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A REVIEW ON MICROSPHERES

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ABSTRACT

Microspheres can be used to deliver medications in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix.[1] The current review provides an in-depth discussion of therapeutic aspects of microsphere drug delivery including the types of polymers used, methods of preparation, factors affecting the release, types of microspheres and pharmaceutical applications of Microspheres.

KEYWORDS: Microspheres, Targeted Drug Delivery, Polymers, Controlled Release.

INTRODUCTION

Microspheres can be characterized as solid, approximately spherical particles with a diameter having between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape. Both the terms microcapsules and microspheres are often used as synonyms.[2] Medication That is simply transmitted in from gastrointestinal tract (GIT) and also has a short half-life is immediately destroyed from the circulatory system in the blood. The oral sustained or controlled release (CR) has also been developed to avoid this problem, as that will Slowly discharge the substance into the GIT and retain a steady medication intensity in the plasma For a prolonged time period.

A suitable dosage formulation is one that reaches the required plasma therapeutic Drug concentration and remains constant throughout the treatment period. This can be achieved by delivering a traditional dosage type in a fixed dose and at a specific frequency.[3] A benefit is that they are not microcarriers over nanoparticles migrate across the range of 100 nm carried by the lymph into the interstitium, and therefore function locally. Probably toxic chemicals

can be transported Encapsulated, and in place of liquid the dried microparticles may be known as solids. The intake dose is delivered in several tiny different for multi particulate particles, which hold and discharge a part of the dosage; therefore the breakdown of a specific subunit does not affect the whole dosage failure.[4]

Microparticles used in skin applications required to benefit the release of the medication into the skin ensure that now the drug remains localized at the application site and does not enter the systemic circulation unnecessarily.[5] They act as a reservoir which releases an active ingredient over a longer period of time to maintain effective concentration of drug products in the skin while decreasing undesired side effects.[6] Consequently, cycles of over- and under-medication are reduced. It is especially relevant for the reduction of antimicrobial resistance in the management of infectious diseases. These distribution mechanisms can also boost product safety or integration into appropriate vehicles.[7,8]

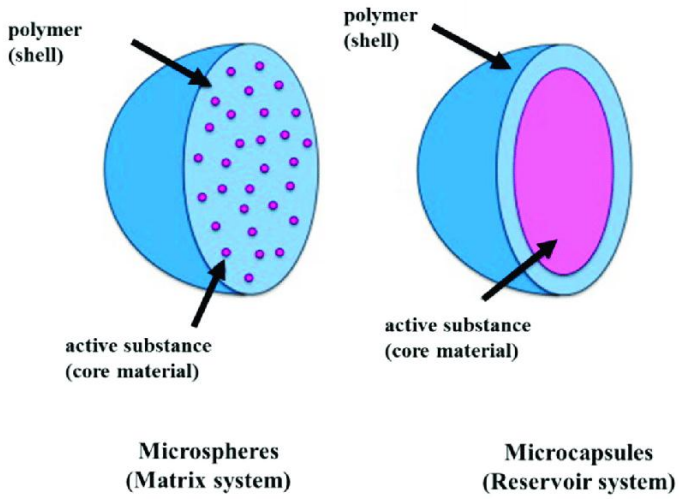

Fig: Microspheres and Microcapsules.

Advantages of Microspheres

- Decrease of the size contributes to an increasing the surface area and can increase the potency of the poorly soluble material.
- Providing a steady quantity of medications in the body that can improve patent compliance;
- Dose and risk reduced.
- Drug packaging with polymers prevents the drug avoid enzymatic cleavage while making it suitable for drug method delivery system.
- Less duration of dosing contributes to higher patient compliance.

- Effective usage of medications can enhance bioavailability, and decrease harmful effects occurrence or severity.
- Helps protect the GIT from opioid irritants.
- Transform liquid into solid shape and block the unpleasant taste.
- Reliable means, if changed, to transmit the medication to the target location with precision and to sustain the targeted concentrations at the targeted site and with no undue impact.
- Reduce central reactivity related to the external world.
- Degradable microspheres get the benifit over large polymer implants through that they just don't really necessarily involve medical treatments for implantation and reduction.
- Controlled release delivery degradable microspheres are being used to regulate release of drug prices while also reducing toxicity, and reducing the discomfort of repeated injection.[9]

Disadvantages

- Modified Versions of Formulations.
- The release rate of the dose-regulated process of release which differ from a number of factors such as diet and transfer levels through the gut.
- Variations in activation rate from dose to dose the following.
- Controlled release formulations usually have a higher dose loading and therefore any lack of release quality properties of the drug may contribute to
- Potentially dangerous.
- These types of measures must not break or chewed.[10]

TYPES OF MICROSPHERES

Bioadhesive Microspheres

Adhesion can be defined as the adhesion of the drug to the membrane using the binding property water-soluble polymers. Adhesion of the drug delivery device to the mucous membrane such as buccal, ocular, rectal, nasal, etc. can be described as bioadhesion. The term "bioadhesion" describes materials that bind to biological substrates," such as mucosal extremities. membership of Bioadhesive drug delivery devices to mucosal tissue offer the possibility of creating a intimate and prolonged contact at the site of administration. This long stay may result in better absorption and in combination with controlled drug release also improvement of patient compliance by reducing the frequency of administration. carrier

technology offers a smart approach to drug delivery by coupling the drug to a carrier particle such as in the form of microspheres, nanospheres, liposomes, nanoparticles, etc., which modulate the release and drug absorption. Microspheres constitute most of these particles. drug delivery systems due to their small size and efficient transport capacity.[11]

Magnetic Microspheres

This type of delivery system is very important because it localizes the drug to the site of disease. In this case, a larger amount of free-flowing drug can be replaced with a smaller amount of magnetic targeting drug. Magnetic carriers receive magnetic responses to a magnetic field. The integrated materials used for the magnetic beads are chitosan, dextran, etc.[12] Different types of therapeutic magnetic beads are used to deliver a chemotherapy drug to a liver tumor. Drugs such as proteins and peptides can also be targets. By this system.[13] Diagnostic microspheres.[14] The technique of magnetic drug transport relies on the fact that the drug can be encapsulated in a magnetic microsphere or conjugated to the surface of the microsphere. The accumulation of carriers at the destination location allows them to distribute the drug locally.[15]

Floating Microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form.[16]

Radioactive Microspheres

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.[17]

Mucoadhesive Microspheres

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.[18]

Polymeric microspheres

The different types of polymeric microspheres can be classified as:

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.[19]

Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.[20]

Methods used in preparation of microspheres

The choice of method mainly depends on the character of the polymer used, the drug, factors erroneously determined by many formulations and technological factors such as the required particle size and the drug or protein should not be significantly affected by the process, the reproducibility of the release profile and the method, there should be no stability issues with

respect to the finished product. The different types of procedures. It is used to prepare microspheres using hydrophobic and hydrophilic polymers as matrix materials.[21]

- The ability to integrate doses of medications that they are relatively small.
- Stability of the preparation after synthesis with a shelf clinically acceptable spam.
- Particle size and dispersibility controlled for injection into aqueous vehicles.
- Efficient release of reagents with strong control over a large time scale.
- Biocompatibility with controllable biodegradability and response to chemical weathering.

1. Spray Drying[22]

In Spray Drying technique, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution with high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of this process is feasibility of operation under aseptic conditions.

2. Solvent evaporation[22,23]

This process is carried out in a liquid manufacturing vehicle phase. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

3. Single emulsion technique[24]

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. In the next step, the

cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation3 The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology, loading, drug release, and bio performance of the final multiparticulate product.

4. Double emulsion technique[25]

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited for water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. A number of hydrophilic drugs like luteinizing hormone releasing hormone (LH-RH) agonist, vaccines, proteins/peptides and conventional molecules are successfully incorporated into the microspheres using the method of double emulsion solvent evaporation/ extraction.

5. Phase separation coacervation technique[26,27]

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Poly lactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a

suitable speed stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the formed particles since there is no defined state of equilibrium attainment.

6. Spray drying and spray congealing[26,27]

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm. Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. One of the major advantages of the process is feasibility of operation under aseptic conditions. The spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethylthiadizole are encapsulated in a mixture of mono- and diglycerides of stearic acid and palmiticacid using spray congealing. Very rapid solvent evaporation, howeverleads to the formation of porous microparticles.

7. Solvent extraction[26,27]

Solvent evaporation method is used for manufacturing of microparticles, involves removal of the organic phase by extraction of the or non aqueous solvent. This method involves water miscible organic solvents as isopropanol. Organic phase can be removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct incorporation of the drug or protein to polymer organic solution. Rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and solubility profile of polymer.

8. Quassi emulsion solvent diffusion[26,27]

A novel quasi-emulsion solvent diffusion method to manufacture the controlled release microspheres of drugs with acrylic polymers has been reported in the literature. Microsponges can be manufactured by a quasi emulsion solvent diffusion method using an external phase containing distilled water and polyvinyl alcohol. The internal phase consists of

drug, ethanol and polymer. The concentration of polymer is in order to enhance plasticity. At first, the internal phase is manufactured at 60ºC and then added to the external phase at room temperature. After emulsification process, the mixture is continuously stirred for 2 hours. Then the mixture can be filtered to separate the microsponges. The product is then washed and dried by vacuum oven at 40ºC for a day.

Factors Affecting The Release of Microspheres

Controlled release is a feasible and desirable solution characteristic of drug delivery systems. the Factors affecting drug release rate revolve around the matrix structure where the drug is contained and the chemical properties associated with both the polymer and the drug. Conventional oral administration is not rate controlled. Drug encapsulated in a substance that slowly breaks down the matrix offers the possibility of slowing down release effects, but polymer degradation is not the only drug release mechanism. Drug release is also controlled by diffusion as the drug can travel through the pores formed during hardening of the sphere. In some cases, drugs containing nucleophilic groups can cause increase in the chain scission of the polymer matrix, which also increases the drug expulsion rate. Polymer molecular weight, drug distribution, polymer blend, crystallinity and other factors are important in manipulating release profiles.[28]

Summary of Drugs Microencapsulated

Table 1.

Category	Drugs	Polymers Used
Anti-cancer	• Fluorouracil • Cisplatin • Mitoxantrone • Oxantrazol	• Glutaraldehyde, Chitosan • Chitosan, Chitin • Glutaraldehyde saturated toluene • Chitosan
NSAIDs	• Aceclofenac	• Eudragit
Antibiotic	• Amoxicillin • Gentamicin	• Sodium tripolyphosphate • PLGA and PCL
Anti-inflammatory	• Indomethacin • Diclofennac • sodium • Ketoprofen	• Chitosan • Chitosan, chondroitin sulphate • Chitosan
Cardiac Agents	• Nifedipine • Propranolol • Dilitazam	• Chitosan • Chitosan • Casein, chitosan
Steroidal	• Progesterone	• Glutaraldehyde, chitosan
Antidiabetic Agents	• Insulin	• Chitosan
Diuretics	• Furosemid	• Chitosan

Pharmaceutical Application of Microspheres

1. Vaccine delivery
2. Monoclonal antibodies
3. Imaging
4. Topical porous microsphere
5. Nasal drug delivery
6. Oral drug delivery
7. Targeting drug delivery
8. Gastroretentive controlled delivery system
9. Bio-medical application
10. Pharmaceutical application

1. Vaccine delivery[29]

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, Safety and convenience in application and cost. In 2000 limin et al. prepared polymicroparticle by using solvent evaporation method as a drug carrier for insulin.[30] The aspect of safety and minimization of adverse reaction is a complex issue.[31] The aspect of safety degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen.

Lamprecht et al. in 2000 prepared nanoparticle preparation of bovine serum albumin (BSA) by double emulsion method, found that on increase the protein concentration in the inner aqueous phase BSA encapsulation efficiency decreased while particle size was not influenced significantly. There is higher release rate with PLGA NP compared with PCL NP.[32]

2. Monoclonal antibodies

There are numbers of antibiotic drugs which are administrate in microsphere form, for improve the efficiency as well as compatibility with other salt. Such as amoxycilline, ampicillin, tetracilline, sulfadiazine, sulfathiazole, griseofulvine. Monoclonal antibodies

targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods:

1. Non specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling via reagents

3. Imaging

The particle size plays an important role in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labeled human serum albumin microspheres[9] Hejazi and Amiji (2003) Prepared microsphere by ionic crosslinking and precipitation method Studied the gastric residence time of tetracycline loaded chitosan microspheres. Following their oral administration in gerbils chitosan microsphere suspension in the nonacid-suppressed and acid suppressed states. Animals were sacrificed at different time points, and the radioactivity in tissues and fluids was measured with a gamma counter.[34]

4. Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300µm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner.[35]

5. Nasal Drug Delivery

Intranasal (IN) administration has many theoretical and practical advantages for the local and systemic delivery of a diverse therapeutic compound. IN delivery is needle-free, non-

invasive, and essentially painless, does not require sterile preparation, and can be self-administered. The large surface area of the nasal mucosa originated from the presence of a large number of microvilli, a porous endothelial membrane, and a highly vascularized epithelium serves a rapid onset of therapeutic effect.[36,37]

6. Oral drug delivery

Shefi angel timmy[38] et al. work on delivery of insulin by oral route by making microsphere with cyclodextrin making inclusion complex with drug molecule. In oral delivery of insulin for the treatment of diabetes mellitus. The main problem with insulin was degradation of drug due to enzyme in GI tract. Aliginate and enteric polymers, which protecting the insulin in acidic condition. Polk et al used chitosan alginate membranes for delayed release of protein.[39]

7. Targeting drug delivery

Microspheres exhibit a prolonged residence time at site of application and thus contribute to better therapeutic performance of drugs. Microspheres have been developed for oral, buccal, ocular, rectal, nasal and vaginal routes for either systemic or local effects. This article presents introduction and the advanced pharmaceutical applications of bioadhesive microspheres. There are number of drugs which are given by different route of administration and having good targeting effect some of example are given in below table 2.[40]

Table 2: Target drug delivery of different drug by microsphere.

Drugs	Route of Administration	Polymers Used
Acyclovir[41]	Ocular	Chitosan
Insulin[41]	Nasal	Degradable starch microspheres and lysophosphatidylcholine
Gentamicine[42]	Nasal	Degradable starch microspheres and lysophosphatidylcholine
Furosemide[43]	GI	Polyglycerol esters of fatty acids
Insulin[44]	Colonic	PGEF coated with Eudragit S 100
Insulin[45]	Vaginal	Hyaluronic acid esters

8. Gastroretentive controlled delivery system:[46]

In which Floating systems are low-density systems (fig) that have float over the gastric contents and remain in the stomach for a prolonged period than conventional dosage forms.

Gastric emptying of dosage form is extremely variable process and ability to control the emptying time is valuable asset for dosage forms, there are several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability.[47] While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.[48,49,50]

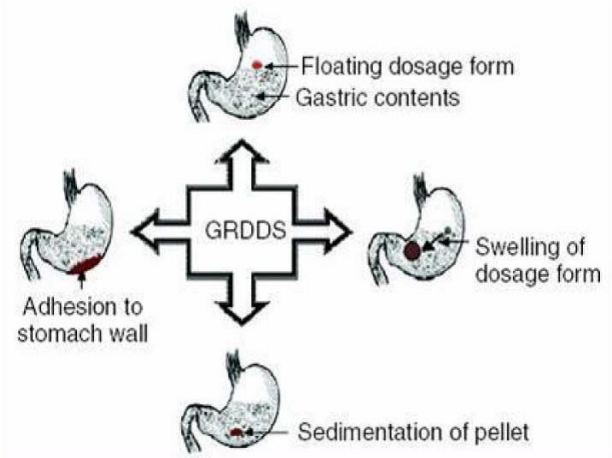

Figure: Gastroretentive drug delivery systems.

9. Implantable devices

Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones,[51,52] which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materials until their activity is needed. The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of this products.[53]

10. Pharmaceutical applications

A number of pharmaceutical microencapsulated products are currently on the market, such as aspirin, theophylline and its derivatives, vitamins, pancrelipase, antihypertensives, potassium chloride, progesterone, and contraceptive hormone combinations.[54] Microencapsulated KCL (Micro-K, R.H. Robins, Richmond, VA) is used to prevent gastrointestinal complications associated with potassium chloride. The dispersibility of the microcapsules and the controlled release of the ions minimize the possibility of local high salt concentrations, which could result in ulceration, hemorrhage, or perforation. Microspheres have also found potential

applications as injection[55,56] or inhalation products.[57,58,59,60] The number of commercially available products does not reflect the amount of research that has been carried out in this area, nor the benefits that can be achieved using this technology. Economic considerations have been a key factor in determining the number of pharmaceutical microencapsulated products. Most encapsulation processes are expensive and require significant capital investment for equipment. An exception is pan or sprays coating and spray drying, since the necessary equipment may already be available within the company. An additional expense is due to the fact that most microencapsulation processes are patent protected.

CONCLUSION

Overall conclusion is microspheres are good carrier for the drug in case of targeting delivery of the drug, microspheres drug delivery is safe and effective and utilized in various areas like floating, drug targeting, and vaccine delivery etc. procedure for preparation & evaluation for microspheres formulations are widely available with effective reproducibility. Microspheres drug delivery covers large area of drug targeting hence required consistence performance study to correlate the invivo performance. The present review article shows that microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

REFERENCES

1. Neelesh K Varde, Daniel W Pack “Microspheres for controlled release drug delivery” Expert Opinion on Biological Therapy informa world January, 2004; 4(1): 35-51.
2. B. Venkateswara Reddy. et. al., Formulation and evaluation of efavirenz microspheres, Der Pharmacia Lettre, 2015; 7(6): 1-9.
3. S. M. Sarode, et. al., Formulation and evaluation of floating microspheres of Glipizide, Journal of Chemical and Pharmaceutical Research, 2011; 3(3): 775-783.
4. Miléna Lengyel, Review Microparticles, Microspheres, and Microcapsules for Advanced Drug Delivery, Scientia. Pharmaceutica, 2019; 87- 20.
5. Badilli U, Sen T, Tarimci N. Microparticulate based topical delivery system of Clobetasol Propionate. AAPS PharmSciTech., 2011; 12: 949-57.

6. Basarkar G, Shirsath G, Patil S. Development of microspheres containing Diclofenacdiethylamine as sustained release topical formulation. Bull Pharm Res., 2013; 3: 14-22.
7. Labouta H, El-Khordagui L. Polymethacrylate microparticles gel for topical drug delivery. Pharm Res., 2010; 27: 2106-18.
8. S. Y. RAI, et. al., Development and Evaluation of Microsphere-based Topical Formulation using Design of Experiments, Indian Journal of Pharmaceutical Sciences, 2016; 78(2): 182-192.
9. Tarun Virmani, et. al., Pharmaceutical Application of Microspheres: An Approach for The Treatment of Various Diseases, International Journal of Pharmaceutical Sciences and Research, 2017; 7: 3252-3260.
10. B. Sree Giri Prasad, et. al., Microspheres as Drug Delivery System – A Review, Journalof Global Trends in Pharmaceutical Sciences, 2014; 5(3): 1961–1972.
11. Patel J. Bioadhesion is a topic of current interest in the design of controlled or targeted drug delivery system.
12. Li SP, Kowalski CR, Feld KM, Grim WM. Recent Advances in Microencapsulation Technology and Equipment. Drug Deivery Ind. Pharm., 1988; 14: 353-76.
13. Patel JK. Www.Pharmainfo.Net/Reviews/Bioadhesive microspheres- review, 24th Nov 2010.
14. 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.
15. Chandrawanshi P, Patidar H. Magnetic microsphere: As targeted drug delivery. J. of Pharmacy Res., 2009.
16. 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(2): 83-87.
17. Yadav AV, Mote HH. Development of Biodegradable Starch Microspheres for Intranasal Delivery, Indian Journal of pharmaceutical Sciences, 2008; 70(2): 170-74.
18. Chowdary KPR, Yarraguntla SR. Mucoadhesive microsphere for controlled drug delivery. Biol. Pharm. Bull., 2004; 1717-24.
19. Saralidze K, Leo H., Koole, Menno L, Knetsch W. Polymeric Microspheres for Medical Applications, Materials, 2010; 3: 3357-64.

20. Trivedi P, Verma AML, Garud N. Preparation and Characterization of Acclofenac Microspheres, Asian Journal of pharmaceutics, 2008; 2(2): 110-15.
21. E Veena Rani, et. al., Preparation and Evaluation of Aspirin Loaded Microspheres by Solvent Evaporation Technique, Journal of Medicine and Biology, 2019; 1(1): 27-32.
22. Ramteke K.H., Jadhav V.B., Dhole S.N., Microspheres: As carrieres used for novel drug delivery system, IOSRPHR, 2012; 2(4): 44-48.
23. Patel B., Modi V., Patel K., Patel M., Preparation and evaluation of ethyl cellulose microspheres prepared by emulsification solvent evaporation method, International Journal For Research In Management And Pharmacy, 2012; 1(1): 83-91.
24. Patel N. R., Patel D. A., Bharadia P.D., Pandya V., Modi D.,Microsphere as a novel drug delivery, Int. j. pharm. life sci., 2011; 2(8): 992-7.
25. Patel N. R., Patel D. A., Bharadia P.D., Pandya V., Modi D.,Microsphere as a novel drug delivery, Int. j. pharm. life sci., 2011; 2(8): 992-7.
26. Bansal H., kaur S. P., Gupta A. K., Microsphere: Methods of preparation and applications;A comparative study, Int J Pharm Sci Rev Res., 2011; 10(1): 69-78.
27. Alagusundaram M., Chetty. C. M. S., Umashankari.K, Badarinath A. V., Lavanya.C., Ramkanth. S., Microspheres as a novel drug delivery sytem- A review, Int J ChemTech Res., 2009; 1(3): 526-34.
28. J.J. Torrado, L. Illum, S.S. Davis Particle size and size distribution of albumin microspheres produced by heat and chemical stabilization International Journal of Pharmaceutics, 1 April 1989; 51(1): 85-93.
29. Sinha V R, Bansal K, Kaushik R, Kumria R, Trehan A. Polycaprolactone microspheres and nanospheres, International Journal of Pharmaceutics, 2004; 278: 1–23.
30. Bayomi M A, al-Suwayeh S A, el-Helw A M, Mesnad A F, Preparation of casein–chitosan microspheres containing diltiazem hydrochloride by an aqueous coacervation technique. Pharm. Acta Helv., 1998; 73: 187–192.
31. Jameela S R, Kumary T V, Lal A V, Jayakrishnan A,Progesterone-loaded chitosan microspheres: a long acting biodegradable controlled delivery system. J. Control Rel., 1998; 52: 17–24.
32. Huang H, Tian H, Li X, Zhao G, Hypoglycemic effect of chitosan-microcapsulated insulin on the blood glucose level of streptozotocin-diabetic Wistar rats. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi, 2008; 18: 425–427.
33. Swarbrick b j, Spray drying and Spray Congealing of Pharmaceuticals, In: Encyclopedia of Pharmaceutical Technology, Marcel Dekker, 1992; 207-221.

34. Funden berg H H, Stites D P, Caldwel J L, Wells J V, In: Basic and clinical immunology, Lange Medical, Los Altosca, 1978; 2: 1346-1348.
35. Lamprecht A, Ubrich N, Hombreiro Perez M, Lehr C, Hoffman M, Maincent P, Influences of process parameters on nanoparticle preparation performed by a double emulsion pressure homogenization technique. Int. J. Pharm., 2000; 196: 177–182.
36. Shah S, Qaqish R, Patel V, Amiji M, Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for Helicobacter pylori infection. J. Pharm. Pharmacol, 1999; 51: 667–672.
37. Giunchedi P, Genta I, Conti B, Muzzarelli R A, Conte U, Preparation and characterization of ampicillin loaded methylpyrrolidinone chitosan and chitosan microspheres. Biomaterials, 1998; 19: 157–161.
38. Illum L, Farraj N F, Davis S S, Johansen B R, O'Hagan D T Investigation of the nasal absorption of biosynthetic human growth hormone in sheep-use of a bioadhesive microsphere delivery system. Int. J. Pharm., 1990; 63: 207-211.
39. Vasir J K, Tambwekar K, Garg S, Bioadhesive microspheres as a controlled drug delivery system. Int. J. Pharm., 2003; 255: 13–32.
40. Critchley H,Davis S S, Farraj N F, Illum L, Nasal absorption of desmopressin in rats and sheep-effect of a bioadhesive microsphere delivery system. J. Pharm. Pharmacol., 1994; 46: 651-656.
41. Singh M, Briones M, O'Hagan D T. A novel bioadhesive intranasal delivery system for inactivated influenza vaccines. J. Control. Release, 2001; 70: 267-276.
42. Nachts S, Martin K.The microsponges a novel topical programmable delivery formulation, Marcel Dekker Inc, Newyork, 5th, 1990; 299.
43. Vasir J K, Tambwekar K, Garg S, Bioadhesive microspheres as a controlled drug delivery system. Int. J. Pharm., 2003; 255: 13–32.
44. Shefi A T, Sunita P V, Chandra P S, Valsala K J, Betacyclodextrine complexed insulin loaded alginate microspheres-oral d
45. Polk A, Amsden B, De yao, K Peng T, and Goosena A, J pharm Sci., 1993; 83: 178-185.
46. Gental I, Conti B, Perugini P, Pavanetto F, Spadaro A, Puglisi G, Bioadhesive microspheres for ophthalmic administration of Acyclovir. J. Pharm. Pharmacol, 1997; 49: 737-742.
47. Akiyama Y, Nagahara N, Novel formulation approaches to oral mucoadhesive drug delivery system. In: Mathiowitz E, Chickering DE, Lehr CM. (Eds.),Bioadhesive Drug Delivery Systems-Fundamentals, Novel Approaches and Development, 1998; 477–505.

48. Geary S, Schlameus H W, Vancomycin and insulin used as models for oral delivery of peptides. J. Control. Release, 1993; 23: 65-74.
49. Illum L, Farraj N F, Fisher A N, Gill J, Miglietta M, Benedetti L M, Hyaluronic acid ester microsphere as a nasal delivery system for insulin. J. Control. Release, 1994; 29: 133-141.
50. Punam.G, Floating Microspheres: A Review, Pharmainfo, 2008; 6: 5.
51. Akiyama Y, Yoshioka M, Horibe H, Inada Y, Hirai S,Kitamori N, Toguchi H, Anti-hypertensive effect of oral controlled release microspheres containing an ACE inhibitor (Delapril hydrochloride) in rats. J. Pharm. Pharmacol, 1994; 46: 661-665.
52. Patel JK, Patel RP, Amin AF, Patel MM Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS PharmSciTech., 2005; 6: 49-55.
53. Patel J K, Amin A F, Patel M M Formulation optimization and evaluation of controlled release mucoadhesive microspheres of glipizide for oral drug delivery using factorial design. Drug Delivery Technology, 2004; 4: 48-53.
54. Geary S, Schlameus H W,Vancomycin and insulin used as models for oral delivery of peptides. J.Control. Release, 1993; 23: 65-74.
55. Chang, T M S. Artificial Liver and Artifical Cells, Plenum Press, New York, 1978; 34-35.
56. Chang, T M S. Biomedical Applications of Microencapsulation, Lim, F., Ed, CRC Press, Boca Raton, FL, 1984; 85.
57. Donbrow, M Microcapsules and Nanoparticles in Medicine and Pharmacy, Donbrow, M, Ed, CRC Press London, 1991; 1–14.
58. Kissel, T, Demirdere, A Controlled Drug Delivery Mu ller, B W, Ed, Wissen-Schaftliche Verlagsge-Sellschaft mbH: Stuttgart, 1984; 103–131.
59. Gurney R, Peppas, N A Harrington, D D, Banks, G S,Drug Dev. Ind. Pharm., 1981; 7: 1–25.
60. Maggi G C, Di Roberto F M, Microencapsulation Nixon J R, Ed, Marcel Dekker, Inc, New York, 1976; 103–111.