

A BRIEF REVIEW ON MICROSPHERES

Mr. Tejas Gondhavne¹, Adinath Sangale², Dr. Megha Salve³

¹Shivajirao Pawar College of Pharmacy, Pachegoan, Maharashtra, India.

^{2,3}Department of Pharmacy, Maharashtra, India.

DOI: <https://www.doi.org/10.58257/IJPREMS36434>

ABSTRACT

Microspheres are one of the cutting-edge drug delivery methods that effectively replace conventional or immediate-release single-unit dosage forms. Solid particles with a diameter between 1 and 1000 μm are called microspheres. Different types of microspheres are described. After manufacturing, these microspheres are either physically compressed, filled with a hard gelatin, or compressed directly. The efficacy and mode of administration of the microspheres produced using different methods differ from those of traditional dosage forms. The quality of the microsphere will be evaluated using a range of methods. The microspheres that will ultimately be essential to novel drug delivery. If modified, it is the most reliable way to transport the drug specifically to the target region while maintaining the right concentration at the site of interest. Because of their prolonged release and capacity to target anticancer drugs, microspheres generated a lot of interest. In particular, the fields of diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted, and effective in vivo delivery, and supplements as microscopic replicas of the body's diseased organs and tissues will all benefit greatly from the use of microspheres in novel drug delivery in the future when combined with a variety of other techniques. A controlled drug delivery system can improve a medicine's therapeutic efficacy and solve the issues with standard medication therapy. Microspheres are one of the cutting-edge drug delivery methods that can be utilized as an effective therapeutic alternative to conventional or rapid release single-unit dosage forms.

Keywords: Microspheres, Type of Microspheres, Techniques for creating microspheres, Application of Microspheres, Advantages and Disadvantages of Microspheres.

1. INTRODUCTION

Achieving optimal treatment efficacy requires minimizing side effects and reducing toxicity by delivering the medication to the target tissue in the right quantity at the right time. There are several ways to use controlled, sustained release techniques to get a medication to the intended location. One such tactic is the use of microspheres as drug delivery systems. The development of innovative drug delivery systems with controlled release capabilities is one of the most exciting fields in pharmaceutical science research. A well-designed controlled drug delivery system can increase a medicine's therapeutic potency and overcome some of the shortcomings of traditional therapy. To achieve maximum therapeutic efficacy, the drug must be delivered to the target tissue in the right amount and at the right time to cause the least amount of toxicity and adverse effects. There are numerous ways to deliver a medication to the target site in a way that permits a steady, controlled release. [1]

Microparticles are an alternate term for microspheres. Modified natural products such as starches, gums, proteins, lipids, and waxes, as well as biodegradable synthetic polymers. Some examples of synthetic polymers are polyglycolic acid and polylactic acid, while albumin and gelatin are examples of natural polymers. Considering factors such as process safety, drug and polymer solubility and stability, and economic concerns, the solvents utilized to dissolve the polymeric components were selected. [2]

In order to decrease or eliminate gastrointestinal tract irritation while preserving the drug's release, oral microspheres have been employed. Additionally, the multiparticulate delivery systems circulate more uniformly throughout the gastrointestinal tract. This results in more constant medication absorption and less local pain than single-unit dose forms, such as non-dispersing polymeric matrix tablets. Additionally, it is possible to avoid the undesired intestinal retention of the polymeric ingredient that may occur with long-term matrix tablet use. [3]

Microspheres are tiny, spherical particles that fall inside the micrometres range and range in size from one to a thousandth of an inch. Microparticles are another term for microspheres. The subject of medication delivery has drawn a lot of attention because the microspheres were created using various polymers and subsequently assessed for certain applications. Over time, a steady plasma concentration is kept, which for a gradual dosage reduction with few adverse effects. [4]

Microspheres include both micrometrics and microcapsules. The entrapped material is surrounded by distinct capsule walls in both micrometrics and microcapsules, where it is dispersed throughout the microsphere matrix. Polyethylene microspheres are frequently used as either a temporary or permanent filler. Polyethylene microspheres with a lower

melting temperature can create porous architectures in ceramics and other materials. Because of their excellent sphericity, availability of colorful and fluorescent microspheres for process debugging, and several research applications, polyethylene microspheres are highly sought after for fluid flow analysis and visualization, microscopy methods, and the health sciences. Moreover, charged polyethylene microspheres are used in electronic paper digital displays. Mostly used as a weight reduction filler, a retro-reflector for road safety, and a component in adhesives and cosmetics, glass microspheres have few applications in medical technology. Using ceramic microspheres as grinding media is their primary use. Microspheres differ substantially in terms of their quality, sphericity, homogeneity, and size distribution. Choosing the appropriate microsphere is essential for each unique application.[5]

The variety of methods available for producing microspheres allows for the management of different aspects of medication administration. Small doses of extremely powerful drugs can be administered precisely with this technique, which also reduces drug concentration at non-target areas and protects the unstable chemical during and after administration as well as before it appears at the site of action. The drug's in vivo behavior can be altered when combined with a carrier particle. The drug's metabolism, cellular interaction, tissue distribution, and clearance kinetics are all significantly impacted by the carrier's activity. Making use of these pharmacodynamics behavior changes may improve the effectiveness of treatment. Nevertheless, an ingenious therapeutic approach that makes advantage of Drug carriers are capable of controlling pharmaceuticals in vivo by binding a drug to a carrier particle. But doing so necessitates a deep comprehension of drug carrier technology's carrier interaction. The drug's metabolism, cellular interaction, tissue distribution, and clearance kinetics are all significantly impacted by the carrier's activity. Making use of these pharmacodynamic behavior changes may improve the effectiveness of treatment. The goal of any drug delivery system is to swiftly achieve and then maintain the desired drug concentration by delivering a therapeutic dose of the drug to the appropriate site in the body.[6].

Historically, the most practical and popular way to administer medications has been orally. Drugs that are easily absorbed from the GIT and have a short half-life leave the bloodstream quickly. Techniques for oral administration of controlled substances that release the drug gradually into the GIT and maintain a constant drug concentration in the serum for a long period of time have been developed in order to avoid these problems. Partial drug release and a shorter dosage form residence time in the upper gastrointestinal tract—a common site for medication absorption—will lead to decreased bioavailability. Efforts to improve the bioavailability of oral medications have grown along with the pharmaceutical industry. As the number and chemical diversity of pharmaceuticals have increased, so too has the necessity for new methods to develop oral active medicines. As a result, gastro-retentive dosage forms were created, which improve the drugs' bioavailability and prolong their time in the stomach.[7]

2. HISTORY & DEVELOPMENT

Drug distribution has changed dramatically as attempts have been made to make sure that patients get the most out of their prescriptions. Delivering the drug to certain target areas at a rate and concentration that maximizes therapeutic efficacy and minimizes side effects is important. Another crucial aspect of drug administration to take into account is patient compliance throughout medication therapy. For nearly fifty years, there has been a lot of interest in the concept of an enhanced drug delivery system, especially one that provides a regulated and prolonged action of the treatment to the intended area of effect. However, the advent of timed release coating for tablets or solid medicine particles to cover up or improve their poor taste brought about the actual practice of controlled release. Between 1940 and the 1960s, the concept of employing microencapsulation technology as a substitute for traditional drug delivery methods first surfaced. In the 1980s, the continuous pursuit of increasingly complex systems led to the rise in popularity of polymer/membrane technology. Furthermore, attaching bioactive compounds to implants, liposomes, bioerodible polymers, monoclonal antibodies, and various particulate carriers (such nanoparticles and microspheres) may facilitate the process of site-specific delivery and precise targeting. Delivery methods for microparticles are thought to be a reliable way to deliver medicine precisely where it is needed. A great example of how one of the microspheres was created is the Microspheres for the Treatment of Vascular Complications of the Eye. This study aimed to develop sustained-release poly lactide-co-glycolide (PLGA) microspheres with SAR 1118, a lymphocyte function-associated antigen-1 antagonist, for 1, 3, and 6 months using Design of Experiments. Particle size, burst release, and drug loading were found to be influenced by the types of polymers, concentrations, and drug-to-polymer ratio, respectively. To ascertain whether polymers were suitable for degradation in 1, 3, and 6 months, the full factorials design was utilized. PLGA (50:50), PLGA (75:25), and PLGA (85:15) are the polymers that can degrade in 1, 3, and 6 months, respectively, and have intrinsic viscosities of 0.3 to 0.5 dL/g. based on the full-factorial approach. Based on the Box-Behnken design, which established the optimal polymer concentration (12% w/v) and drug to polymer ratio (0.15), tests for drug loading, burst release, and sustained drug release were performed using SAR 1118-encapsulated microspheres composed of the three polymers indicated above. The drug loading in these three batches ranged from 15% to 18%, and the burst release was less than 20%. The 50:50,

75:25, and 85:15 PLGA microspheres produced more than 90% of the SAR 1118 release in 1, 3, and 6 months, respectively. AS a result, the in vitro cumulative release measures are remarkably close to what was anticipated. The results demonstrated that the experiment design approach was capable of producing SAR 1118 microspheres with high loading efficiency, little burst release, and sustained release for the desired duration.[8]

3. MATERIAL USED IN MICROSPHERES FORMULATION

Numerous materials, both biodegradable and non-biodegradable, have been investigated for the production of microspheres. These materials include both manufactured and natural polymers, as well as modified natural substances. Polymer microspheres are used most frequently. They can be divided into two categories.

1. Synthetic polymers

2. Natural polymers

There are two types of synthetic polymers.

Biodegradable polymers : that are not Acrylein, polymethyl methacrylate (PMMA), glycidyl methacrylate, and epoxy polymers

Biodegradable polymers: Lactides and glycosides, as well as their Copolymers Acrylates of poly alkyl cyano Polyanhydrides Carbs and proteins

Examples of natural polymers that originate from various sources include chemically modified polysaccharides.

A] Proteins: albumin, collagen, and gelatin⁹

B] Glucose: Carrageenan starch, chitosan, and arose

C] Carbohydrates that have undergone chemical alteration: Poly starch Poly dextran ¹¹.

[9, 10, 11, 12]

4. TYPE OF MICROSPHERES

1. Microspheres that are bioadhesive

2. Microspheres with magnetism

3. Microspheres that levitate

4. Microspheres that emit radiation

5. Microspheres made of polymeric material

1. Polymeric microspheres that degrade biodegradably

2. Microspheres made of synthetic materials

1. Microspheres that are bioadhesive

The term “adhesion” refers to the process of a medicine adhering to a membrane by means of the water to a mucosal membrane, such as the buccal, nasal, ophthalmic, or rectal membranes. This kind of microsphere has a longer half-life at the target location and has superior medicinal effects.[13]

2. Microspheres with magnetism

This type of delivery technique localizes drugs to the desired location. A drug or therapeutic radioisotope coupled to a magnetic component is introduced into the systemic circulation and halted by applying a powerful magnetic field at the disease or target site. Magnetic microspheres, which are ferromagnetic molecules that are small enough to fit through capillaries without blocking the oesophagus (less than 4 μm), are highly vulnerable to being trapped in micro-vessels and drawn through nearby tissues by a magnetic field. In this case, a greater amount of freely circulating drug can be replaced with a smaller amount of magnetically focused medication.

Numerous varieties of magnetic microspheres exist.

- Therapeutic microspheres: These are specifically made to target liver tumors with anticancer medications. This is useful for eliminating tumor cells without harming nearby cells.
- Diagnostic microspheres: These produce supramagnetic iron oxides, which are tiny particles that can be used to distinguish intestinal loops from other abdominal structures and to image liver metastases.[14]

3. Microspheres that levitate :

Because its bulk density is smaller than that of gastric fluid, the floating form of food remains buoyant in the stomach without affecting the rate of gastric emptying. The system is found to be floating on the stomach contents, reducing the amount of time the stomach stays in the stomach and enhancing the fluctuation in plasma concentration when the drug is gradually released at the proper rate. Additionally, it reduces the likelihood of dose dumping. Its long-lasting effects result in lower dosage frequencies.[15]

4. Microspheres that emit radiation :

The diameter of the capillary bed is larger than that of the 10–30 nm-sized radio embolization therapy microspheres. Radioactive microspheres provide a high dose of radiation to the desired sites for each of these illnesses without endangering the surrounding healthy tissues. They are administered by injection into the arteries that supply the targeted tumor. Although it operates at a normal distance within a radioisotope, microspheres do not produce heat radiation. These are the several types of radioactive microspheres that emit α , β , and γ . [16,17]

5. Microspheres made of polymeric material :

Two types of polymeric microspheres exist: Polymeric microspheres that degrade biodegradably & Microspheres made of synthetic material

1. Polymeric microspheres that degrade biodegradably:

Since natural polymers like starch are biodegradable, biocompatible, and naturally bioadhesive, they are utilized. Because biodegradable polymers have a high degree of swelling property with aqueous medium, which results in gel formation, they have a longer residence duration when in contact with mucosal membranes.

2. Microspheres made of synthetic material:

The primary drawback of synthetic polymeric microspheres is their tendency to migrate away from the injection site, which increases the risk of embolism and subsequent organ damage. These microspheres are also used as bulking agents, fillers, embolic particles, drug delivery vehicles, etc. And have been shown to be safe and biocompatible. [18]

5. TECHNIC FOR CREATING MICROSPHERES

The drug, the method's stability in relation to the final product, the reproducibility of the release profile and the method, and the size of the particles required are the main factors that influence the choice of method. Other factors include the drug's characteristics, the polymer being used, and the factors that are unambiguously determined by numerous formulations and technological factors. The many processes that were employed to create the microspheres employing matrix materials made of hydrophobic and hydrophilic polymers. [19]

- The ability to incorporate the relatively tiny amounts of medication.
- The preparation's consistency upon synthesis with a clinically acceptable shelf span.
- Modified particle size and dispersibility for aqueous vehicle injection.
- Robust control over an extended period of time in the effective release of reagent.
- Chemical alteration response and controlled biodegradability that are biocompatible.

1. Coating with wax and hot melting :

Melted wax is utilized to dissolve or disperse the product, encasing the primary ingredients. High-intensity blending with cold water releases the waxy paste or combination, such as Frozen liquid paraffin. For at least an hour, the water is heated. For a minimum of one hour, the substance is agitated. The microspheres are then submerged in a non-miscible solvent after the outer layer—liquid paraffin—is decanted, and they must dry in dry air. To achieve desired properties, it is recommended to blend carnauba wax and beeswax as surface elements. [20,21]

2. Method of spray drying :

This was utilized to create drug-charged polymer microspheres. To do this, the raw material must be dissolved into the liquefied coating liquid, and the mixture must then be sprayed into the air to cause rapid solvent evaporation and surface solidification. Microspheres containing prescription drugs are created by mixing and spraying a polymer solution and organic solvent in different weight ratios under particular lab settings. Although it is quick, the quick drying process could cause the crystallinity to disappear.

3. Intolerability :

A thick coacervate layer that is relatively condensed in macromolecules and a distilled layer of equilibrium are the two immiscible types of material that are separated from the macromolecular fluid using this simple procedure. When there is only one macromolecule present, this process is known as fundamental coacervation. Complex coacervation is defined as the involvement of two or more macromolecules with opposing charges. Certain causes, such as temperature shift, are to blame for the former using micro-ions or non-solvents that contribute to macromolecule dehydration because they promote contacts between polymers through polymer solvent interactions. It is possible to engineer this to produce various microsphere qualities. [20]

4. Evaporation of solvents:

Solvent evaporation is a widely utilized technique in the production of PLA and PLGA microspheres containing a wide range of medicines. A number of factors, including drug solubility, internal morphology, solvent type, diffusion rate,

temperature, polymer composition, viscosity, and drug loading, have been found to have a substantial impact on microspheric properties. Because the successful entanglement of the active ingredient into the particles is essential to the solvent evaporation system's ability to produce microspheres, this process works especially well for medications that are either partially or completely soluble in the liquid medium that makes up the constant phase.[22]

5. Rainfall :

It is an alteration of the evaporation process. Polar droplets dispersed across a non-polar liquid make up the emulsion. The solvent can be extracted from the droplets by using a co-solvent. The ensuing increase in polymer concentration causes precipitation, which results in the formation of a microspheric suspension.[23]

6. Utilizing Freezer :

Drying When preparing protein API microspheres, freeze-drying works well. Freezing, sublimation, primary drying, and secondary drying are the techniques used. The components' eutectic point is taken into consideration at the freezing step. Lyoprotectants and cryoprotectants work to stabilize API molecules by eliminating water, establishing a glass matrix, and reducing intermolecular interaction through the formation of hydrogen bonds or dipole-dipole interactions. Considering its high cost, it's a useful cycle for molecules that can withstand heat. Particles in an aqueous medium can then be reconstituted after solidification via freeze-drying.[24]

7. Method of Single Emulsion Solvent Evaporation :

This procedure calls for the emulsification of an aqueous environment containing the emulsifying agent, followed by the dissolution of the polymer in an organic solvent. After allowing the solvent to evaporate over many hours of stirring in an air environment, the resultant emulsion is cleaned, rinsed, and dried in desiccators. Created and produced medication microspheres using polymers and an emulsion solvent using the diffusion-evaporation process[25]

8. The method of double emulsification :

When using the Doppel-emulsion technique, the double emulsion must be processed by combining w / o / w or o / w / o. The product's aqueous solution is dispersed within a continuous lipophilic organic phase. The primary emulsion is formed by a continuous step wherein a polymer solution eventually wraps the drug observed in the scattered aqueous layer. The pre-formed emulsion is homogenized or sonicated before being added to the alcohol aqueous solution to generate the primary emulsion. The drug-filled microspheres extended the drug's release by 24 hours and were found to be regulated in terms of diffusion and erosion.[25]

9.The method of ionic gelation:

In the presence of counter ions, ionotropic gelation is dependent on the propensity of polyelectrolytes to cross link to form hydrogel beads, also known as Gelispheres. Gelispheres are circular cross-linked polymeric hydrophilic agents that can significantly thicken and gel in simulated biological fluids. They can also be used to release drugs under the control of polymer relaxation. By adding a drug-filled polymeric solution to an aqueous solution containing polyvalent cations, hydrogel beads are created. The drug-loaded hydrophilic molecules allow the cations to move through them, forming a three-dimensional lattice in which the moiety is crosslinked by ionization. These gelispheres can also hold biomolecules in order to preserve their three-dimensional shape in milder environments.[26]

6. EVALUATION OF MICROSPHERES

1. Analyzer of particle sizes :

The particle size is provided as volume mean diameter in micrometres after 50 mg of microspheres are suspended in 5 mL of distilled water with 2%w/v tween 80 to stop microsphere aggregation.[31]

2. Optical Microscopy:

Using an optical microscope (Meizer OPTIK), this technique measures particle size. I measured 100 particles under 450x (10x eye piece and 45x objective) and calculated the results. [32]

3. SEM, Scanning Electron Microscopy:

The SEM method determines surface morphology. Using double-sided sticky tape, the microcapsules are placed directly on the SEM sample slab, coated with a gold coating at low pressure, and then examined. [33]

4. Index of Swelling :

Microspheres of sodium alginate are characterized using this method. Alginate microspheres (100 mg) and various solutions (100 mL), such as distilled water and buffer solution of pH (1.2, 4.5, 7.4), are put in a wire basket and left on top of the aforesaid solution, with swelling permitted at 37 °C. Therefore, weight is taken periodically and soaked with filter paper to assess variations in the weight variation between the initial weight of the microspheres and the weight owing to swelling. [34]

5. Effectiveness of entrapment :

An ultrasonic stirrer is used to smash and dissolve drug-containing microspheres (5 mg) in distilled water for three hours. The microspheres are then filtered and subjected to uv-vis spectroscopic analysis. The ratio of actual to hypothetical drug content is the same as entrapment efficiency. [34]

6. Diffraction of X-rays:

This method can be used to determine a change in the drug's crystallinity. The XRD instrument is used to analyze microparticles and their constituent parts. Angle of scanning range between 80°C and 70°C.[35]

7. Zeta Potential:

By adding chitosan with varying molecular weights to the W2 phase, the polyelectrolyte shell is created, and the resultant particles are identified by zeta potential testing. [36]

7. ADVANTAGES OF MICROSPHERES

- 1.A reduction in size can boost the efficacy of the poorly soluble substance by increasing its surface area.
2. Maintaining a constant level of medication in the body, which might enhance patient adherence.
3. Lowering dosage and risk.
4. The use of polymers in drug packaging shields the medication from enzymatic cleavage and allows for a variety of drug delivery methods.
5. Shorter dosing intervals increase patient compliance.
6. Sufficient use of drugs can improve bioavailability and lessen the likelihood or intensity of adverse effects.
7. Assists in shielding the GIT from irritating opioids. H. Convert a liquid into a solid state and eliminate the disagreeable flavor.
8. Microspheres have a long-lasting and consistent therapeutic impact.
9. Lowers the frequency of dose, which enhances patient compliance.
10. Because of their smaller size and spherical shape, they may be injected into the body. 11. More effective use of the medication will increase its bioavailability and lessen the frequency or severity of side effects.
12. Controllable variability in drug release and degradation is made possible by the shape of microspheres.[28]

8. DISADVANTAGES OF MICROSPHERES

1. The modified formulas' releases.
2. The controlled dose process's release rate, which varies depending on a number of variables including nutrition and levels of transfer via the gastrointestinal tract.
3. The rate of discharge varies depending on the dosage.
4. Because controlled release formulations usually have a larger dose load, any deficiency in the drug substance's release qualities may make it more likely that
5. will occur.
6. It is not permitted to break or chew these dosage forms.
- 7.Less reproducibility exists.
- 8.The expenses associated with materials and processing are higher than those of traditional preparations.
- 9.Variations in temperature, pH, solvent addition, agitation/evaporation, and other process variables may have an impact on the stability of core particles.
- 10.The future of additives and the polymer matrix.[29,30]

9. APPLICATION OF MICROSPHERES

1.Delivery of vaccines using microspheres :

Safety against microorganisms and their harmful components is a basic requirement for vaccines. Efficacy, protection, cost-effectiveness, and application affordability should all be met by the perfect vaccination. Avoiding negative impacts and maintaining safety are complex issues. A close relationship exists between the mode of application and the degree of antibody response generation and safety. One potential solution to address the shortcomings of conventional vaccines is the use of biodegradable delivery systems for parenterally administered vaccines. Even while parenteral (subcutaneous, intramuscular, and intradermal) carriers provide several benefits, such as:

1. Modulation of antigen release
2. Improved antigenicity, there is still participation in these

3. Security of antigens[37]

2.Delivery of Genes using Microspheres:

Technologies for genotype medication delivery include microcapsules, polycation complexes, non-ionic liposomes, and viral vectors. Despite the fact that viral vectors are highly effective and have a wide range of cell objectives, they are still crucial for genotype delivery. However, when applied in vivo, they activate the immune system and have harmful effects. The problems with viral vectors have led to the development of non-viral gene therapy delivery methods. Simple preparation, cell/tissue targeting, weakened immune system, unrestricted plasmid size, and large-scale repeatable production are the benefits of non-viral delivery systems. In gene delivery applications, polymers are employed as DNA transporters.[38,39]

3.Oral medication administration:

Rabbits have been used to test the oral medication transport capacity of a polymer matrix containing diazepam. Research revealed that even a film with a drug-polymer ratio of 1:0.5 would have been a useful dosage form that was on par with current tablet formulations.[37]

4.Transdermal administration of medications:

Good film-forming properties are exhibited by polymers. Both the membrane thickness and a film's crosslinking affect the release profile from the system. For possible applications in controlled release systems, surgical equipment, and packaging, chitosan-alginate polyelectrolyte structures have been synthesized in-situ in beads and microspheres. In addition to having a delayed release action that increases therapeutic efficacy, polymer gel beads are a highly biocompatible medium for chemotherapy of inflammatory cytokines for drugs like prednisolone. It was discovered that the properties of the cell wall utilized affected the amount of medication release. A superb all-inclusive method for regulated drug release and release kinetics is a combination of chitosan membrane and chitosan hydrogel with lidocaine hydrochloride, a local anesthetic.[40]

5.Utilizing Micro Particulate Carriers for Targeting :

Targeting is a well-known idea that is currently receiving a lot of attention. The drug's accessibility and capacity to interact with the binding site determine its effectiveness. Pellets are typically made via the extrusion/spheronization process, such as chitosan and microcrystalline cellulose (MCC).[41]

6.Monoclonal antibodies:

Microspheres that target monoclonal antibodies are physiologically immunomicrospheres. Since monoclonal antibodies are extremely accurate substances, they can be used to direct microspheres containing bioactive substances to specific locations. There are several ways to bind monoclonal antibodies to microspheres:

- a. Non-specific adsorption
- b. Selective adsorption
- c. Direct coupling
- d. Coupling via reagent [41,42]

10. REFERENCE

- [1] N. K. Jain, Controlled and Novel drug delivery, 04 Edition, CBS Publishers New Delhi, India; 236-237.
- [2] Chein YW. Oral Drug Delivery Systems: In Novel Drug delivery systems. Vol.50, Marcel Dekker, Inc., New York. 1992, 139- 177.
- [3] Mathew Sam T., Devi Gayathri S., Prasanth V.V., Vinod B; NSAIDs as microspheres, The Internet Journal of Pharmacology. 2008, 67-73.
- [4] Patel MB, Patel KS. Creation and assessment of nicorandil-containing chitosan microspheres. Pharmaceutical investigation's International Journal, 2014; :32; doi: 10.4103/2230-973X.127738;
- [5] Rajput S, Agrawal P, Pathak A, Shrivastava N, Baghel SS, Baghel RS. A review on microspheres: methods of Preparation and evaluation. World journal of Pharmacy and pharmaceutical sciences. 2012,422-38.
- [6] Thanoo BC, Sunny MC, and Jayakrishnan A. Cross-linked chitosan microspheres: Synthesis and assessment as a matrix for regulated drug release. J Pharm Pharmacol. 283-286, 1992.
- [7] International Journal of Pharmaceutical Sciences Review and Research, 2010,10–15; Gholap SB, Banerjee SK, Gaikwad DD, Jadhav SL, and Throat RM. Hollow microsphere: a review.
- [8] Khar R.K and Vyas S.P Targeted and Controlled Drug Delivery- Novel Carrier Systems, 1st Edition, CBS Publication and Distributors, New Delhi, 2002; Pg 417- 425.
- [9] Biodegradable micro particulate system of captopril, P.M. Dandagi, VS. Mastiholimath, M.B. Patil, M.K. Gupta. 307, 2006, International Journal of Pharmaceutics.

- [10] Sai Kiran M, Vimal Kumar Varma M, Sleeva Raju M, Chinna Gangadhar B, Shyam Sunder R, Using both natural and synthetic polymers as controlled release dosage forms, indomethacin microspheres were developed and evaluated. *Journal of Drug Discovery International* 2010; 8–16.
- [11] Formulation and in vitro evaluation of natural polymers based microsphere for colonic drug delivery, Rana Mazzder, Lila K. Nath, Anwarul, Haque, Tarasankar Maity, Prasant K. Choudhary, Bhupendra Shreshta, *International Journal of Pharmacy and Pharmaceutical Sciences*, 2010, 211-219.
- [12] Kavitha K, Chintagunta Pavanveena, Anil Kumar S. N., Tamizh Mani T, creation and assessment of a gelatin microsphere filled with trimetazine hydrochloride. *International Journal of Pharmaceutical Sciences and Pharmacy*, 2010: 67–70
- [13] Garud N, Guard A, Bhandari A, Sharma S, and Chaware P. The preparation and in-vitro characterisation of bioadhesive microspheres are reviewed. *Global journal* 2014, 423-36.
- [14] Magnetic Microspheres: A Novel Drug Delivery System, Farah Hamad Farah, et al., *Analytical and Pharmaceutical Research*. 2016, 1–10. 10.20959/wjpps20179-10054 is the DOI.
- [15] A review of floating microspheres was published in the *Brazilian Journal of Pharmaceutical Sciences* in 2012 by Jagtap Yogesh Mukund et al.
- [16] Review of Radioactive Microspheres for Medical Uses, Urs Hafeli et al., *Cleveland Clinic Foundation, Radiation Oncology Department T28*, pages 1-29.
- [17] Lieberman HA, Lachman LA, and Kanig JL. *Industry pharmaceutical theory and practice*. Third edition (1991), Varghese Publishing House, Mumbai, India; P-414–415.
- [18] Saralidze, Ketie, et al. (2010) *Polymeric Microspheres for Medical Applications: Materials*, 3537–3564.
- [19] *Journal of Medicine and Biology*, 2019, Pages 27–32; E Veena Rani, et al., Preparation and Evaluation of Aspirin-Loaded Microspheres by Solvent Evaporation Technique.
- [20] A review of the microsphere as a novel drug delivery system was published in the *Journal of Pharmacy Research* in 2012 on pages 420–424. Saravana Kumar K, et al.
- [21] *International Journal of Pharmaceutical Sciences Review and Research*, 2011, Article-012, Harsh Bansal et al., Microsphere: Methods of Preparation and Applications; a Comparative Study.
- [22] The preparation of microspheres using the solvent evaporation process was described by Patrick B. O'Donnell and colleagues in *Advanced Drug Delivery Reviews* (1997), pages 25–42.
- [23] *Methods in Molecular Biology*, 2017, 1575, pages 341-352, Tibor Renkecz et al., Preparation of Molecularly Imprinted Microspheres by Precipitation Polymerization.
- [24] *Journal of Drug Targeting*, 1994, Pages 9–21; Xinghang Ma, et al., Stability Study of Drugloaded Proteinoid Microsphere Formulations during Freeze-drying.
- [25] Microspheres as Managed Drug Delivery System: A Reviewed Analysis, Shweta Saini et al., *International Journal of Pharmaceutical Science and Research*, 2018, 1760-1768.
- [26] A Review of the Ionotropic Gelation Method: A Novel Approach for Controlled Gastroretentive Gelispheres by Poonam Patil et al. Was published in the *International Journal of Pharmacy and Pharmaceutical Sciences* in 2012, volume ,pages 27–32.
- [27] Albumin Microspheres: A Novel System as Drug Delivery Carriers for Non-Steroid Anti-Inflammatory Drugs, Kavita Kunchu, Raje Veera Ashwani, et al. 2010.
- [28] Pharmaceutical Application of Microspheres: A Method for Treating Different Illnesses, Tarun Virmani et al., *International Journal of Pharmaceutical Sciences and Research*, 2017, Page 3252-3260.
- [29] *The Journal of Global Trends in Pharmaceutical Sciences*, pages 1961–1972, reviewed by B. Sree Giri Prasad et al., Microspheres as Drug Delivery Systems.
- [30] Pharmaceutical Use of Microspheres: A Method for the Management of Different Illnesses, by Virmani Tarun and Gupta Jyoti, *International Journal of Pharmaceutical Sciences and Research*, 2017, 3257–3259. 10.13040/IJPSR.0975-8232 is the doi
- [31] Formulation and Assessment of Acetazolamide Sustained Release Microspheres by Solvent Evaporation Technique, Kannan.K., Karar.K.P., and Manavalan.R., *J.Pharm.Sci&Res*. 2009; 36-39.
- [32] Brain-Targeted Nasal Clonazepam Microspheres, Shaji J., Poddar A., Iyer S. *Indian Journal of Pharmaceutical Sciences*, 2009; 715–718.
- [33] Permeability of Ethylene Vinyl Acetate Copolymer Microcapsules: Impact of Solvents, Chowdary K.P.R., Suri B.J., *Indian Journal of Pharmaceutical Sciences*, 2003:62-66
- [34] Sodium alginate microspheres for prolonging drug release: formulation and in vitro assessment, Soni L.M., Kumar M., and Namdeo P.K., *International Journal of Drug Delivery*, 2010:64-68.

-
- [35] Mahmood A., Ghulam M., Naveed A., and Fatima R.A., Comparative analysis of several microencapsulation methods. Microcapsule characteristics and the impact of polymer viscosity, Pak.J.Sci.2009; 291-300.
- [36] Chitosan Coated Plga-Microspheres: A Modular System for Targeting Drug Delivery, Fischer S., Foreg C., Merkle P.H., Gander B., European Cells and Materials, 2004; 11-12.
- [37] Microsphere: A Review by Kataria Sahil et al., International Journal of Research in Pharmacy and Chemistry, 2011; 1184-1198.
- [38] "Biomedical applications of microspheres," Journal of Modern Drug Discovery and Drug Delivery Research, 2015, 1-5.
- [39] Abbaraju Krishna Shailaja et al. Prog Biomater, 2014;1-19; Kazi M. Zakir Hossain et al., Development of microspheres for biomedical applications: a review.
- [40] Microspheres for biomedical applications: creating reactive and tagged microspheres, Reza Arshady et al., Biomaterials, 1993, 5-15
- [41] Pharmaceutical Use of Microspheres: A Method for Treating Different Illnesses, Tarun Virman et al., International Journal of Pharmaceutical Science and Research, 2017;3252-3260. 10.13040/IJPSR.0975-8232
- [42] MK The Tropical Journal of Pharmaceutical Research, 2012;11(5):695-702; Shahzad et al., Formulation and Optimization of Celecoxib-Loaded Microspheres Using Response Surface Methodology. 10.4314/tjpr.v11i5 is the DOI.