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Review Article

Microspheres: A Review

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A B S T R A C T

Multiparticulate drug delivery systems called microspheres are made to deliver drugs for extended periods of time or under controlled conditions, enhancing stability and bioavailability while delivering the drug to a specific location at a predefined rate. They are composed of natural, semi-synthetic, and synthetic polymers, as well as polymeric waxy or other protective materials. Microspheres are free-flowing powders made of proteins or synthetic polymers with particle sizes between 1 and 1000 µm. The different kinds of microspheres, their preparation techniques, and their uses are highlighted in this review. There are many different kinds of microspheres, including bio adhesive, magnetic, floating, radioactive, polymeric, biodegradable, and synthetic. They are made using techniques like spray drying, solvent evaporation, single and double emulsion, phase separation coacervation,Spray drying and spray congealing, Solvent extraction. Microspheres have wide range of applications because of controlled and sustained release.

Keyword: Microspheres, types, method, advantages, application.

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INTRODUCTION:

Microspheres are small, spherical particles typically ranging from 1 µm to 1000 µm in diameter. They are composed of a continuous phase of one or more miscible polymers, in which therapeutic agents, either in molecular dispersion or as particles, are distributed throughout the matrix. These microspheres can be made from biodegradable synthetic polymers such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA), or from modified natural polymers like starches, gums, proteins, fats, and waxes. Examples of natural polymers include albumin and gelatin. The choice of solvents used to dissolve the polymers depends on factors such as drug solubility, stability, process safety, and economic considerations.[1]

Oral dosage forms that offer modified release, particularly multiparticulates, are considered superior to traditional single-unit immediate-release forms. In these systems, microspheres are often used to achieve controlled drug release. The microspheres are usually incorporated into capsules, and their design not only facilitates extended release but also allows for drug targeting. This makes them a valuable tool in drug delivery systems that aim to control the timing and location of drug release.[1]

Controlled release systems are crucial in modern drug delivery, allowing for both the spatial targeting of drugs to specific tissues or organs and the temporal regulation of the release rate. Microspheres can encapsulate various types of drugs, such as small molecules, proteins, and nucleic acids, and can be administered through syringes. These systems are known for their biocompatibility, high bioavailability, and sustained release capabilities over extended periods.[2]

Microspheres have become an essential component in particulate drug delivery systems, thanks to their efficient carrier properties and small size. They are primarily used to encapsulate drugs and proteins, releasing the active substance over time. The release mechanisms can be passive, relying on size-based trapping, or active, using techniques like magnetic targeting. The duration and efficiency of drug release depend on factors such as the polymer type, drug-to-polymer ratio,

solubility of the drug, and the structural characteristics of the microsphere matrix.

These microspheres are particularly useful in the controlled delivery of biologically active substances such as proteins, where maintaining stability and prolonging the release of the drug is critical. By adjusting various parameters, such as the loading efficiency and release kinetics, microspheres can be tailored for specific therapeutic applications.[3]

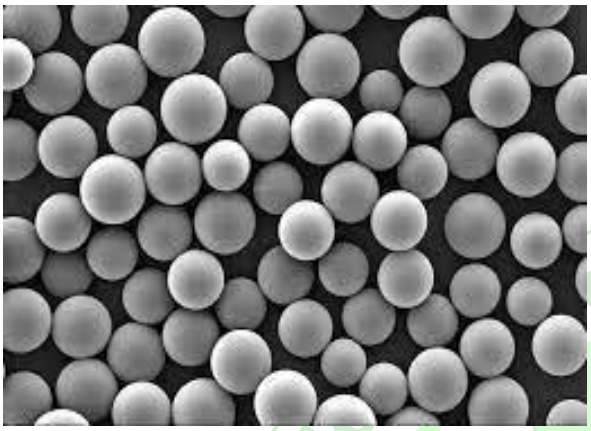

Figure 01: Microspheres

TYPES OF MICROSPHERES:

1. Bioadhesive microspheres:

Adhesion refers to the process by which a drug attaches to a membrane, utilizing the adhesive properties of water-soluble polymers. When a drug delivery system adheres to mucosal membranes, such as those found in the buccal, ocular, rectal, or nasal regions, it is referred to as bioadhesion. Microspheres that exhibit bioadhesion can remain at the application site for an extended period, ensuring close contact with the absorption site, which can enhance therapeutic effectiveness.[4]

2. Magnetic microspheres:

This type of drug delivery system is crucial for targeting drugs directly to the site of disease. It allows for a significant reduction in the amount of circulating drug by using a smaller amount of drug that is magnetically targeted. Magnetic carriers respond to an applied magnetic field, and materials such as chitosan and dextran are commonly used to form magnetic microspheres. These microspheres are classified into two main types: therapeutic magnetic microspheres and diagnostic microspheres.[4]

a) **Therapeutic Magnetic Microspheres**:

These are used to deliver chemotherapeutic agents directly to liver tumors. Additionally, this system can target drugs like proteins and peptides to specific sites in the body.

b) **Diagnostic Microspheres**:

These are utilized for imaging purposes, such as detecting liver metastases, and can also help differentiate bowel loops from other abdominal structures. This is achieved by creating nanosized particles of superparamagnetic iron oxides.

3. Mucoadhesive microspheres:

Mucoadhesive microspheres, ranging in size from 1 to 1000 microns, are composed either entirely of mucoadhesive polymers or have a mucoadhesive polymer coating on their surface. The incorporation of mucoadhesive properties into microspheres offers several advantages, such as improved drug absorption and enhanced bioavailability. This is due to the increased surface-to-volume ratio, which allows for better interaction with the mucus layer. Moreover, drug targeting can be achieved by attaching specific molecules, such as plant lectins, bacterial adhesions, or antibodies, to the surface of the microspheres. These microspheres are designed to adhere to various mucosal tissues, including those in the eyes, nasal passages, urinary tract, and gastrointestinal tract. This ability enables both localized and systemic controlled drug release.[5]

4. Floating microspheres:

In floating drug delivery systems, the bulk density is lower than that of gastric fluids, allowing the system to remain buoyant in the stomach without interfering with the gastric emptying rate. This buoyancy enables the drug to be released gradually at a controlled rate while the system stays afloat on the gastric contents. This mechanism enhances the duration of gastric residence time and helps maintain more consistent plasma drug concentrations. Additionally, it minimizes the risk of dose dumping and sudden drug release. As a result, floating systems can provide a prolonged therapeutic effect, reducing the need for frequent dosing.[4]

5. Radioactive microspheres:

Radioactive microspheres, typically ranging from 10 to 30 microns in size, are larger than capillaries, causing them to become trapped in the first capillary bed they encounter. These microspheres are injected into the arteries that supply blood to the tumor of interest. As a result, the radioactive microspheres deliver a high dose of radiation directly to the targeted area, minimizing damage to surrounding healthy tissues. Unlike traditional drug delivery systems, radioactive microspheres do not release radiation; instead, the radiation is emitted from within the microspheres, at a specific distance determined by the radioisotope. Different types of radioactive microspheres include beta emitters and alpha emitters.[4]

6. Polymeric microspheres:

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.

A. Biodegradable polymeric microspheres

Natural polymers like starch are used in drug delivery systems because of their biodegradability, biocompatibility, and bioadhesive properties. Biodegradable polymers increase the residence time when in contact with mucosal membranes due to their ability to swell significantly in the presence of aqueous media, leading to gel formation. The rate and extent of drug release can be controlled by adjusting the polymer

concentration, ensuring sustained release over time. However, a key challenge in clinical applications is the complexity of drug loading efficiency in biodegradable microspheres, which can make it difficult to control the release of the drug effectively.[4]

B. Synthetic polymeric microspheres

Synthetic polymeric microspheres have gained significant interest for various clinical applications, including their use as bulking agents, fillers, embolic particles, and drug delivery vehicles, all of which have been shown to be safe and biocompatible. However, a major drawback of these microspheres is their tendency to migrate away from the injection site, which can pose potential risks, including embolism and damage to other organs.[4]

METHOD OF PREPARATION OF MICROSPHERES:

1. Solvent Evaporation Technique:

The required amount of polymer was taken in 100ml glass beaker previously containing 10ml acetone/ethanol. Then the mixture was thoroughly stirred until a clear solution of polymer was formed. The beaker was kept for microsphere preparation. 1ml of Span 80 was taken in properly washed and dried 1000ml plastic beaker. 100ml light liquid paraffin was added to Span 80 and the mixture was stirred at 1000 rpm for 5 minutes. Then required amount of drug was added to the respective formulation to form a suspension. Stirring was continued for 10 minutes. Then polymer solution was poured drop by drop into the drug suspension with simultaneous stirring. The stirring was continued until hard, uniform shaped microspheres were formed which required about 3 hours. The container was then kept static to allow the microspheres for settling down. Serial washing of microspheres was carried out with n-hexane/petroleum ether. Then the microspheres were spread over a filter paper and left for drying in a desiccator for a day. The dried microspheres were kept in a vial with proper identification.[6]

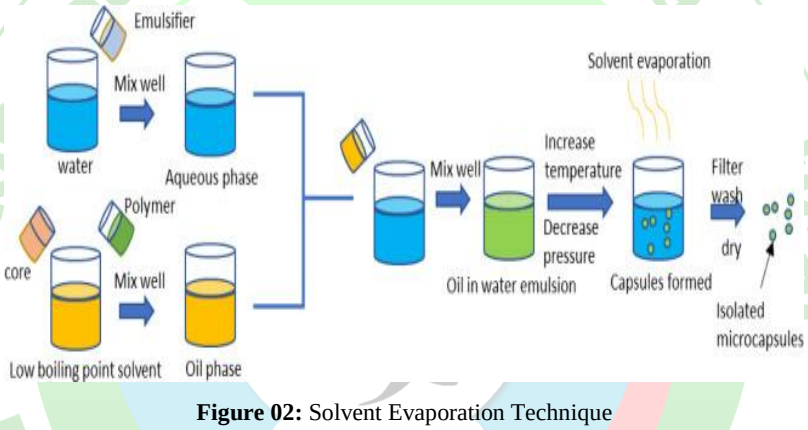

Figure 02: Solvent Evaporation Technique

2. Single Emulsion Technique:

Natural polymer microspheres are typically prepared using the single emulsion technique. In this process, the drug and polymer are dissolved or dispersed in an aqueous medium, which is then mixed with an organic medium (e.g., oil). This leads to the formation of globules, which are subsequently cross-linked either by applying heat or by using chemical cross-linkers. Common chemical cross-linkers include formaldehyde, glutaraldehyde, and diacid chlorides.[2]

Figure 03: Single Emulsion Technique

3. Hot Melt Microencapsulation:

In this method, the polymer is first melted and mixed with solid product particles that have been sieved to sizes below 50 µm. The mixture is then suspended in a non-miscible solvent, such as silicone oil, and continuously stirred while being heated to 5°C above the polymer's melting point. Once the emulsion is stabilized, it is cooled in a refrigerator until the polymer particles solidify. The resulting microspheres are separated by decanting and washed with petroleum ether. The main goal of this technique is to develop a microencapsulation process that is suitable for water-sensitive polymers, such as polyanhydrides. Microspheres with diameters ranging from 1 to 1000 µm can be produced, and their size distribution can be controlled by adjusting the stirring

speed. The only limitation of this method is the moderate temperature at which the drug is exposed.[7]

4. Spray Drying:

In this technique, the drug can either be dissolved or dispersed within a polymer solution and then spray dried. The quality of the spray-dried microspheres can be enhanced by adding plasticizers, such as citric acid, which help the polymer to coalesce around the drug particles, promoting the formation of spherical, smooth-surfaced microspheres. The size of the microspheres can be controlled by adjusting factors like the spraying rate, the feed rate of the polymer-drug solution, nozzle size, and drying temperature. This microencapsulation method is particularly advantageous because it is less reliant on the solubility properties of the drug and polymer, and it is simple, reproducible, and scalable.[3]

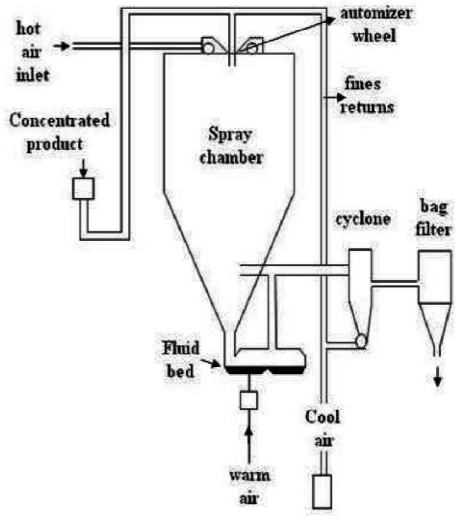

Figure 04: Spray Drying Technique

5. Multiple Emulsion Technique:

In this method, natural polymers such as proteins and carbohydrates are prepared using a primary oil-in-water (o/w) emulsion technique. The drug is dissolved in a water-soluble protein, and an emulsifier is added to the mixture. Next, the organic phase is dispersed into the solution. This primary o/w emulsion is then homogenized. A non-aqueous solution of polyvinyl alcohol is added to the primary emulsion, resulting in the formation of a double emulsion, oil-in-water-in-oil (w/o/w). The double emulsion is then subjected to solvent evaporation or extraction, leading to the formation of low-density floating microspheres.[8]

6. Ionic Gelation Method:

In this method, the drug is mixed with an aqueous solution of sodium alginate. Stirring is continued until a complete solution is formed, after which the mixture is added drop by drop into a solution containing Ca^{2+} or Al^{3+} ions. The microspheres that form are left in the original solution for 24 hours to allow internal gelation to occur. Afterward, they are separated by filtration.[9]

7. Emulsion Cross Linking:

To prepare the microspheres, a specific amount of chitosan and 400 mg of the drug were dissolved in 20 ml of 4% w/v acetic acid with the help of a magnetic stirrer. The resulting drug-polymer dispersion was injected dropwise using an 18-gauge needle into 200 ml of liquid paraffin containing 2 ml of Span 80. The emulsion was stirred using a propeller at 1500 RPM. After 15 minutes, a 25% aqueous solution of glutaraldehyde was added, and the mixture was stirred continuously for 3 hours. The suspension of chitosan microspheres in liquid paraffin was left to stand for 15 minutes to allow the microspheres to settle under gravity. The liquid paraffin was then decanted and filtered. The microspheres were washed with n-hexane to remove any residual oil and subsequently washed with water to eliminate excess glutaraldehyde. Finally, the microspheres were dried at 50°C for 12 hours.[10]

ADVANTAGES OF MICROSPHERE:[11]

1. Size reduction leads to increase in surface area which can enhance solubility of the poorly soluble drug.
2. Provide constant drug concentration in blood which can increase patient compliance Decrease dose and toxicity.
3. Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
4. Less dosing frequency leads to better patient compliance.
5. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
6. Protects the GIT from irritant effects of the drug.
7. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without unto ward effects.
8. Biodegradable microsphere have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.

9. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects.

APPLICATION OF MICROSPHERES:

1. Microspheres in vaccine delivery:

A vaccine's primary goal is to provide protection against a microorganism or its toxic product. An ideal vaccine should meet key criteria such as efficacy, safety, ease of application, and affordability. Safety, particularly minimizing adverse reactions, is a complex challenge. The safety profile and the effectiveness of antibody production are closely linked to the method of vaccine administration. Biodegradable delivery systems for vaccines administered through parenteral routes could address some of the limitations associated with conventional vaccines. Parenteral delivery methods (such as subcutaneous, intramuscular, or intradermal injection) offer several advantages, including: i) enhanced antigenicity through adjuvant action, ii) controlled release of the antigen, and iii) stabilization of the antigen.[12]

2. Monoclonal antibodies mediated microspheres targeting:

Microspheres that are targeted using monoclonal antibodies are known as immune-microspheres. This targeting strategy is used to direct the microspheres to specific sites. Monoclonal antibodies (MAbs) are highly specific molecules, and their precision can be leveraged to deliver microspheres containing bioactive molecules to targeted areas. MAbs can be covalently attached to the surface of the microspheres. The attachment can occur through free aldehyde, amino, or hydroxyl groups on the microsphere surface. There are several methods to attach MAbs to microspheres, including: i) non-specific adsorption, ii) specific adsorption, iii) direct coupling, and iv) coupling via chemical reagents.[12]

3. Oral drug delivery:

The capability of polymer-containing microspheres to form films makes them suitable for use in film dosage forms, offering an alternative to traditional pharmaceutical tablets. Their pH sensitivity, along with the reactivity of primary amine groups, enhances the potential of these microspheres for oral drug delivery applications. Examples of such polymers include chitosan and gelatin.[11]

4. Gene delivery:

Microspheres can serve as effective oral gene carriers due to their adhesive and transport properties within the gastrointestinal (GI) tract. Examples of materials used for this purpose include chitosan, gelatin, viral vectors, cationic liposome-polycation complexes, and DNA plasmids for gene therapy, as well as for insulin delivery. They also offer advantages in vaccine delivery, as the primary objective of a vaccine is to provide protection against a microorganism or its toxic byproducts. Biodegradable delivery systems for vaccines administered via the parenteral route can help address some of the limitations of conventional vaccines.[11]

5. Intratumoral and local drug delivery:

To deliver paclitaxel at therapeutic concentrations to the tumor site, polymer films are developed. A combination of drugs shows significant potential for controlled delivery within the oral cavity. Examples of materials used for this purpose include gelatin, PLGA, and chitosan.[11]

6. Ocular drug delivery:

Drug-loaded ophthalmic delivery systems are commonly used in the treatment of glaucoma, particularly for cholinergic agonists such as pilocarpine. The brief elimination half-life of aqueous eye drops, which is typically between 1 to 3 minutes, can be extended to a longer duration (15 to 20 minutes) by using microspheres with biodegradable properties, such as polyalkylcyanoacrylate.[4]

7. Nasal drug delivery:

Polymer-based drug delivery systems, including microspheres, liposomes, and gels, have shown excellent bioadhesive properties. When in contact with the nasal mucosa, they tend to swell, which enhances the bioavailability and prolongs the residence time of the drugs administered via the nasal route. Examples of such polymers include starch, dextran, and albumin.[11]

8. Gastrointestinal drug delivery:

Polymer granules with internal cavities, created by deacidification, become buoyant when introduced into acidic or neutral media, offering controlled release of drugs like Prednisolone. Floating hollow microcapsules containing melatonin demonstrate a gastroretentive controlled-release system, with the drug release significantly slowed, lasting between 1.75 to 6.7 hours in simulated gastric fluid. Many mucoadhesive microcapsules remain in the stomach for over 10 hours. Examples include chitosan microspheres loaded with Metoclopramide and Glipizide.[13]

9. Buccal drug delivery:

Chitosan is an ideal polymer for buccal drug delivery due to its muco/bioadhesive properties and its ability to enhance absorption. Buccal tablets made from chitosan microspheres containing Chlorhexidine Diacetate provide prolonged drug release in the buccal cavity, thereby enhancing the antimicrobial activity of the drug. Even polymer microparticles without incorporated drugs exhibit antimicrobial properties due to the polymer itself. Buccal bilayer devices, such as bilaminated films or layered tablets, which use a combination of drugs like Nifedipine and Propranolol hydrochloride along with chitosan, either with or without anionic crosslinking polymers (such as polycarbophil, sodium alginate, or gellan gum), show significant potential for controlled drug delivery in the oral cavity.[14]

10. Vaginal drug delivery:

The polymer, modified by adding thioglycolic acid to its primary amino groups, incorporates Clotrimazole, an imidazole derivative commonly used for treating mycotic infections of the genitourinary tract. The introduction of

thiol groups enhances the mucoadhesive properties of polymer-based drug delivery systems, such as microspheres, liposomes, and gels. These systems exhibit strong bioadhesive characteristics, allowing them to swell upon contact with the nasal mucosa, which improves the bioavailability and extends the residence time of drugs administered via the nasal [route. Examples of such polymers include starch, dextran, and albumin. [16]

11. Transdermal drug delivery:

The polymer exhibits excellent film-forming abilities. The drug release from these devices is influenced by factors such as the membrane thickness and the degree of cross-linking of the film. A chitosan-alginate polyelectrolyte complex has been developed in situ into beads and microspheres for use in various applications, including controlled release systems, packaging, and wound dressings. Polymer gel beads serve as promising biocompatible and biodegradable carriers for treating local inflammation, with drugs like Prednisolone showing sustained release and enhanced therapeutic effects. The rate of drug release depends on the type of membrane used. A combination of chitosan membranes and chitosan hydrogel, incorporating lidocaine hydrochloride (a local anesthetic), forms an effective transparent system for controlled drug delivery and optimal release kinetics.[17]

12. Colonic drug delivery:

A polymer has been utilized for targeted insulin delivery to the colon. Chitosan capsules, coated with an enteric coating (Hydroxypropyl methylcellulose phthalate), were formulated to contain insulin along with various absorption enhancers and enzyme inhibitors. It was observed that these capsules disintegrated specifically in the colonic region. This disintegration was believed to be caused either by the lower pH in the ascending colon compared to the terminal ileum, or by the presence of bacterial enzymes capable of degrading the polymer.[15]

13. Topical porous microspheres:

Microsponges are porous microspheres, ranging in size from 5 to 300 µm, with numerous interconnected voids. These microsponges are capable of trapping a wide variety of active ingredients, including emollients, fragrances, and essential oils. They are used as a delivery system for topical applications and can be incorporated into products such as creams, lotions, and powders. Microsponges feature non-collapsible structures with a porous surface, allowing the controlled release of the active ingredients.[18]

CONCLUSION:

This review article highlights the advantages of microspheres as an advanced drug delivery system, offering superior benefits compared to other delivery methods. Microspheres are considered safer due to their ability to enhance patient efficiency and precision in targeting specific areas. They offer several key benefits, including controlled, sustained release of drugs, enhanced stability, reduced frequency of drug administration, and improved bioavailability. These features make microsphere-based drug delivery one of the most effective options available. Beyond drug delivery, microspheres have applications in drug targeting, flotation, combating drug resistance, and are also valuable tools in tumor imaging, biomolecular interaction detection, and cancer treatment. Methods for preparing and assessing microspheres are thorough and practical, supporting their broad range of uses.

REFERENCE:

1. Chein YW. Novel drug delivery systems. Marceljekker Inc., New York. 1992; 13.
2. Kumari N, Aggarwal G, Hari kumar SL. Mucoadhesive microspheres:A review. Journal of Drug Delivery and Therapeutics. 2014 Sep14; 4(5):48-54.
3. Dhakar RC, Maurya SD, Sagar BP, Bhagat S, Prajapati SK, Jain CP. Variables influencing the drug entrapment efficiency of microspheres: A pharmaceutical review. Der Pharmacia Lettre. 2010;2(5):102-16..
4. Singh C, Purohit S, Singh M, Pandey BL. Design and evaluation of microspheres: A Review. Journal of drug delivery research. 2013;2(2):18-27..
5. Rajput S, Agrawal P, Pathak A, Shrivasatava N, Baghel SS, Baghel RS. A review on microspheres: Methods of preparation and evaluation. World journal of pharmacy and pharmaceutical sciences. 2012;1(1).
6. Ayon NJ, Hasan I, Islam MS, Reza MS. Preparation and characterization of gliclazide incorporated cellulosic microspheres: studies on drug release, compatibility and micromeritics. Dhaka University Journal of Pharmaceutical Sciences. 2014;13(2):149-66.
7. .Patel S, Kumhal RP, Dinesh PA, Gorantli CC. A review on microspheres: types, methods of preparation, effects of process variables and applications. American Journal of Pharm Tech Research. 2020;10(4):123-40.
8. Garg A, Upadhyay P. Mucoadhesive microspheres: A short review. Asian journal of pharmaceutical and clinical Research. 2012;5(3):24-7.
9. Kaurav H, Hari Kumar SL, Kaur A. Mucoadhesive microspheres as carriers in drug delivery: a review. International journal of drug development & research. 2012 Apr;4(2):21-34.
10. Patel R, Patel K, Patel Z, Patel DR, Solanki KP. Formulation and evaluation of sustained release microspheres of itopride hydrochloride. AEGAEUM J. 2020;8:1913-23.
11. Virmani T, Gupta J. Pharmaceutical application of microspheres: an approach for the treatment of various diseases. Int J Pharm Sci Res. 2017;8(8):3253-60
12. Dhamapurkar SP, Desai DM. A review on microsphere for novel drug delivery system. World Journal of Advanced Research and Reviews. 2022;16(3):529-38.
13. Meena KP, Dangi JS, Samal PK, Namedo KP. Recent advances in microsphere manufacturing technology. International journal of pharmacy and technology. 2011 Mar;3(1):854-5.
14. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. Int J Chem Tech Res. 2009 Jul;1(3):526-34.
15. Sudhamani T, Reddy KN, Kumar VR, Revathi R, Ganesan V. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal of Pharma Research and Development. 2010;2(8):120-1.
16. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: A review. Int. J. Res. Pharm. Chem. 2011; 1(4):1184-98.
17. Athira K, Vineetha K, Krishnananda Kamath K, Shabaraya AR. Microspheres As A Novel Drug Delivery System-A Review. International Journal of Pharmaceutical Sciences Review and Research. 2022; 75(1):160-6.
18. Tadwee IA, Shahi S, Thube M. Ankit S. Review on Microspheres. International Journal of Pharmaceutical Research Allied Sciences. 2012; 1(1):24-33.