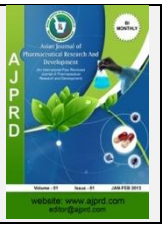
Available online on 15.08.2023 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

An Overview on Novel Drug Delivery System of Microsphere and its Types, Materials, Method of Preparation

Varda Joshi *, Atish Velhal, Swapnali Patil, Vivek Kumar Redasani, Poonam Raut, Nikita Bhosale

YSPM's YTC Faculty of pharmacy Wadhe phata, Satara

A B S T R A C T

Today, there is a lot of interest in medication delivery systems based on microspheres. Microspheres can be created using both natural and artificial polymers and are typically free-flowing powders. The microspheres' diameters range from 1 to 1000 m. In microspheres, the medicine is evenly spread, dissolved, or suspended in a matrix system. Drugs that are either solid or liquid are dissolved or disseminated in a matrix system in microspheres. The current review gives a thorough overview of recent and innovative advancements on microsphere forms that have been claimed to boost bioavailability, improve stability, lengthen biological half-life, and lessen drug toxicity. Many different proteins and peptide compounds can be delivered effectively by microsphere. Microspheres come in a variety of forms, including bioadhesive, magnetic, polymeric, floating, and floating microspheres. In order to create microspheres, a variety of techniques are employed, including simple emulsion-based, double emulsion-based, interfacial deposition, interfacial polymerisation, phase separation, and spray drying. Through a variety of delivery methods, including oral, topical, naso-pulmonary, and gene therapy, microspheres administer the medication in a regulated manner. Due to their ability to encapsulate a variety of medications, biocompatibility, high bioavailability, and continuous drug release nature, polymeric based microspheres serve as ideal carriers for several controlled delivery applications. As a result, by creating novel procedures, it can increase therapeutic results and enhance drug safety. The development of microspheres has been linked to improvements in the drug's stability, bioavailability, biological half-life, and toxicity.

Keywords: Microspheres, Drug delivery, types of microspheres, Method of preparation,

A R T I C L E I N F O: Received 17 April 2023; Review Complete 25 May 2023; Accepted 05 July 2023; Available online 15 Aug. 2023

Cite this article as:

Joshi V, Atish V, Patil S , Kumar RV, Raut P, Bhosale N, An Overview on Novel Drug Delivery System of Microsphere and its Types, Materials, Method of Preparation, Asian Journal of Pharmaceutical Research and Development. 2023; 11(4):106-114.
DOI: http://dx.doi.org/10.22270/ajprd.v11i4.1290

*Address for Correspondence:
Varda Joshi, YSPM's YTC Faculty of pharmacy Wadhe phata, Satara

INTRODUCTION:

To achieve optimum therapeutic efficiency, it is essential to transport the drug to the target tissue in the ideal quantity and at the proper timing, generating low toxicity and side effects in the process [1].In order to deliver a medicinal chemical to the target region with a continuous regulated release, there are several different methods. One of the most effective medication delivery methods is the oral route[2]. It has a brief half-life in circulation and only a little amount may be absorbed via a certain intestinal barrier.[3] Due to this pharmacokinetic flaw, drug dose must be increased often to achieve therapeutic effect.[3] Bioavailability rises when pharmacokinetic and pharmacodynamic profiles are improved. The achievement of the medicine's intended concentration in blood or tissue is used to define the efficacy of the therapeutic therapy. The dosage plan's effectiveness aids in target achievement [4].Many medicines found in the contemporary drug development process have poor water solubility. A little over 40% of commercially available oral immediate-release medications are essentially insoluble.[3] The medications' poor water solubility led to a number of issues, including poor bioavailability, dosage escalation, rising production costs, inaccurate results from in vitro and in vivo assay performances, and inadequate therapeutic outcomes.

The health care system has been greatly impacted by drug delivery systems (DDS) that can precisely regulate release rates or direct medications to a particular bodily spot. Throughout the course of therapy, the perfect drug delivery system administers medication at a pace determined by the

body's needs, and it only distributes the active ingredient to the site of action. Therefore, by attaching the drug to a carrier particle like microsphere, nanoparticles, liposome, etc. which regulates the release and absorption properties of the medication, carrier technology offers an intelligent way for drug delivery[6].

Types of Drug Delivery System:

1. Liposome
2. Niosomes
3. Nanoparticle
4. Microsphere

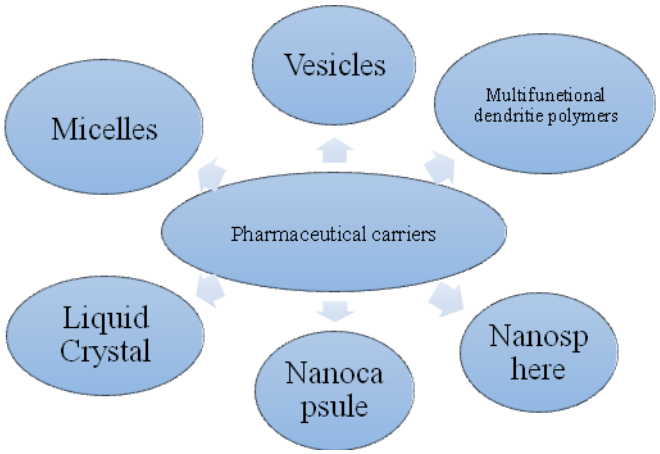


Figure1: Pharmaceutical carriers

In the case of chronic patients, the medication must be administered over an extended length of time, and several medications must be taken at the same time. When a drug's half-life is shorter and patient compliance declines as a result, frequent administration is required. [1] A variety of controlled release dosage forms are created and modified in order to address the aforementioned issues. The goal is to promote patient compliance by prolonging the effects and reduce side effects by reducing peak plasma concentration.[7]The controlled release dosage form releases the medication at a predefined pace over a lengthy period of time to maintain a comparatively consistent drug level in the plasma. One approach to a controlled release dosage form in a unique medication delivery system is to use microspheres as drug carriers.[8]

Microspheres

Microspheres can be described as either a "monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) as a "structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level."[4] Its particles range in size from 1 to 1000 nm.[8]Microspheres are matrix systems with evenly distributed, dissolved, or suspended active ingredients. Drugs that are dissolved or disseminated in a matrix system are included in microspheres [9]. Inter-individual variances are eliminated when microspheres smaller than 800 m pass past the pyloric sphincter without affecting stomach emptying. The administering site retains microsphere particles larger than 100 nm until phagocytic clearance. The lymphatic system significantly absorbed microspheres between the size ranges of 10 and 80 nm [10]. The aggregation of particles is significantly influenced by the surface charge. Particle accumulation reduces dosage homogeneity and interferes with blood flow normally [11,12]. They are spherical, freely moving particles made of artificial polymers or proteins. The microspheres are naturally occurring free-flowing powders made of biodegradable synthetic or protein-based polymers. Two different kinds of microspheres exist

- Microcapsules
- Micromatrices

Oral microencapsulation has been used to minimize or completely remove gastrointestinal tract discomfort while maintaining medication release. Multiparticulate delivery methods are also available. dispersed out more evenly throughout the digestive system. Compared to single-unit dose forms such polymeric matrix tablets with no disintegration, this leads to more consistent drug absorption and lessens local discomfort. Additionally, matrix tablets' potential for causing unwanted intestinal retention of the polymeric substance can be avoided.[13] Drug release can be modified and delayed via microencapsulation. As a result of their tiny particle size, they are broadly dispersed throughout the digestive system, improving medication absorption and minimizing adverse effects brought on by a localized build up of irritating medicines against the gastrointestinal mucosa.[14]

Drug release mechanism through microsphere:

The drug diffuses via the pores that are filled with aqueous fluid or the entire integrated polymer system. Drugs that are hydrophilic may dissolve in aqueous fluid-filled pores. Aqueous fluid absorption causes the polymer network to expand, which shows the emergence of new holes and increases osmotic pressure. Swelled polymer increases volume, improving the drug's beneficial diffusion coefficient and allowing more drug molecules to enter the aqueous phase. Additionally, the microspheres' bulk or surface may degrade the polymer matrix [15,16].

Ideal Characteristics of Microsphere [18,19]

The micro encapsulation process may be used to include solids, liquids, or gases into one or more polymeric

coatings[32]. Particle size, route of administration, length of drug release, and these aforementioned characteristics linked to rpm, technique of crosslinking, drug of crosslinking, evaporation time, coprecipitation, etc. are all factors that affect the varied procedures utilised to prepare distinct microspheres [18]. Certain requirements should be met for creating microspheres [19]:

1. Better stability and a clinically acceptable shelf life following synthesis
2. Proper particle size and injectable dispersibility in aqueous mediums.
3. The controlled release of a substance over an extended period of time.
4. Excellent biocompatibility and manageable biodegradability.

Types of Microsphere:

1. Bioadhesive Microsphere[20] :

Adhesion is the attaching of a substance to a membrane using the adhesive properties of water soluble polymers. Bio adherence can be defined as adhesion to the mucosal membrane of the drug delivery device, including the buccal, ophthalmic, rectal, nasal, etc. These types of microspheres interact intimately with the absorption site, remain at the application site for an extended period of time, and yield better therapeutic outcomes. Mucoadhesive microspheres, which also encourage intimate physical contact, enable prolonged contact time at the application or absorption site. the area beneath the skin where absorption is supposed to occur, increasing or improving the therapeutic efficiency of the medicine.

2. Magnetic Microsphere [21]

Microspheres are typically tiny, freely moving, spherical particles made of biodegradable proteins or synthetic polymers, ranging in size from 1 to 1000 m. They are regarded as one of the crucial methods for releasing medicinal substances into the target area in a safe and regulated manner. The many types are

a) **Therapeutic magnetic microsphere:**Known for using chemotherapy to treat liver tumours. Additionally, this gadget can target pharmaceuticals like proteins and peptides.

b) **Diagnostic Microspheres :**Utilised to produce supramagnetic iron oxide nanoparticles, which may be used to distinguish the intestinal loops of other abdominal tissues and to visualise liver metastases.

3. **Radioactive microspheres [24]:**Radio embolization treatment microspheres are 10–30 nm–larger than capillary diameter and are injected into the first capillary bed as they pass. These are injected into the arteries that supply an interesting tumour, and they cause increased radioactivity in each of these circumstances. without endangering the normal tissues around them, microspheres to the targeted locations. The numerous forms of radioactive microspheres are emitters, emitters, emitters, which differs from the medication delivery mechanism in that radioactivity is not emitted from microspheres instead it acts from a distance characteristic of a radioisotope.

4. **Floating Microspheres [25,26]:** Since floating forms have a lower bulk density than gastric fluid, they float unaffected in the stomach without slowing down the process of gastric emptying. As the body floats on stomach content and reduces gastric residency and plasma concentration fluctuation, the medicine is released at the correct rate gradually. Additionally, this lessens the chance of striking and dosage dumping. It does this in one method by producing a long-lasting therapeutic impact, which lowers the dosage frequency.

5. **Polymeric microspheres [27]**The many kinds of polymeric microspheres may be divided into two categories: synthetic polymeric microspheres and biodegradable polymeric microspheres.

a) **Biodegradable Polymeric microspheres:** It is believed that natural polymers like starch are biodegradable, biocompatible, and even bioadhesive by nature. Due to their strong swelling characteristics in aqueous media, biodegradable polymers prolong their time spent in contact with the mucous membrane. Polymer concentration and release pattern effectively control the rate and extent of medication release. The main drawbacks of biodegradable microspheres in clinical usage are significant dependability issues and challenging medication release control. However, they do provide a wide range of microsphere-focused applications.

b) **Synthetic Polymeric microspheres:** Synthetic polymeric microspheres are frequently utilised in therapeutic applications, in addition to their frequent use as bulking agents, fillers, embolic particles, drug delivery vehicles, etc. These microspheres have been shown to be safe and biocompatible, but their main drawback is that they appear to migrate away from the injection site, increasing the risk of harm, embolism, and further organ damage.

Polymers:

Microspheres used usually are polymers. They are classified into two types:

- Synthetic Polymers
- Natural polymers

Synthetic polymers are divided into two types.

a) **Non-biodegradable polymers**
Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b) **Biodegradable polymers**

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically Modified carbohydrates.

Proteins: Albumin, Gelatin, Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran**,** Poly starch.[31]

METHODS OF PREPERATION:

1. Emulsion solvent evaporation technique
2. Emulsion cross linking method

3. Coacervation method
4. Spray drying technique
5. Emulsion-solvent diffusion technique
6. Multiple emulsion method
7. Ionic gelation method
8. Hydroxyl appetite (HAP) microspheres in sphere morphology

The microencapsulation process can be used to incorporate solid, liquid, or gas into one or more polymeric coverings.[32] The numerous techniques utilised to prepare distinct microspheres rely on the particle size, administration route, length of drug release, and the aforementioned factors. Characters pertaining to rpm, crosslinking techniques, drugs, evaporation rates, coprecipitation, etc.[33] The numerous preparatory techniques include

1. Emulsion solvent evaporation technique

This method involves dissolving the medication in a polymer that has previously been dispersed in chloroform, and then adding the resultant solution to an aqueous phase that contains 0.2% sodium PVP as an emulsifying agent. The aforementioned combination was stirred at 500 rpm, and the medicine and polymer (Eutragit) were then separated into tiny droplets that were then filtered, rinsed with demineralized water, and dried at room temperature for 24 hours. Using this method, aceclofenac microspheres were created. [34]

2. Emulsion cross linking method

In this procedure, the medication was dissolved in an aqueous gelation solution that had been heated for an hour at 40°C beforehand. Without forming an emulsion after being stirred at 1500 rpm for 10 minutes at 35°C, the solution was added drop by drop to liquid paraffin. 10 minutes at 15 °C. Thus, the microspheres were washed three times with acetone and isopropyl alcohol before being air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for three hours for cross linking before being treated with 100mL of 10mm glyciene solution containing 0.1%w/v tween 80 at 37oC for ten minutes to block unreacted glutaraldehyde. [35]Gelatine A microspheres are a prime illustration of this tactic. [35]

3. Coacervation method

Coacervation thermal change was produced by heating cyclohexane to 80°C while vigorously swirling ethyl cellulose to dissolve it. The medication was then added to the solution above, finely ground, and vigorously stirred. Phase separation was then accomplished by lowering temperature and utilising an ice bath. Following two cyclohexane washes and air drying of the aforementioned product, sieve no. 40 was used to separate the product into individual microcapsules. [36]Coacervation without the use of a solvent was achieved by dissolving ethyl cellulose in toluene containing propyl isobutylene in a closed beaker with magnetic stirring at 500 rpm for six hours. It is given a 15-minute stir after the medicine has been distributed throughout it. Petroleum benzoin is then used to perform phase separation.14 times while stirring continuously. The microcapsules were then cleaned with n-hexane, allowed to air dry for two hours, and then placed in an oven set to 50°C for four hours.

4. Spray drying technique

This was used to manufacture microspheres made of polymeric blends and filled with the medication ketoprofen. It entails scattering the core material into a liquid coating substance, spraying the combination outside allowing the coating to solidify, and then quickly evaporating the solvent. In order to create drug-loaded microspheres, an organic solution of poly (epsilon caprolactone), cellulose acetate butyrate (CAB), and ketoprofen was produced and sprayed under various experimental conditions. This is quick, however the quick drying process might cause crystallinity to be lost.[37]

5. Emulsion-solvent diffusion technique

Ketoprofen floating microparticles were created utilising the emulsion solvent diffusion approach to increase the residence duration in the colon. The drug polymer combination was dissolved in a 1:1 mixture of dichloromethane and ethanol before being added drop by drop to a sodium lauryl sulphate (SLS) solution. At room temperature, the solution was agitated for 1 hour at 150 rpm using a propeller-style agitator. As a result, the produced floating microspheres were cleaned before being dried at room temperature in a dessicator. The following microparticles were sorted using a sieve and gathered.[38]

6. Multiple emulsion method

This method was used to create oral controlled release drug delivery of several medications. Drug powder was first dissolved in a solution (methyl cellulose), then it was emulsified with an ethyl cellulose solution in ethyl acetate. Reemulsification of the main emulsion in aqueous media followed. During this phase[39], distinct microspheres were created under optimal conditions.

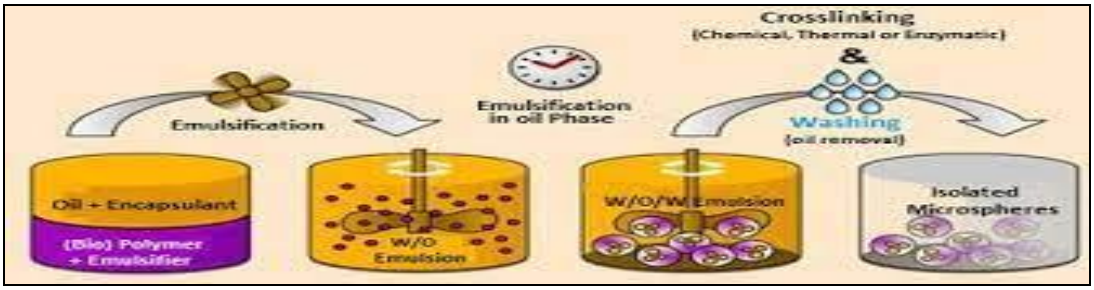


Figure 2: Multiple emulsion method

7. Ionic gelation method

This method was used to create an alginate/chitosan particulate system for Diclofenac sodium release. 1.2% (w/v) of sodium alginate in an aqueous solution was mixed with 25% (w/v) of Diclofenac sodium. Stirring is kept up until the solution is fully dissolved, and then was dropped into an acetic acid-based mixture of chitosan, Ca2+/Al3+, and other ingredients. In order to separate the produced microspheres, they were filtered after being left in the original solution for 24 hours to allow internal gellification. While the medication did not release in an acidic pH range, the full release was achieved there.[39]

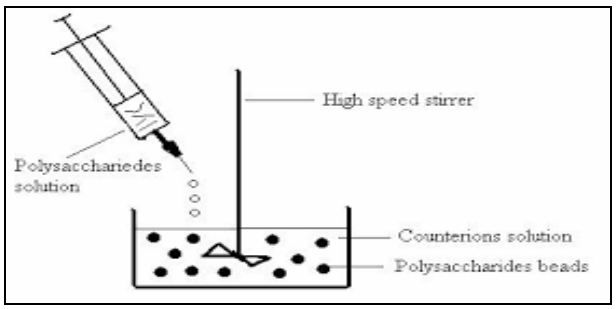


Figure 3: Ionic gelation method

8. Hydroxyl appetite (HAP) microspheres in sphere morphology

This method was used to create microspheres with unusual spherical morphologies. It involved creating an o/w emulsion and then letting the solvent evaporate. The organic phase was first dispersed in the aqueous phase of the surfactant to create an o/w emulsion. The organic phase was distributed as teeny droplets that were encircled by surfactant molecules. This helped the droplets maintain their individuality by preventing co-solvencing.DCM was gently evaporating while being stirred, and the droplets individually solidified to form microspheres.[40]

Need of Microsphere:

A drug proposed for clinical use must have an optimal therapeutic index (ratio of minimum effective to the maximum safe concentration of drug). Many chemotherapeutic agents have a narrow therapeutic window leading to restricted clinical use and increased toxic side effects. So, these kinds of drugs are incorporated in a polymer system, which ensures the controlled release of drugs to provide optimum drug levels at the target site [41]. Numerous targeted drug delivery systems have come up with different techniques to attain controlled and targeted drug delivery. Microsphere based targeted drug delivery system is gaining substantial importance in the modern era [42]. The size of microspheres ranges from 1 to 1000 µm. Microspheres are matrix systems containing active ingredient uniformly dispersed, dissolved or suspended. Drugs that are either solid or liquid can be dissolved or disseminated in a matrix system using microspheres [43]. Inter-individual variances are eliminated when microspheres smaller than 800 m pass past the pyloric sphincter without affecting stomach emptying. The administering site retains microsphere particles larger than 100 nm until phagocytic clearance. The lymphatic system specifically absorbed microspheres between the size ranges of 10-80 nm [44]. The aggregation of particles is significantly influenced by the surface charge. Aggregation of particles leads to a decrease in the uniformity of dose and disturbs the normal flow of blood [45, 46].

List of drugs and polymers used in microspheres:

Sr No	Drug	Polymer	Method of preparation	Comment	Reference
1	Naltrexone	PLGA	Double emulsion (oil in water)	Compared to the reference naltrexone sustained-release capsulesbhad superior bioavailability and a sustained-release action.	47
2	Risperidone	PLGA	Double emulsion (oil in water)	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	48
3	Octreotide	PLGA-glucose	Phase separation method (oil in water)	dosage form could reduce the dosing frequency and improve patient compliance	49
4	Leuprolide	PLGA or PLA	Double emulsion (w/o/w)	Increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount.	50
5	Somatropin	PLGA	Cryogenic spray drying	Increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount.	51
6	Lanreotide	PLGA	Phase separation	dosage form could reduce the dosing frequency and improve patient compliance	52
7	Buserelin	PLGA	Double emulsion (w/o/w)	dosage form could reduce the dosing frequency and improve patient compliance	52
8	Triptorelin	PLGA or PLA	Phase separation	dosage form could reduce the dosing frequency and improve patient compliance	52
9	Bromocriptine	PLGA-glu	Spray drying	dosage form could reduce the dosing frequency and improve patient compliance	50
10	Minocrydine	PLGA	solid-in-oil-in-water (S/O/W) , co-solvent method	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	50

11	Goserelin acetate	PLGA	Solvent evaporation method	Reduce the dosing frequency and improve the patient compliance	[49]
12	Metformin Hcl	Sodium alginate	Ionic gelation method	It was found that drug release rate decreased with the amount of polymer increased in formulation.	[48]
13	Amoxicillin trihydrate	Ethyl cellulose, khaydsenegalensis	Spary drying		[53]
14	Ibuprofen	Sodium alginate	O/w emulsion solvent evaporation	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased. The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[54]
15	Pioglitazide Hcl	Carbopol 934	Ionotropic external gelation	dosage form could reduce the dosing frequency and improve patient compliance	[55]
16	Trimetazidine Hcl	chitosan	Ionic gelation	dosage form could reduce the dosing frequency and improve patient compliance	[56]
17	Furocemide	Sodium alginate , chitosan, carbopol	Ionic cross linking	The research study provided useful information for the formulation scientists on formulation, characterization during development of controlled drug delivery systems of drug using these polymers	[57]
18	Insulin	Sodium alginate , chitosan,	W/o/w multiple emulsion solvent evaporation technique	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[58]
19	Furazolodine	Eutragit RS100, carbopol934p, HPMC	Simple emulsification Phase separation	Prepared by using various grades of HPMC as polymer to retard the release and achieve the retard dissolution profile.	[59]
20	Aceclofenac	Sodium alginate , HPMC , chitosan , carbopol	Single emulsion Spary drying	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[59]
21	Acyclovir	Chitosan, sodium alginate	Ionic emulsion Non-aq solvent evaporation	Increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount.	[59]
22	Atenolol	Polyacrylic acid	solvent diffusion method	Polymer that delays release. Drug distribution via the intestine is possible with it.	[60]
23	Propranol	Polyvinyl pyrrolidine	solvent diffusion method	Polymer that delays release. Drug distribution via the intestine is possible with it.	[14]
24	Rantidine Hcl	Sodium alginate	solvent evaporation, double emulsion, coacervation phase separation.	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[25]
25	Glipizide	Chitosan	Emulsion cross linking method	polymer that delays release. Drug distribution via the intestine is possible with it.	[26]
26	Captoril	Sodium alginate, HPMC, chitosan , carbopol934p,	Ionic crosslinking method	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[27]
27	Ketoprofen	Sodium alginate , chitosan , pectin, xanthum gum	spray drying, emulsion cross-linking, ionotropic gelation	It was found that drug release rate decreased with the amount of polymer increased in formulation.	[28]
28	Salbutamol sulphate	Carbopol , HPMC	modified solvent evaporation method	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[31]
29	Torsemide	Sodium alginate , HPMC	Solvent evaporation or spray drying	prepared by using various grades of HPMC as polymer to retard the release and achieve the retard dissolution profile.	[42]
30	Ketorolac	Eutragit RS100, Eutragit RL100	Solvent evaporation	Reduce the dosing frequency and improve the patient compliance	[61]
31	Acetazolamide	Eutragit RS100, Eutragit RL100	Solvent evaporation	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[62]
32	Metronidazole	Guar gum,	Solvent evaporation	It was found that drug release rate decreased with the amount of	[63]

		sodium alginate		polymer increased in formulation.	
33	Famotidine	Sodium CMC, sodium alginate	Solvent evaporation or spray drying	Drug release was retarded with an increase in polymer concentration due to the gelling property of polymers	[64]
34	Monteleukast sodium	HPMC, Eutragit Carbopol	Solvent evaporation or spray drying	Increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount.	[65]
35	Nizatidine		Solvent evaporation	Drug release was retarded with an increase in polymer concentration due to the gelling property of polymers	[66]
36	Lafutidine	Sodium alginate, HPMC, chitosan , carbopol934p, cellulose acetate , phthalate	Solvent evaporation	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[67]
37	Metronidazole Benzoate	HPMC, Carbopol 934	Solvent evaporation (oil in water)	prepared by using various grades of HPMC as polymer to retard the release and achieve the retard dissolution profile.	[68]
38	Esomeprazole	Sodium alginate, HPMC, chitosan , carbopol934p, cellulose acetate , phthalate	Non aqueous solvent evaporation method	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	[68]
39	Roxatidine	Chitosan, sodium alginate	Ion tropic gelation method	Drug release was retarded with an increase in polymer concentration due to the gelling property of polymers	[68]

Ideal characteristics of microspheres: [5,6]

1. The capability of incorporating medication concentrations that are reasonably high.
2. After synthesis, the preparation must be stable and have a shelf life that is therapeutically acceptable.
3. Particle size and dispersibility in aqueous injection vehicles are controlled.
4. Controlled release of the active reagent over a broad time frame.
5. Biodegradability that is controlled and biocompatible.
6. Chemical modification vulnerability.

Advantages of microspheres:[6]

7. Reducing the size of the particles to improve a drug's low solubility.
8. Offer a consistent and long-lasting therapeutic impact.
9. Maintain a steady drug concentration in the blood, boosting the compliance with patents.
10. Reduce toxicity and dosage.
11. Protect the drug from enzymatic and photolytic cleavage, making it the ideal option for protein drug delivery.
12. Decrease the dosage frequency to increase patient compliance.
13. More effective medicine use will increase bioavailability and lessen the frequency or severity of side effects.

9. The shape of the microspheres provides for predictable fluctuation in medication release and breakdown.

10. Convert a liquid into a solid and cover up the bitter flavour.

11. Guards against the drug's irritating side effects on the GIT.

12. Compared to big polymer implants, biodegradable microspheres offer the benefit of not requiring surgery for installation or removal.

13. Deliveries with controlled release Drug release rates are regulated using biodegradable microspheres, which reduces harmful side effects and does away with the hassle of frequent injections.

Limitation:[5]

Some of the disadvantages were found to be as follows

1. Compared to ordinary formulations, the prices of the components and processing for the controlled release preparation are significantly greater.
2. How polymer matrix decays and how it affects the environment.
3. What happens to polymer additives such fillers, stabilisers, antioxidants, and plasticisers.
4. There is less reproducibility.
5. Process factors like temperature changes, pH changes, solvent additions, and agitation and evaporation might affect how stable the core particles are before encapsulation.
6. The impact on the environment of the polymer matrix breakdown products created in reaction to heat, hydrolysis, oxidation, solar radiation, or biological agents.

CONCLUSION:

Microspheres have revealed immense promise for the delivery of remedial agents owing to their biocompatibility, easiness of administration and potential for lasting sustained release. Additionally, microspheres are valuable for delivering numerous types of compounds, as well as small molecule drugs, vaccines, gene therapy agents and protein therapeutics. For past several years of studies, it has been exhilarating development in methods of production, managing of drug release rates and particularly stabilization of the encapsulated materials. In the coming decade, the development in macro-molecular pharmaceuticals will compel more advances in particle fabrication and drug encapsulation techniques, in addition to common methods of stabilizing protein and gene therapeutics. Improvements in developed technologies, novel strategy for stabilization of delicate therapeutics and progress of novel approaches for site-specific particle targeting will ensure that microspheres play a significant job in the drug delivery field in the coming decade, too.

REFERENCES:

1. N. K. Jain, Controlled and Novel drug delivery, 04 Edition, CBS Publishers New Delhi, India; 21, 236-237.
2. Ganesan P, Jonson AJD. Review on microspheres. Am J Drug Discovery Dev 2014;4:153-79.
3. Whelehan M, Marison IW. Microencapsulation using vibrating technology. J Microencapsul 2011;28:669–88.
4. Yang Q, Forrest L. Drug delivery to the lymphatic system. In: Wang B, Hu L, Siahaan TJ. editors. Drug Delivery Principles and Applications. 2nd ed. Hoboken: John Wiley and Sons Inc; 2016. p. 503-48.
5. Kadam N. R., Suvarna V. Microspheres: A Brief Review. Asian J of Biomedical and Pharmaceutical Sci, 5(47); 2015: 13-19.
6. Joseph S and Selvin CDS. Formulation and evaluation of losartan microspheres. Int J Res Pharmacy Chem. 2015; 5(4): 555-563.
7. Sharma N, Purwar N and Gupta PC. Microspheres as drug carriers for controlled drug delivery: a review. Int J Pharm Sci Res. 2015; 6(11): 4579-4578.
8. Shanthi NC, Gupta R, Mahato KA, Traditional and Emerging Applications of Microspheres: A Review, International Journal of Pharm. Tech Research. 2010; 2(1):675- 81.
9. Shanthi N.C., Dr.Gupta R., Mahato K.A., Traditional and Emerging Applications of Microspheres: A Review, International Journal of Pharm Tech Research. 2010; 2(1):675- 681.
10. Najmuddin M., Ahmed A., Shelar S., Patel V., Khan T., Floating Microspheres Of Ketoprofen :Formulation and Evaluation, International Journal Of Pharmacy and Pharmaceutical sciences. 2010; 2(Suppl2):83-87.
11. Lengyel M, KallaiSazabo, N Microparticles. Microspheres and microcapsules for advanced drug delivery. Sci Pharm 2019;87:1-31.
12. Senthil A. Mucoadhesive microspheres. Int J Pharm Res Ayurveda Pharm 2011;2:55-9.
13. Lohani A, Chaudhary GP. Mucoadhesive microspheres: a novel approach to increase gastroretention. Chron Young Sci 2012;3:121-8.
14. Deshmukh MT, Mohite SK. Preparation and evaluation of mucoadhesive microsphere of fluoxitine HCL. Int J Pharm Sci Res 2017;8:3776-85.
15. Samanta K.M., Tamilvanan S., Babu K., Suresh B., Formulation and Evaluation of Chlorpromazine Hydrochloride Loaded Self- Cross-Linked Gelatin Microcapsules, Indian Journal of pharmaceutical Sciences. 1997; 59(2):68-74.
16. Chowdary K.P.R., Koteshwara R.N., Malathi K.., Ethyl Cellulose Microspheres of Glipizide: Charecterization, InVitro and In Vivo Evaluation, Indian Journal of pharmaceutical Sciences. 2004; 66(4): 412- 416.
17. KalyanShweta, Sharma Parmod Kumar et al. Recent Advancement In Chitosan Best Formulation And Its Pharmaceutical Application. Pelagia Research Library. 2010;1(3):195-210.
18. Dr. Fishers Microsphere Selection Bangs laboratories inc, Tech Notes 201 A, 1-4 Available from URL http://www.bangslabs.com/sites/default/files/bangs/docs/pdf/201A.pdf
19. P. Dutta, J.Struti, Ch. Niranajanpatra, M.E. Bhaojirao, Floating Microsphere: Recents Trends in the Development of Gastroretentive Floating Drug Delivery System. International Journal of Pharmaceutical Science and nanotechnology, 4(1), 2011, 1293-1306.
20. Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Ito, Preparation of multiple unit hollow microspheres (microbal loons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (invivo). J. Control. Release, 16, 1991, 279-290.
21. Kawatra M., Jain U., Ramana J., Recent advances in floating microspheres as gastroretentive drug delivery system: A review, IJRAPR. 2012; 2(3): 5-23.
22. Dupinder K., Seema S., Gurpreet S., Rana A.C., Biodegradable microspheres: A review, IRJP.2012; 3(12):23-27.
23. Prasanth v.v., Moy A. C., Mathew S. T., Mathapan R., Microspheres: An overview, Int. J. Res. Pharm. Biomed. Sci., 2011; 2: 3328.
24. Saralidze K., Koole L.H., Knetsch M. L. W., Polymeric microspheres for medical applications, Materials. 2010; 3: 3537-64.
25. Trivedi P, Verma AML and Garud N: Preparation and Characterization of Aceclofenac Microspheres. Asian Journal of Pharmaceutics 2008; 2:110-115.
26. Pandey K, Prajapati G and Patel MR: A Review on Microspheres. International Journal of Pharmaceutical Sciences 2012; 2:53-57.
27. Prasanth VV, Chakraborty A, Mathew ST, Mathappan R and Kamalakkannan V. Formulation and evaluation of Salbutamol sulphate microspheres by solvent evaporation method. Journal of Applied Pharmaceutical Science 2011; 1:133-137.
28. Sahu M, Satapathy T, Bahadur S, Saha S, Purabiya P, Kaushik S, et al. Preparation methods for nanoparticle: A smart carrier system for treatment of cancer. March 2018; 7(19): 216- 26.
29. Madhav NVS and Kala S: Review on microparticulate drug delivery system. International Journal of Pharm Tech Research 2011; 3:1242-1254.
30. Parmar H, Bakhliwal S and Gujhrati N et al: Different methods of formulation and evaluation of Mucoadhesive microspheres. International Journal of Applied Biology and Pharmaceutical Technology. 2010; 1: 1160-1163.
31. Dixit M, Kulkarni PK, Kini AG and Shivakumar HG. Spray Drying: A crystallization Technique: A review. Int J Drug Formulation and Res. 2010; 1: 1-29
32. Patel N. R., Patel D. A., Bharadia P.D., Pandya V., Modi D. Microsphere as a novel drug delivery. Int J Pharm. Life Sci. 201; 2(8): 992-7.
33. Parmar H, Bakliwal S, Gujarathi N, Rane B, and Pawar S. Different methods of formulation and evaluation of mucoadhesive microsphere. Int J Applied Bio Pharm Tech. Nov, 2010; 1(3): 1157-67.
34. Pachuau L, Bhaskar M. A study on the effects of different surfactants on ethyl cellulose microspheres. Int J Pharm Tech 2009; 4: 966-71.
35. Kavanagh N, Corrigan OI. Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices--influence of agitation rate and dissolution medium composition. Int J Pharm 2004; 279(1-2): 141-52
36. Trivedi P, Verma AML, Garud N. Preparation and Characterization of Acclofenac Microspheres, Asian Journal of pharmaceutics. 2008;2(2): 110-15.
37. Kreuter J, Nefzger M, Liehl E, Czokr. And Voges R. Polymer sci. and tech. J. Pharm. sci.(1983) 72, 1146.
38. Dandagi MP, Masthiolimath SV, Gadad PA, Iliger R.S. Mucoadhesive Microspheres of Propanalol Hcl for Nasal Delivery, Indian Journal of pharmaceutical Sciences. 2007;69 (3): 402-07.
39. Li SP, Kowalski CR., Feld KM., Grim WM. Recent Advances in Microencapsulation Technology and Equipment, Drug Delivery Ind. Pharm.1988; 353-76.
40. Mathew Sam T, Devi Gayathri S, Prasanthv VV, Vinod B. NSAIDs as microspheres, The Internet Journal of Pharmacology. 2008;6: 11-15.
41. Pradesh TS, Sunny M., Varma KH, Ramesh P. Preparation of microstructured hydroxyapatite microspheres using oil in water emulsion, Bull Matter. Sci. 2005; 28(5): 383- 90.
42. Punitha S, Girish Y. Polymers in mucoadhesive buccal drug delivery system. International Journal of Research and Pharmaceutical Sciences 2010; 1(2): 170-186.
43. Gavin PA, Laverty TP, Jones DS. Mucoadhesive Polymeric Platforms for Controlled Drug Delivery. European Journal of Pharmaceutics and Biopharmaceutics 2009; 71: 505-518.

44. Ganga S. Mucosal Drug Delivery. Pharmainfo.net 2007; 5.

45. Sachan NK, Bhattacharya A. Basic and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems. International Journal of Pharmaceutical and Clinical Research 2009; 1: 10- 14.

46. Moy AC, Mathew ST, Mathapan R, Prasanth VV. Microsphere-An Overview. International Journal of Pharmaceutical and Biomedical Sciences 2011; 2(2): 332-338.

47. Lehr CM, Bouwstra JA, Sahacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. International Journal of Pharmaceutics 1992; 78: 43-48.

48. Ranga KV, Buri P. A novel in situ method to test polymers and coated for microparticles bioadhesion . International Journal of Pharmaceutics 1989; 52: 265.

49. Masareddy RS, Bolmal UB, Patil BR, Shah V. Metformin Hcl loaded sodium alginate floating microspheres prepared by ionotropic gelation technique. Indian Journal of Novel Drug Delivery 2011; 3(2): 125-133.

50. Yellanki SK, Singh J, Syed JA, Bigala R, Garanti S. Design and characterization of Amoxicillin trihydrate mucoadhesive microspheres. International Journal of Pharmaceutical Science and Drug Research 2010; 2(6): 112-114.

51. Khazaeli P, Pardakhty A, Hassanzadeh F. Formulation of Ibuprofen Beads by Ionotropic Gelation. Iranian Journal of Pharmaceutical Research 2008; 7(3):163-170.

52. Kalyankar TM, Nalanda T, Mubeena K, Hosmani A, Sonawane A. International Journal of Pharma World Research 2010; 1(3): 1-14.

53. Pavanveena C, Kavitha K, Kumar A, Formulation and evaluation of Trimetazidine Hydrochloride loaded chitosan microspheres. International Journal of Applied Pharmaceutics 2010; 2(2): 11-14.

54. Das MK, Senapati PC. Furosemide loaded alginate microspheres prepared by ionic cross linking technique. International Journal of Pharmaceutial Sciences 2008; 70(1): 77-84.

55. Kumar TM, Paul W, Sharma CP, Kuriachan MA. Bioadhesive pH Responsive Micromatrix for oral drug delivery of insulin. 2005; 18(2): 198-202.

56. Venkateshwaramurthy N, Sambathkumar R, Vijaybaskaran M. Formulation and evaluation of Furazolidine mucoadhesive microspheres. International Journal of Pharmacy and Pham Sciences 2010; 2(3): 104-106.

57. Parsad BSG, Setty CM, Gupta VRM, Devi RM. Scholars Research Library. (2011).

58. ShadabMd, Ahuja A, Khar RK, Baboota S, Mishra AK, Ali Javed. Gastroretentive drug delivery system of acyclovir-loaded alginate mucoadhesive microspheres. www.informahealthcare.com 2011; 18(4). 255-264.

59. Patil B, Gawali VU, Hardikar SR, Bhosale AV. Preparation and evaluation of mucoadhesive microspheres of atenolol and propranolol. International Journal of Pharm Tech Research 2009; 1(3): 639-643.

60. Jaiswal D, Bhattacharya A, Yadav IK, Singh HP, Chandra D, Jain D.A. Formulation and evaluation of oil entrapped floating alginate beads of rantidine hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences 2009; 1(1): 128-140.

61. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS PharmSciTech 2005; 6.

62. Mohammed GA, Satish KB, Kiran KG. Formulation and evaluation of gastric mucoadhesive drug delivery system of captopril. Journal of Current pharmaceutical research 2010; 2(1): 26-32.

63. Sivakumar R, Rajendran NN, Narayanan N. Design of mucoadhesive hydrophilic beads entrapped with ketoprofen for delivery into small intestine. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2011; 2(1): 706-713.

64. Prasanth VV, Chakarabarty A, Mathew TS, Mathappan R, Kamalakkannan V, Formulation and evaluation of salbutamol sulphate microspheres by solvent evaporation method. Journal of Applied Pharmaceutical Sciences 2011; 1(5): 133-137.

65. Mishra B, Sahoo S, Biswa PK, Sahu SK, Behera BC, Jana GK. Formulation and Evaluation of Torsemideintragastric buoyant sustained release microspheres. Journal of Pharmacy Research 2010; 3(2): 742-746.

66. Verma A, Tripathi A, Shubini AS, Shailendra S. Fabrication and evaluation of sustained release microspheres of ketorolac tremethamine. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(4): 44-48.

67. Kannan K, Karar PK, Manavalan R. Formulation and evaluation of sustained release microspheres of acetazolamide by solvent evaporation technique. Journal of Phamaceutical Sciences and Research 2009; 1(1): 36-39.