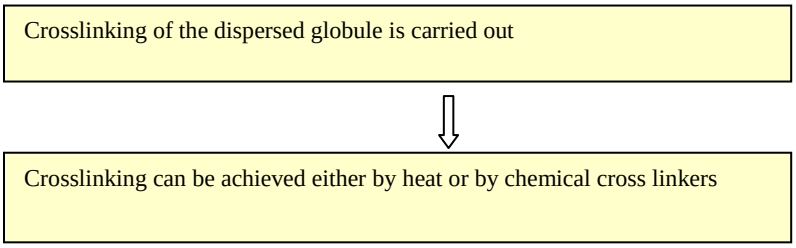


Fig. 1 Flowchart method of single emulsion method.

Double Emulsion Technique:

This method of microspheres preparation includes the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to aqueous soluble drugs, peptides, proteins, and the vaccines. In the double emulsion technique, the aqueous protein solution is dispersed in a lipophilic organic continuous phase. The protein solution may contain the active substances. The emulsification method uses an external oil phase and thereby may diminish the drug diffusion throughout the encapsulation process and develop the drug entrapment effectiveness **[44].** The continuous phase generally consists of the polymer solution that eventually encapsulates of the protein containing in dispersed aqueous phase. The primary emulsion is subjected to the homogenization or the sonication before addition to the aqueous solution of the polyvinyl alcohol. This results in the formation of a double emulsion. The emulsion is then subjected to removal either by solvent evaporation or by solvent extraction method.**[45]**

Phase Separation Coacervation technique:

This method is based on the principle of decreasing the solubility of the polymer in the nonaqueous phase to affect the formation of the polymer-rich phase called the coacervates. Here, the drug particles are dispersed in the solution of the polymer and an incompatible polymer is then added to the system which makes the first polymer to separate and engulfment of the drug particles. Addition of organic results in the solidification of the polymer. Polylactic acid (PLA) microspheres have been manufactured by this method by using butadiene as an incompatible polymer. The process variables are very useful because the rate of achieving the coacervates denotes the distribution of the polymer film, the size of particles and agglomeration of the formed particles. The agglomeration must be avoided by continuous stirring of the suspension using an optimum speed stirrer because as the process of microspheres formation starts the formed polymerize globules start to stick and form the

agglomerates. So the process variables are critical as they control the kinetics of the particles because there is no defined state of equilibrium attainment. **[46, 47]**

Spray Drying and Spray Congealing:

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 to the formation of microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclones separator while the trace of solvent is removed by vacuum drying.One of the major advantages of this process is the feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethyl thiadiazole 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. **[46, 47]**

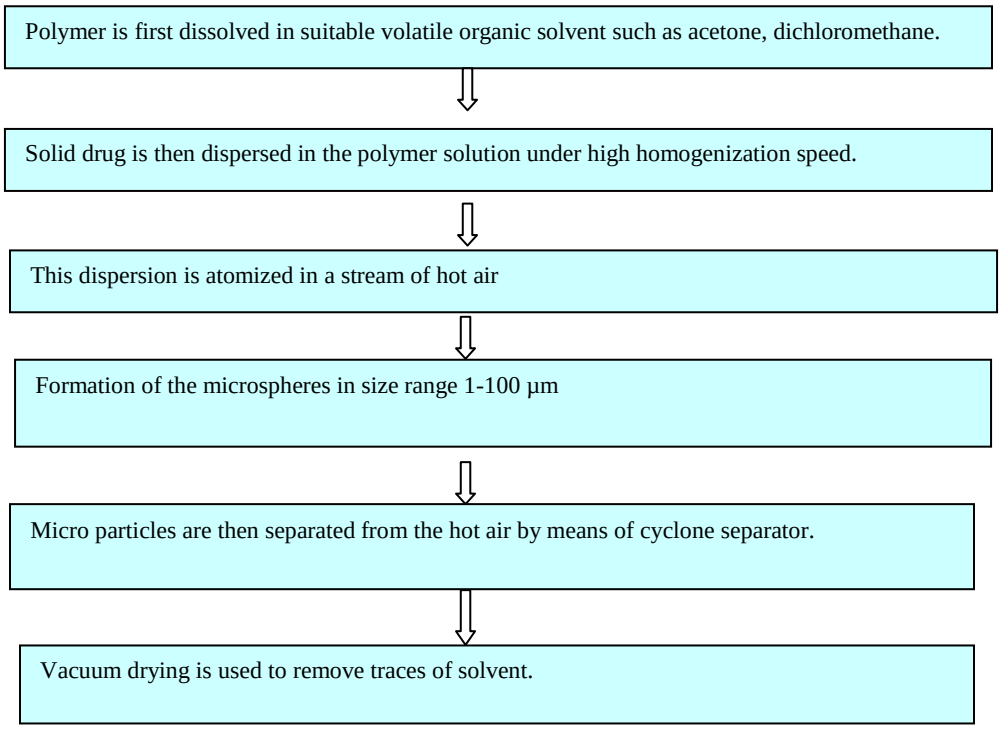


Fig 2. Flowchart method of spray drying and spray congealing method.

Solvent extraction: [48, 49, 50]

A solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the or nonaqueous solvent. This method implies water-miscible organic solvents as isopropanol. The organic phase can be abstracted by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, the ratio of emulsion volume to the water and solubility profile of polymer.

Quasi emulsion solvent diffusion: [51, 52]

A 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 consists of drug, ethanol, and polymer.

The concentration of polymer is 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 the 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.

Polymerization techniques: [53, 54, 55, 56]

The polymerization techniques conventionally used for developing the microspheres are mainly classified as:

Normal polymerization

Interfacial polymerization.

Both are carried out in the liquid phase.

I.Normal polymerization:

It is carried out by using different techniques as bulk, suspension, precipitation, emulsion, and micellar polymerization methods. In bulk, a monomer or a combination of monomers along with the initiator or catalyst is normally heated to initiate polymerization. The polymer so prevailed may be molded as microspheres. Drug loading may be performed during the polymerization process. Suspension polymerization also referred as a

bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also comprise an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence of an initiator in the aqueous phase, which afterward permeates to the surface of micelles. Bulk polymerization has merits of formation of pure polymers.

II. Interfacial polymerization:

This involves the reaction of various monomers at the interface betwixt the two immiscible liquids to form a film of polymer that basically envelops the dispersed phase.

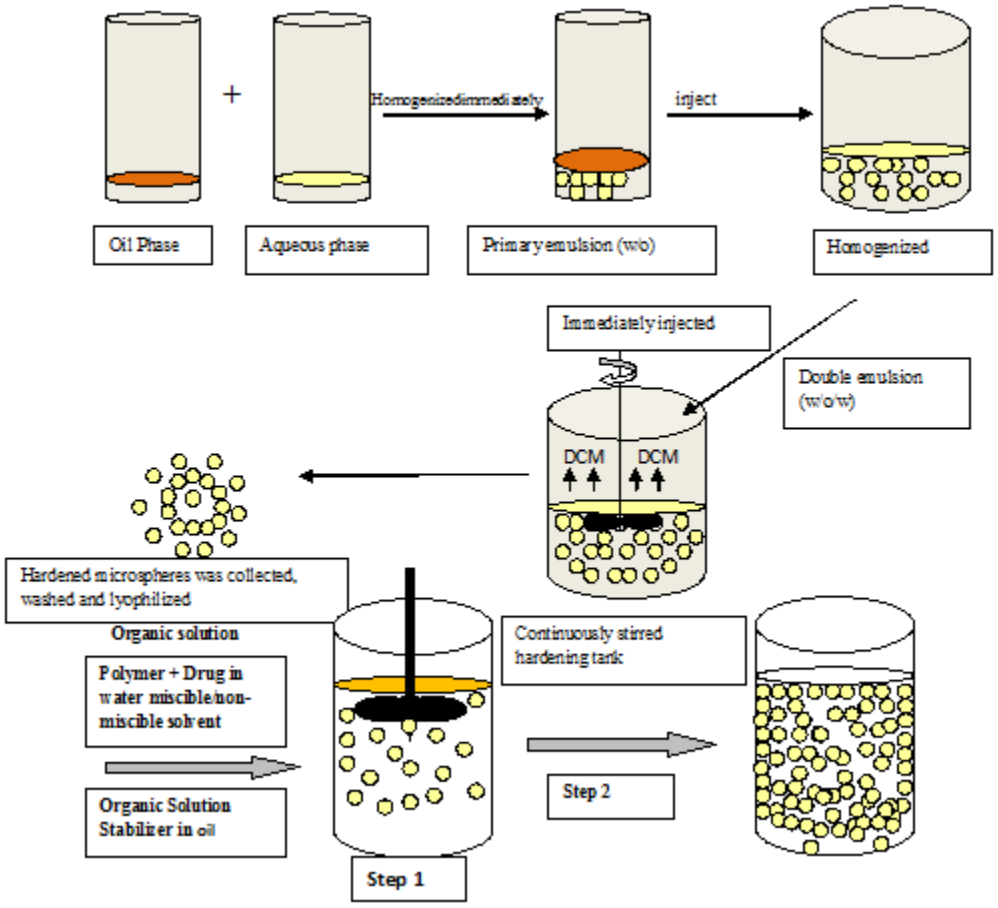


Fig 4. Solvent Evaporation Method.

DRUG RELEASE MECHANISM OF MICROSPHERES DELIVERY SYSTEM

The release mechanism of microsphere follows first-order kinetics having dissolution and diffusion are two main mechanisms for drug release. The outer layer of polymer is first dissolved, and the dissolution media will diffuse the polymer matrix makes the entrapped drug to release in the matrix. The rate of drug release depends

on the type of matrix used and drug/polymer concentration. Most of the drug delivery through micro particles inhibits a matrix type internal solid dispersion morphology structure. The drug may be insoluble in the polymeric matrix and the drugs are released by erosion. Initially, water diffuses into the matrix dissolving the resulting adjacent to the surface of the device. The resulting osmotic pressure is relieved by forming a channel to the surface releasing a defined amount of drug in the initial drug burst. **[57]**

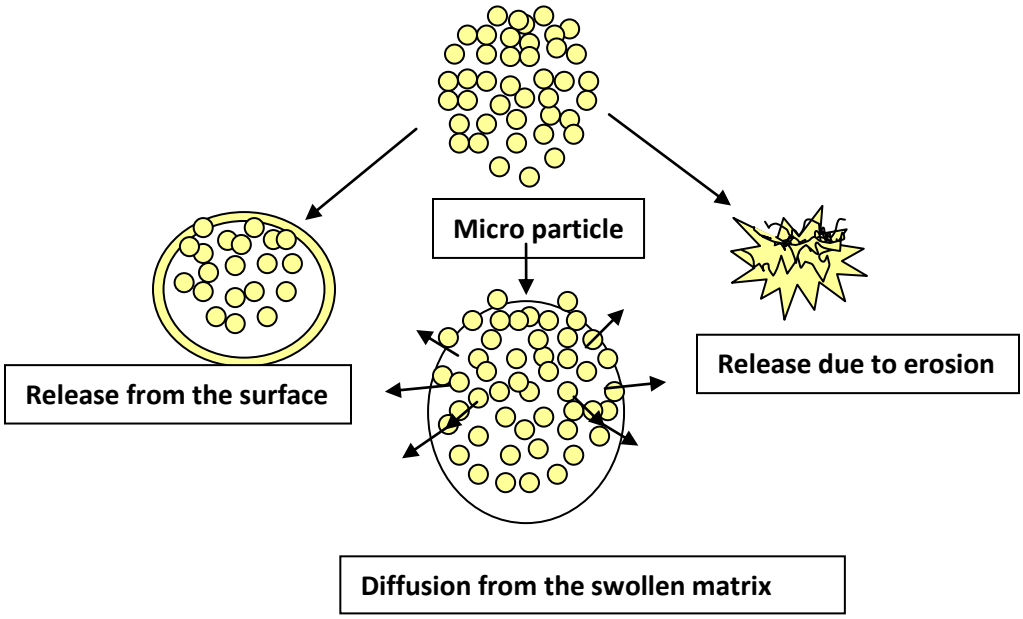


Fig 5. Drug release Mechanism of Microspheres.

Mechanism of drug release includes: [58]

- Degradation controlled monolithic system
- Diffusion-controlled monolithic system
- Diffusion-controlled reservoir system

- **Degradation controlled monolithic system :**

  In this system, the drug is uniformly dispersed in the polymer matrix and rate of diffusion depends upon degradation of the matrix. Generally, the rate of diffusion is slow as compared with degradation of the matrix. The formula for calculating release of the sphere is governed by the following equation:

  $Mt/ M_{\infty} = 1- [1-t/t_{\infty})] ^{3}$

  Where Mt is the amount of drug released at time t, Mω is an amount at time tω for total erosion.

- **Diffusion-controlled monolithic system:**

  In this system, the drug is dispersed in a polymer matrix. With the degradation of the polymer matrix, the drug starts diffusing out. Here release rate is highly affected by matrix degradation.

- **Diffusion-controlled reservoir system :**

  In this system, a controlling membrane is present around the drug through which drug starts diffusing out. Here, the release rate is not affected by matrix degradation. After complete Ω diffusion membrane gets eroded. Fig. 5 shows the diffusion of drug through controlling membrane.

APPLICATIONS OF MICROSPHERES DRUG DELIVERY SYSTEM

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers that are used mostly for oral and recently for topical administration. It offers the formulator a range of alternatives to develop drug and cosmetic products. Microspheres are designed to deliver an active pharmaceutical ingredient efficiently at minimum dose and also to enhance stability, reduce side effects and modify drug release. The system can have the following applications as depicted in [Table 1.]**[59]**

Table-1. Various applications of microspheres drug delivery system.

S.no	Applications	Advantages
1)	Ophthalmic Drug Delivery	Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Eg. Chitosan, Alginate, Gelatin.
2)	Oral drug delivery	The ability of microspheres containing a polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications.

		Eg. Chitosan, Gelatin.
3)	Gene delivery	Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg. Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.
4)	Nasal drug delivery	Polymer-based drug delivery systems, such as microspheres, liposomes, and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Eg. Starch, Dextran, Albumin, Chitosan+Gelatin.
5)	Intratumoral and local drug delivery	In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. A mixture of the drug has promising potential for use in controlled delivery in the oral cavity. Eg. Gelatin, PLGA, Chitosan, and PCL.
6)	Buccal drug delivery	The polymer is an excellent polymer to be used for buccal delivery because it has much/ bioadhesive properties and can act as an absorption enhancer. Chitosan, Sodium Alginate.
7)	Gastrointestinal drug delivery	Polymer granules having internal cavities prepared by deacidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug. Eg. Eudragit, Ethyl cellulose+ Carbopol BSA, Gelatin.
8)	Transdermal drug delivery	The polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Eg. Chitosan, Alginate, PLGA.

9)	Colonic drug delivery	The polymer has been used for the specific delivery of insulin to the colon. Eg. Chitosan.
10)	Vaginal drug delivery	Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Eg. Chitosan, Gelatin, PLGA.
11)	Targeting by using microparticulate carriers	Pellets are prepared with the polymer by using the extrusion/ spheronization technology. Eg. Chitosan, Microcrystalline cellulose.

Evaluation of Microspheres: [60, 61, 62, 63, 64]

- **Particle size and shape**

  The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

- **Electron spectroscopy for chemical analysis:**

  The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

- **Density determination:**

  The density of the microspheres can be measured by using a multi-volume pycnometer.

- **Isoelectric point:** The microelectrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.

- **The angle of contact:**

  The angle of contact is measured to determine the wetting property of a microparticulate carrier.

- **In vitro methods:**

  Release studies for a different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP /BP).

- **Drug entrapment efficiency:**

  Drug entrapment efficiency can be calculated using the following equation,

  % Entrapment = Actual content/Theoretical content x 100.

- **Swelling index:**

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

  Swelling index= (mass of swollen microspheres – a mass of dry microspheres/mass of dried microspheres) 100.

Marketed Formulations Using the Microspheres Drug Delivery System

Microspheres approaches are perfect for skin and personal care products. Marketed formulation based on Microspheres drug delivery approaches mentioned [Table 2.]**[65]**

Table-2. Marketed formulations based on microspheres drug delivery system.

S.no	Drug	Commercial Name	Company	Technology
1)	Risperidone	RISPERDAL® CONSTA®	Janssen®/Alkermes, Inc.	Double emulsion (oil in water)
2)	Naltrexone	Vivitrol®	Alkermes	Double emulsion (oil in water)
3)	Leuprolide	Lupron Depot® Enantone Depot® Trenantone® EnantoneGyn	TAP Takeda Takeda Takeda	Double emulsion (water in oil in water)
4)	Octreotide	Sandostatin® LAR	Novartis	Phase separation
5)	Somatropin	Nutropin® Depota	Genentech/Alkermes	AlkermesProLease® Technology(Cryogenicspraydrying)
6)	Triptorelin	Trelstar™depotDecapeptyl® SR	Pfizer Ferring	Phase separation
7)	Buserelin	Suprecur® MP	Sanofi-Aventis	N/A

8)	Lanreotide	Somatuline® LA	Ipsen-Beafour	Phase separation
9)	Bromocriptine	Parlodel LAR ™	Novartis	Spray dry
10)	Minocyclin e	Arestin®	Orapharma	N/A

Patents Filed Related To Microspheres Drug Delivery System

Table-3. Patents filed related to microspheres approaches [66]

S.no	Patent No.	Contents / Drug Used
1)	US8101209B2(2012)	The invention relates to the microparticulate oral galenical form for the delayed and controlled release of pharmaceutical active principles. In this release of the active principle is governed by a dual release triggering mechanism that is 'time triggering' and 'pH triggering'.
2)	US8092835B1(2012)	The invention is directed at materials and methods for forming injectable PGCLM microspheres which can be used to load drugs and other biologically active agents for controlled release in the body.
3)	WO098404A1(2011)	The invention relates to the synthetic microspheres based on malondialdehyde, its use for diagnostic and pharmaceutical purposes, and specifically its use in a method of selecting antagonists of oxidative stress disease from a repertoire of agents possibly binding to oxidation epitopes.
4)	US0244034A1(2011)	The invention disclosed a controlled release dosage form comprising the effective amount of acyclovir that would release in about 12 hours not more than about 90% of the said amount in the simulated gastric fluid in a first-order rate.
5)	US7374782B2(2008)	The invention relates to the production of protein microspheres by contacting an aq. a solution of macromolecules & a polymer and then heating the solution. These microspheres are useful for preparing pharmaceuticals of

		defined dimensions which can be delivered to a patient by inhalation therapy.
6)	US0207213A1(2007)	The invention is directed to the preparation of injectable drug-laden microspheres from unsaturated functionalized polymeric alcohol esters of polyester by double emulsion method. Microspheres formed thereby are used for controlled release of the drug or biologically active agent in the body
7)	US0264326A1(2007)	The invention relates to the solid oral microparticulate analgesic medicinal formulation which allows the prevention of misuse to certain analgesics and the control of fluctuation in the plasma concentration.
8)	US6998074B1(2006)	The invention relates to a method for manufacturing uniformly sized polymer microspheres using ink jet technology.
9)	US6849271B2(2005)	The invention relates to the development of microspheres that enhance the amount of drug absorbed by a subject across body membranes.
10)	US0147687A1(2005)	The invention relates to the composition of small spherical particles of an active agent prepared by controlled phase separation.
11)	US0043076A1(2004)	The invention relates to the prolonged release microspheres for injection delivery of proteins which are free of any trace of solvent.
12)	US0146459A1(2002)	The invention relates to microspheres containing condensed polyanionic bioactive agents such as DNA, which can be used in gene therapy and also sustaining the delivery for an extended period of time.
13)	US6395302B1(2002)	The invention relates to a method for the preparation of microspheres which can be used as controlled release system for the delivery of active ingredients.
14)	US6264988B1(2001)	The invention provides a composition of fibrinogen-coated cross-linked albumin microspheres which are useful for reducing bleeding time when administered to a human or animal.
15)	US6207197B1(2001)	The invention provides microsphere composition for the controlled release of

		an active agent in the stomach environment over a prolonged period of time in order to provide local treatment of disease of the stomach.
16)	US6036976(2000)	The invention disclosed a method of producing sustained release microspheres which comprises subjecting a w/o/w emulsion or o/w emulsion to an in-water drying method.
17)	CN 201110142359	Ketoprofen
18)	CN 201110313846	Paclitaxel
19)	CN 201210025085	5-fluorouracil
20)	US08455091	Ganciclovir
21)	EP19980924438	Cimetidine
22)	EP20070808011	Risperidone
23)	CA 2217462	Cyclosporin
24)	CA 2579533	Irinotecan
25)	DE1999609777	Levonorgesterel
26)	DE1994632867	Doxorubicin

Recent Advancements In Microspheres Drug Delivery System [67]

1) Important utilizations of chitosan polymer Cholesterol-lowering effects: Chitosan and cellulose were used as examples of fibers with eminent, intermediate and low bile acid-binding capacities, respectively. The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol diet for 3 weeks augmented about 2-fold to 4·3mM and inclusion of any of these fibers at 7·5% of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibers. The three kinds of fibers showed similar hypocholesterolaemic activity; however, cholesterol depletion of liver tissue was greatest with cholestyramine. The mechanisms underlying the cholesterol-lowering effect of cholestyramine were;

1. Decreased cholesterol (food) intake,

2. Decreased cholesterol absorption efficiency, and

3. Increased fecal bile acid and cholesterol excretion.

The latter effects can be attributed to the high bile acid binding capacity of cholestyramine. In contrast, incorporation of chitosan or cellulose in the diet decreased cholesterol (food) intake but did not influence either intestinal cholesterol absorption or fecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol lowering.

2) Increase Stability of Drug: Chitosan polymer is used to augment the stability of the drug in which the drug is complexed with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no.16 and make granules is completely stable in different condition.

3) Orthopedic Patients: Chitosan is a biopolymer that exhibits osteoconductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive coating to improve Osseointegration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration.

4) Cosmetics industry:

Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantial, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-coloring Composition, Hairtoning Composition, Skin Cream, Hair treatment Composition, Gel-form.

5) Chitosan as Permeation Enhancer:

It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number ofstudies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability.

Future Prospects of Microspheres Drug Delivery System [67]

Microspheres drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as it has unique properties like enhanced product performance and elegance, extended release, improved drug release profile, reduced irritation, improved physical, chemical, and thermal stability which makes it flexible to develop novel product forms. The real challenge in future is the development of the delivery system for the topical delivery by varying ratio of polymers. The use of bioerodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material. As these porous systems have also been studied for the drug delivery through pulmonary route which shows that this system can show effective drug release even in the scarce of the dissolution fluid thus colon is an effective site for targeting for drug release. These carriers also require to be developed for alternative drug administration routes like the parenteral and pulmonary route. These particles can also be used as the cell culture media and thus can also be employed for stem cell culture and cellular regeneration in the body. Due to their elegance, these carrier systems have also found their application in cosmetics. These developments enabled researchers to utilize them variably. Future challenges microspheres look bright particularly in the area of the medicinal field because of its wide spectrum of application in molecular biology, eg, the microsphere-based genotyping platform is used to detect six single nucleotide polymorphism, yttrium-90 microspheres are used to prevent a tumour after liver transplantation and it's an advanced way in the delivery of vaccines and proteins**.**

References

1. Mitra, A., & Dey, B. (2011). Chitosan microspheres in novel drug delivery systems. *Indian journal of pharmaceutical sciences*, *73*(4), 355.
2. Charman, W. N., Chan, H. K., Finnin, B. C., & Charman, S. A. (1999). Drug delivery: a key factor in realizing the full therapeutic potential of drugs. *Drug Development Research*, *46*(3-4), 316-327.
3. Yadav, A. V., & Yadav, V. B. (2010). Clarithromycin Floating Microspheres with Calcium Silicate by Using Emulsion Solvent Diffusion System (ESDS). *Research Journal of Pharmacy and Technology*, *3*(3), 784-791.

4. Kopeček, J. (2003). Smart and genetically engineered biomaterials and drug delivery systems. *European Journal of Pharmaceutical Sciences*, *20*(1), 1-16.
5. Agnihotri, S. A., Mallikarjuna, N. N., & Aminabhavi, T. M. (2004). Recent advances in chitosan-based micro-and nanoparticles in drug delivery. *Journal of controlled release*, *100*(1), 5-28.
6. Soppimath, K. S., Aminabhavi, T. M., Kulkarni, A. R., & Rudzinski, W. E. (2001). Biodegradable polymeric nanoparticles as drug delivery devices. *Journal of controlled release*, *70*(1-2), 1-20.
7. Mitra, A., & Dey, B. (2011). Chitosan microspheres in novel drug delivery systems. *Indian journal of pharmaceutical sciences*, *73*(4), 355.
8. Sonje, A., & Chandra, A. (2013). Comprehensive review on Eudragit polymers. *Int Res J Pharm*, *4*(4), 71-74.
9. Radhika, P. R., Luqman, M., & Borkhataria, C. H. (2014). Preparation and evaluation of delayed release aceclofenac microspheres. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*, *2*(4).
10. Bhangale, P. N., Mahajan, H. S., & Wagh, R. D. (2010). Formulation and Development of Sustained Release Microspheres of Metformin Hydrochloride. *Research Journal of Pharmacy and Technology*, *3*(1), 267-271.
11. Rout, P. K., & Nayak, B. S. (2009). Formulation design, preparation of losartan potassium microspheres by solvent evaporation method and it's in vitro characterization. *Archives of Pharmaceutical Sciences and Research*, *1*(1), 166-170.
12. Kalaivani, M., Pulikottil, M. J., Mary, B. M., Sakthivel, R., & Rajasekaran, A. (2010). Preparation and Characterisation of Alginate Coated Chitosan Microspheres for Bacterial Vaccines. *Research Journal of Pharmacy and Technology*, *3*(2), 503-506.
13. KL, S. (2010). Preparation and In-Vitro evaluation of Abacavir Sulphate loaded microspheres cross-linked by different concentrations of glutaraldehyde. *Research Journal of Pharmacy and Technology*, *3*(4), 1128-1131.
14. Jamini, M., & Rawat, S. (2013). A review on microsphere. *Res. j. pharm. boil. chem. sci*, *4*(1), 1223-33.

15. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., & Modi, D. (2011). Microsphere as a novel drug delivery. *International Journal of Pharmacy & Life Sciences*, *2*(8).
16. Kadam, N. R., & Suvarna, V. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, *5*(47), 13.
17. Prasanth, V. V., Moy, A. C., Mathew, S. T., & Mathapan, R. (2011). Microspheres-an overview. *International journal of research in pharmaceutical and biomedical sciences*, *2*(2), 332-338.
18. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system–A review. *Journal of Global Trends in Pharmaceutical Science*, *5*(3), 1961-1972.
19. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system–A review. *Journal of Global Trends in Pharmaceutical Science*, *5*(3), 1961-1972.
20. Mohan, M. E. N. E. S. H. W. A. R. I., Sujitha, H. A. Z. A. R. I., Rao, M., Ashok, M., & Kumar, A. B. (2014). A brief review on mucoadhesive microspheres. *IJRRPAS*, *4*(1), 975-86.
21. Mohan, M. E. N. E. S. H. W. A. R. I., Sujitha, H. A. Z. A. R. I., Rao, M., Ashok, M., & Kumar, A. B. (2014). A brief review on mucoadhesive microspheres. *IJRRPAS*, *4*(1), 975-86.
22. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system–A review. *Journal of Global Trends in Pharmaceutical Science*, *5*(3), 1961-1972.
23. Lachman, L., & Howden, C. W. (2000). Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. *The American journal of gastroenterology*, *95*(1), 57.
24. Freiberg, S., & Zhu, X. X. (2004). Polymer microspheres for controlled drug release. *International journal of pharmaceutics*, *282*(1-2), 1-18.
25. Cao, M., Li, Z., Wang, J., Ge, W., Yue, T., Li, R. ... & William, W. Y. (2012). Food related applications of magnetic iron oxide nanoparticles: enzyme immobilization, protein purification, and food analysis. *Trends in Food Science & Technology*, *27*(1), 47-56.
26. Chilian, W. M., Eastham, C. L., Layne, S. M., & Marcus, M. L. (1988). Small vessel phenomena in the coronary microcirculation: phasic intramyocardial perfusion and coronary microvascular dynamics. *Progress in cardiovascular diseases*, *31*(1), 17-38.

27. Chien, Y. W., Chien, T. Y., & Huang, Y. C. (1990). *U.S. Patent No. 4,906,169*. Washington, DC: U.S. Patent and Trademark Office.
28. Sivakumar, R., Ganesan, V., Viyas, M., Rajendran, N. N., & Kommala, M. (2011). Metronidazole Encapsulation within Chitosan Coated Eudragit RL Microsphers for Site Specific Delivery. *Research Journal of Pharmacy and Technology*, *4*(6), 993-996.
29. Varde, N. K., & Pack, D. W. (2004). Microspheres for controlled release drug delivery. *Expert Opinion on Biological Therapy*, *4*(1), 35-51.
30. Kumar, A., Jha, S., Rawal, R., Chauhan, P. S., & Maurya, S. D. (2013). Mucoadhesive microspheres for novel drug delivery system: a review. *Am. J. Pharm Tech Res*, *3*(4), 197-213.
31. Thummar, A. V., Kyada, C. R., Kalyanvat, R., & Shreevastva, B. (2013). A review on mucoadhesive microspheres as a novel drug delivery system. *International Journal for Pharmaceutical Research Scholars*, *2*(2), 188-200.
32. Mukherjee, S., & Bandyopadhyay, P. (2012). Magnetic microspheres: a latest approach in novel drug delivery system. *J. Pharm. Sci. Innov*, *26*, 21-25.
33. Batra, D., Kakar, S., Singh, R., & Nautiyal, U. (2012). Magnetic microspheres as a targeted drug delivery system: An overview. *Journal of Drug Delivery Research*, *1*(3), 10-17.
34. Dutta, P., Sruti, J., Patra, C. N., & Rao, M. B. (2011). Floating microspheres: recent trends in the development of gastroretentive floating drug delivery system. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *4*(1), 1296-1306.
35. Mukund, J. Y., Kantilal, B. R., & Sudhakar, R. N. (2012). Floating microspheres: a review. *Brazilian Journal of Pharmaceutical Sciences*, *48*(1), 17-30.
36. Kawatra, M., Jain, U., & Ramana, J. (2012). Recent advances in floating microspheres as gastro-retentive drug delivery system: A review. *Int J Recent Adv Pharm Res*, *2*(3), 5-23.
37. Ramteke, K. H., Jadhav, V. B., & Dhole, S. N. (2012). Microspheres: as carrieres used for novel drug delivery system. *IOSRPHR*, *2*(4), 44-48.

38. Dupinder, K., Seema, S., Gurpreet, S., & Rana, A. C. (2012). Biodegradable microspheres: A review. *IRJP*, *3*(12), 23-27.
39. Saravanakumar, A., Minz, S., Pradhan, M., Sure, P., Chandu, A. N., Mishra, U., & Sivakumar, T. (2008). Polylactic acid microspheres as a potential vaccine delivery system for the tetanus toxoid: Preparation and in vitro dissolution study. *Research Journal of Pharmacy and Technology*, *1*(4), 453-459.
40. Virmani, T., & Gupta, J. PHARMACEUTICAL APPLICATION OF MICROSPHERES: AN APPROACH FOR THE TREATMENT OF VARIOUS DISEASES.
41. Ramteke, K. H., Jadhav, V. B., & Dhole, S. N. (2012). Microspheres: as carrieres used for novel drug delivery system. *IOSRPHR*, *2*(4), 44-48.
42. Patel, B., Modi, V., Patel, K., & Patel, M. (2012). Preparation and evaluation of ethyl cellulose microspheres prepared by emulsification-solvent evaporation method. *International Journal for Research in Management and Pharmacy*, *1*(1), 82-91.
43. Venkateswaramurthy, N., Sambathkumar, R., Vijayabaskaran, M., & Perumal, P. (2011). Preparation and Evaluation of Mucoadhesive Microspheres Containing Heparin for Antiulcer Therapy. *Research Journal of Pharmacy and Technology*, *4*(2), 268-270.
44. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., & Modi, D. (2011). Microsphere as a novel drug delivery. *International Journal of Pharmacy & Life Sciences*, *2*(8).
45. Vishnu, P., & Kishore, V. S. (2011). Design and Development of Mucoadhesive Microspheres of Propranolol Hydrochloride. *Research Journal of Pharmacy and Technology*, *4*(1), 92-97.
46. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., & Modi, D. (2011). Microsphere as a novel drug delivery. *International Journal of Pharmacy & Life Sciences*, *2*(8).
47. Bansal, H., Kaur, S. P., & Gupta, A. K. (2011). Microspheres: methods of preparation and applications: A comparative study. *Int J Pharm Sci Rev Res*, *10*(1), 69-78.
48. Alagusundaram, M., Chetty, M. S., Umashankari, K., Badarinath, A. V., Lavanya, C., & Ramkanth, S. (2009). Microspheres as a novel drug delivery system-a review. *Int J Chem Tech Res*, *1*(3), 526-534.

49. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., & Modi, D. (2011). Microsphere as a novel drug delivery. *International Journal of Pharmacy & Life Sciences*, *2*(8).
50. Bansal, H., Kaur, S. P., & Gupta, A. K. (2011). Microspheres: methods of preparation and applications: A comparative study. *Int J Pharm Sci Rev Res*, *10*(1), 69-78.
51. Alagusundaram, M., Chetty, M. S., Umashankari, K., Badarinath, A. V., Lavanya, C., & Ramkanth, S. (2009). Microspheres as a novel drug delivery system-a review. *Int J Chem Tech Res*, *1*(3), 526-534.
52. Sahil, K., Akanksha, M., Premjeet, S., Bilandi, A., & Kapoor, B. (2011). Microsphere: a review. *Int. J. Res. Pharm. Chem*, *1*(4), 1184-98.
53. Pavan Kumar, B., Sarath Chandiran, I., Bhavya, B., & Sindhuri, M. (2011). Microparticulate drug delivery system: a review. *Indian J Pharm Sci Res*, *1*(1), 19-37.
54. Sahil, K., Akanksha, M., Premjeet, S., Bilandi, A., & Kapoor, B. (2011). Microsphere: a review. *Int. J. Res. Pharm. Chem*, *1*(4), 1184-98.
55. Pavan Kumar, B., Sarath Chandiran, I., Bhavya, B., & Sindhuri, M. (2011). Microparticulate drug delivery system: a review. *Indian J Pharm Sci Res*, *1*(1), 19-37.
56. Ramteke, K. H., Jadhav, V. B., & Dhole, S. N. (2012). Microspheres: as carrieres used for novel drug delivery system. *IOSRPHR*, *2*(4), 44-48.
57. Patel, N. R., Patel, D. A., Bharadia, P. D., Pandya, V., & Modi, D. (2011). Microsphere as a novel drug delivery. *International Journal of Pharmacy & Life Sciences*, *2*(8).
58. Liu, C., Desai, K. G. H., Tang, X., & Chen, X. (2006). Drug release kinetics of spray-dried chitosan microspheres. *Drying Technology*, *24*(6), 769-776.
59. Liu, C., Desai, K. G. H., Tang, X., & Chen, X. (2006). Drug release kinetics of spray-dried chitosan microspheres. *Drying Technology*, *24*(6), 769-776.
60. Sahil, K., Akanksha, M., Premjeet, S., Bilandi, A., & Kapoor, B. (2011). Microsphere: a review. *Int. J. Res. Pharm. Chem*, *1*(4), 1184-98.
61. Kadam, N. R., & Suvarna, V. (2015). Microsphere: A Brief Review. *Asian Journal of Biomedical and Pharmaceutical Sciences*, *5*(47), 13.

62. Sahil, K., Akanksha, M., Premjeet, S., Bilandi, A., & Kapoor, B. (2011). Microsphere: a review. *Int. J. Res. Pharm. Chem*, *1*(4), 1184-98.

63. Pavan Kumar, B., Sarath Chandiran, I., Bhavya, B., & Sindhuri, M. (2011). Microparticulate drug delivery system: a review. *Indian J Pharm Sci Res*, *1*(1), 19-37.

64. Prajapati, S. K., & Jain, C. P. (2010). Variables influencing the drug entrapment efficiency of microspheres: A pharmaceutical review. *Der Pharmacia Lettre*, *2*(5), 102-116.

65. Parmar, H., Bakliwal, S., Gujarathi, N., Rane, B., & Pawar, S. (2010). Different methods of formulation and evaluation of mucoadhesive microsphere.

66. Midha, K., Nagpal, M., & Arora, S. (2015). MICROSPHERES: A RECENT UPDATE.

67. Lee, H. Y., Kim, J. S., Shin, E. H., Kim, S. K., Soel, E. Y., Baek, M. J., ... & Choi, H. I. (2007). *U.S. Patent Application No. 11/511,951*.

68. Prasad, B. S. G., Gupta, V. R. M., Devanna, N., & Jayasurya, K. (2014). Microspheres as drug delivery system–A review. *Journal of Global Trends in Pharmaceutical Science*, *5*(3), 1961-1972.

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