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MICROSPHERES AS DRUG DELIVERY SYSTEM – A REVIEW

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ABSTRACT
Oral modified-release multiple-unit dosage forms have always been more effective therapeutic alternative to conventional or immediate release single-unit dosage forms. With regards to the final dosage form, the multiparticulates are usually formulated into microspheres and filling them into hard gelatin capsules. Microspheres have received much attention not only for prolonged release, but also for targeting of drugs. In the current scenario, targeted drug delivery requires an efficient drug carrier which can deliver the drug specifically on the site of action in a sustained and controlled manner. Among many such carriers, microspheres fulfil all the parameters for a potent drug carrier. Microspheres are one of the multiparticulate delivery system which is prepared to obtain prolonged or controlled drug delivery. Microspheres are defined as free flowing powders of spherical shape, consisting of proteins or synthetic polymers, which are either biodegradable or nonbiodegradable in nature and ideally having a particle size ranging from 1–1000 μm. The variety of methods for the production of microspheres offers numerous opportunities to control the aspects of administration of the API. The current aim of this review is to study various aspects of the microparticulates drug delivery system including types of microsphere drug delivery system, method of formulation, evaluation & characterization of microspheres.
Key-Words: Microspheres, Controlled release, Novel Drug Delivery, Therapeutic Efficacy.

INTRODUCTION
The preferred method of pharmaceutical administration is by far the oral route. However, the therapeutic potential of many medicines is constrained by their brief circulation half lives and restricted absorption by a specific intestinal segment. A frequent dose of medication is frequently required to achieve therapeutic efficacy due to such a pharmacokinetic constraint. The release of the drug in a regulated and site-specific manner is a logical way to increase bioavailability and optimise pharmacokinetic and pharmacodynamic profiles. [1]

TYPES OF MICROSPHERE
1. Bioadhesive microspheres
Adhesion is the process by which a medication sticks to a membrane utilising a water-soluble polymer that possesses adhesive properties. Bio adhesion can be defined as the attachment of a medication delivery device to a mucosal membrane, such as the buccal, ocular, rectal, or nasal. These types of microspheres have a prolonged residence duration at the application site, which results in close contact with the site of absorption and improves therapeutic activity. Making bio adhesive microspheres would be beneficial to have a way to ensure that the drug delivery system is in close touch with the absorbent membranes. Due to its exceptional bio adhesive qualities, polycarbophil is

a chosen polymer in the creation of bio adhesive microspheres. [2]

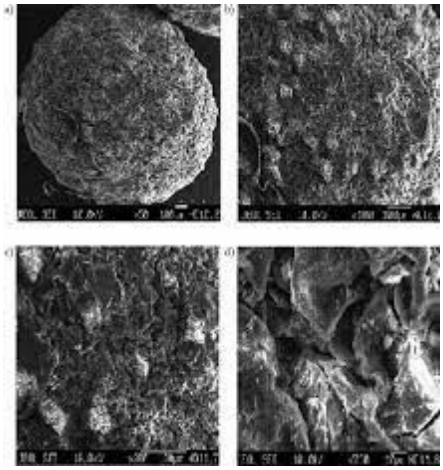

Fig.1 Bioadhesive microsphere [2]

2. Magnetic microspheres

This kind of delivery mechanism, which targets the drug to the site of the ailment, is crucial. In this case, a smaller amount of a medicine that is magnetically targeted can replace a larger amount of a drug that is freely circulating. Magnetic carriers pick up on the magnetic response that magnetic microspheres make. Water-soluble medications (for lipophilic medications, together with the dispersing agents) and 10nm magnetite (Fe3O4) particles are combined in an aqueous matrix solvent to create magnetic microspheres. The oil is then used to emulsify this combination. To create particles with the appropriate size range, ultra sonication or shearing is used. The matrix is then stabilized by chemical cross linking or heating. [3]

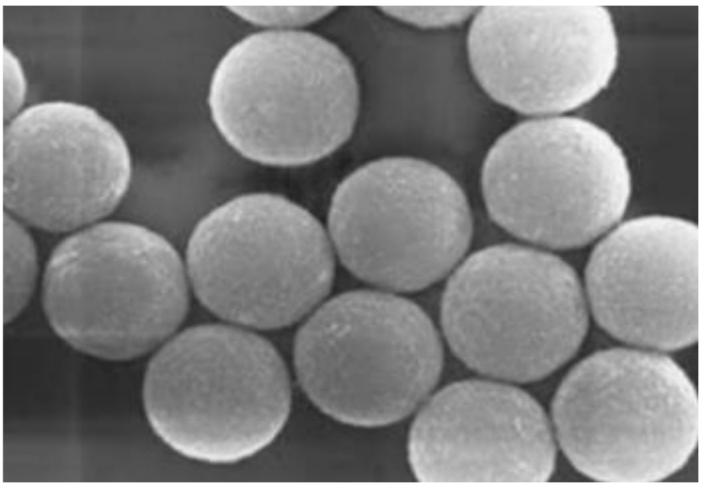

Fig. 2 : Magnetic microsphere [3]

3. Floating microspheres

Because the bulk density of floating kinds is lower than that of gastric fluid, they float unaffected by the rate at which the stomach empties. If the system is floating on, the medication is released gradually at the desired rate. Because the bulk density of floating kinds is lower than that of gastric

fluid, they float unaffected by the rate at which the stomach empties. If the system is floating on, the medication is released gradually at the desired rate. Increases in stomach content, gastric residence, and plasma concentration variation. This technique prolongs the therapeutic effect, which lowers the frequency of dose. Additionally, the risk of dose dumping is decreased because each dose is divided into several subunits.

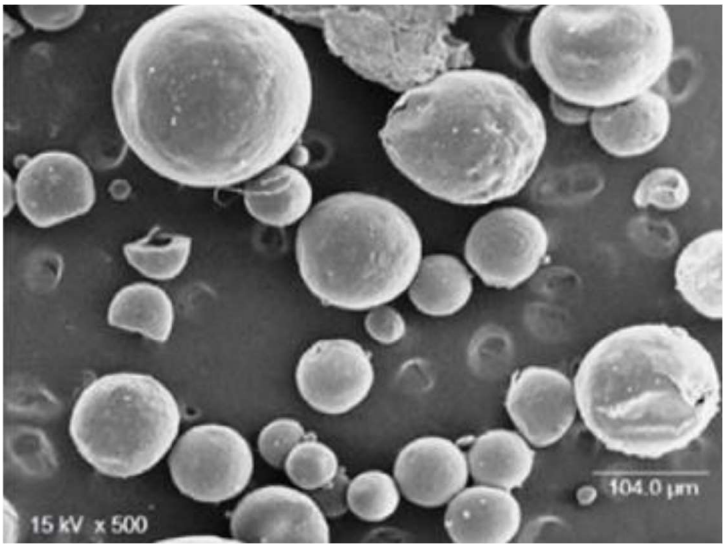

Fig.3 : Floating microsphere [4]

4. Radioactive microspheres

These radiolabeled microspheres exhibit high levels of stability and efficacy in the treatment of both primary and metastatic malignancies. Different malignancies can be specifically targeted using radioactive microspheres without overexposing healthy tissues to radiation. The injected radioactive microspheres These radiolabeled microspheres exhibit high levels of stability and efficacy in the treatment of both primary and metastatic malignancies. Different malignancies can be specifically targeted using radioactive microspheres without overexposing healthy tissues to radiation. To stop tumour growth through the blood supply and enable surgical removal once the tumour size reduces, radioactive microspheres are injected. Emitters, emitters, emitters describe various types of radioactive microspheres. [5]

Fig 4 : Radioactive microsphere [5]

5. Polymeric microspheres

According to whether the polymers are biodegradable or not, the various types of polymeric microspheres can be categorised as follows: Biodegradable polymeric microspheres According to whether the polymers are biodegradable or not, the various types of polymeric microspheres can be categorised as follows: - Biodegradable microspheres made of polymer, due to their ability to be biodegradable, biocompatible, and bioadhesive, natural polymers like starch are employed. Because biodegradable polymers have a high degree of swelling in aqueous media, which causes the formation of gel, they extend their residence time when they come into contact with mucosal membrane. The concentration of polymers regulates the drug's release.

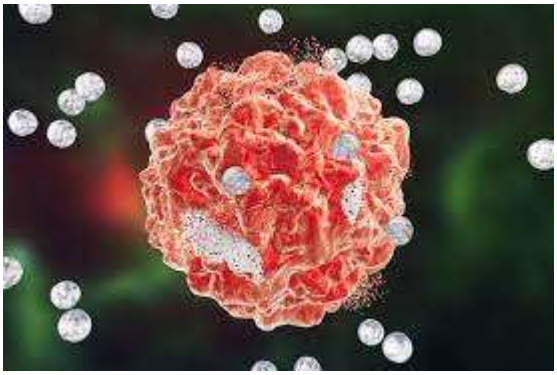

Fig.5: Polymeric microsphere [6]

METHOD OF PREPERATION

The various methods of preparations are:

Emulsion Solvent Evaporation Technique:

The O/W emulsion, which is made by agitating two immiscible liquids, can be produced using the solvent evaporation method. In order to use the solvent evaporation process, the microcapsule coating (polymer) must be dissolved in a volatile solvent that is incompatible with the liquid production vehicle. The O/W emulsion, which is made by agitating two immiscible liquids, can be produced using the solvent evaporation method. A volatile solvent that is immiscible with the liquid production vehicle phase is used in the solvent evaporation process to dissolve the microcapsule

coating (polymer). The coating polymer solution contains a core substance (drug) that needs to be microencapsulated. To create the proper size microcapsules, agitation is used to disseminate the core-coating material mixture in the liquid manufacturing vehicle phase.

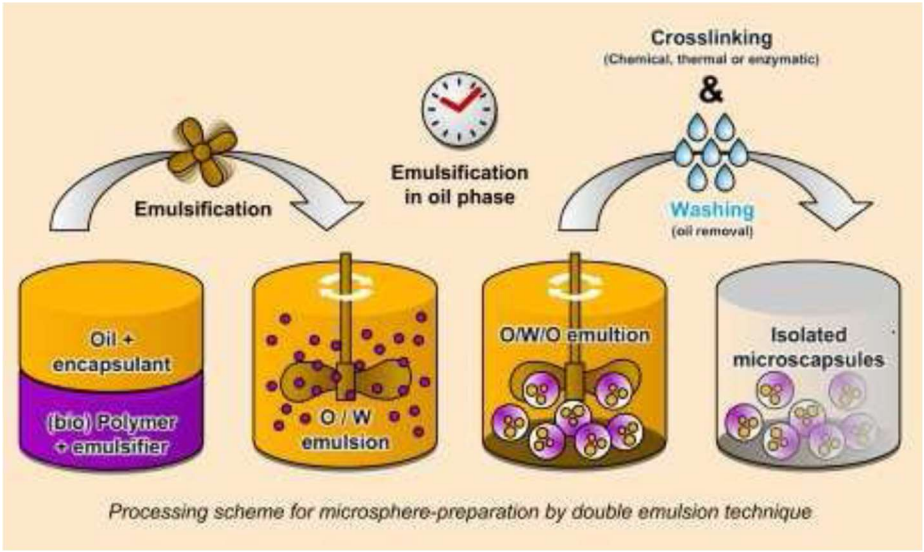

Fig.6: Emulsion solvent evaporation technique [7]

Emulsion Cross Linking Method:

In situ production of protective microcapsule coverings using the polymerization method of microencapsulation. The process involves the reaction of monomeric units that are positioned at the interface between a scattered core material and a continuous phase. The polymerization reaction takes place at the interfaces of liquid-liquid, liquid-gas, solid-liquid, or solid-gas because the continuous or core material supporting phase is typically a liquid or gas. [12]

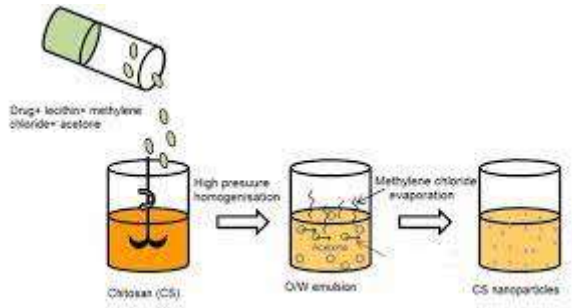

Fig.7: Emulsion crosslinking method [12]

Coacervation Method:

The coating of a liquid polymer around the interface between the liquid vehicle phase and the core material. Phase separation of the polymers can frequently be caused by inducing physical or chemical changes in coated polymer solutions. A two phase liquid-liquid system will result from the formation and coalescence of droplets of concentrated polymer solutions. Adding the coating material directly is possible if it is an immiscible polymer. Additionally, monomers can dissolve in the liquid vehicle phase and then undergo interface-mediated polymerization. Jacketed tanks with variable speed agitators are essential pieces of equipment for the coacervation phase separation method of microencapsulation. [13]

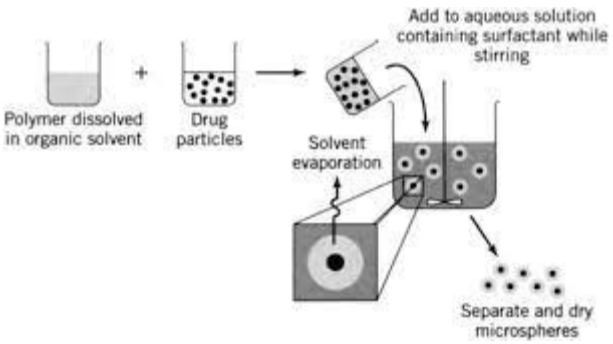

Fig.8: Coacervation method [13]

Spray Drying Technique:

Both the spray drying and the spray congealing techniques for microencapsulation involve dispersing the core material in a liquid coating agent before spraying or exposing the core coating mixture into an environment that influences the relatively quick solidification of the coating. The procedure used to solidify the coating is the fundamental distinction between these two microencapsulation techniques. In the spray drying process, the rapid evaporation of a solvent in which the coating material is dissolved affects how quickly the coating solidifies. In the spray congealing process, the coating solidification is carried out by the thermal congealing of molten coating material or by solidifying a dissolved coating by injecting the coating core material mixture into a non-solvent.

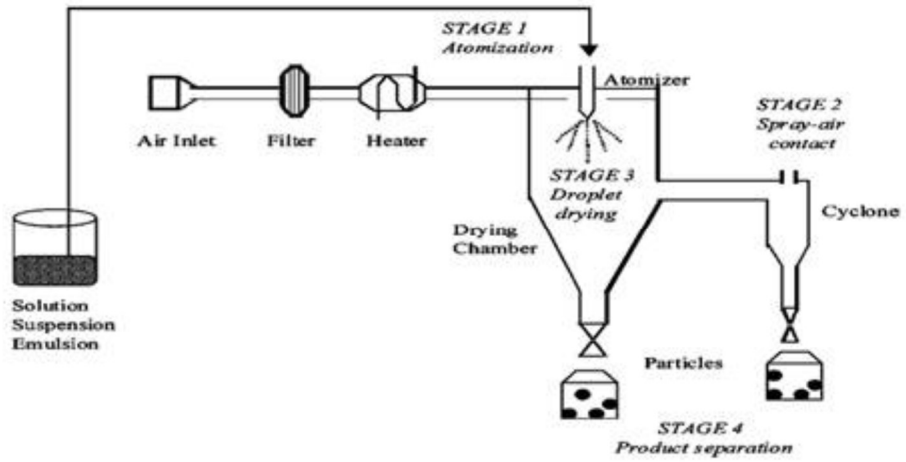

Fig.9: Spray drying technique [14]

Emulsion-Solvent Diffusion Technique:

Ketoprofen floating microperticles were made utilising the emulsion solvent diffusion approach to increase the residence period in the colon. Dropwise additions of the dissolved drug polymer mixture to sodium lauryl sulphate (SLS) solution were made after it had been first dissolved in an ethanol and dichloromethane (1:1) mixture. 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 next set of microparticles were gathered after sieving. [15]

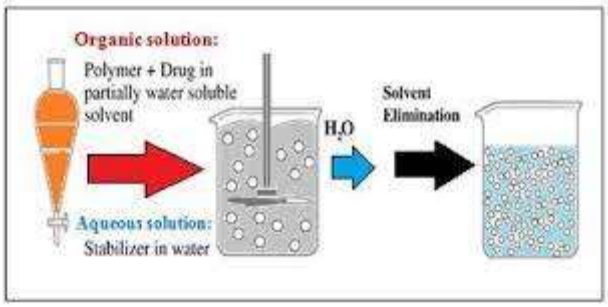

Fig.10: Emulsion solvent diffusion technique [15]

Multiple Emulsion Method:

This method was used to manufacture oral controlled release medication delivery for a variety of medicines. The powdered medication was first dissolved in methyl cellulose solution, then it was emulsified in ethyl cellulose solution in ethyl acetate. Reemulsification of the main emulsion in aqueous media followed. Discrete microspheres were generated during this phase under optimal conditions. [16]

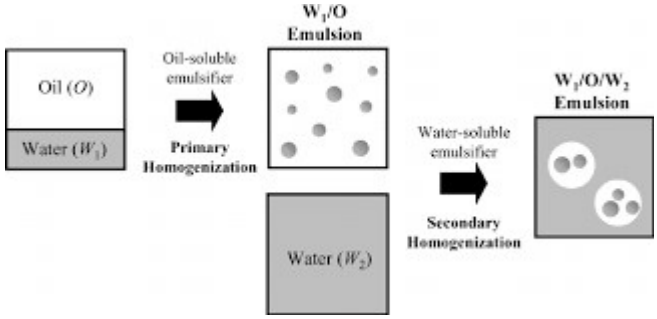

Fig.11: Multiple emulsion method [16]

Ionic Gelation Method:

When there are opposing ions present, polyelectrolytes have a propensity to cross link and form hydrogel beads that are frequently referred to as gelispheres. Gelispheres are hydrophilic circular cross-linked polymeric agents that can significantly thicken and gelate model biological fluids. They can also control medication release through polymer relaxation. A polymeric solution containing drugs is poured into an aqueous solution with polyvalent cations to create the hydrogel beads. The drug-containing hydrophilic molecules allow the cations to move through them, forming a three-dimensional lattice in which the moiety is ionically crosslinked. These gelispheres can also contain biomolecules to keep their three-dimensional shape in mild conditions. [17]

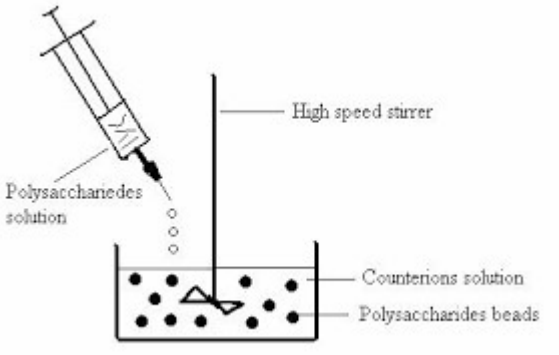

Fig.12: Ionic gelation method [17]

Hydroxyl appetite (HAP) Microspheres in Sphere Morphology:

This method was used to create microspheres with unusual sphere morphologies. It involved creating an o/w emulsion and then letting the solvent evaporate. The organic phase (Diclofenac sodium with 5% w/w of EVA and the proper amount of HAP) was first dispersed in the aqueous phase of the surfactant to create an o/w emulsion. The organic phase was dispersed as a suspension of minute droplets, each of which was surrounded by a surfactant molecule to keep them from cosolving and help them remain distinct droplets. As the mixture was stirred, the DCM slowly evaporated, causing the droplets to solidify individually into microspheres.

Fig.13: Hydroxy appetite(HAP) Microspheres [24]

Quassi Emulsion Solvent Diffusion:

The Doppel-emulsion strategy calls for mixing with no processing at all, or without any processing at all. The product's aqueous solution is dispersed within a continuous lipophilic organic phase. A polymer solution used in a continuous process finally encapsulates the drug that was initially visible in the scattered aqueous layer to create primary emulsion. The pre-formed emulsion is homogenised or sonicated before being added to the aqueous alcohol solution to generate the primary emulsion. The drug-filled microspheres extended the medication's release for 24 hours and were observed to be controlled for diffusion and erosion .[24]

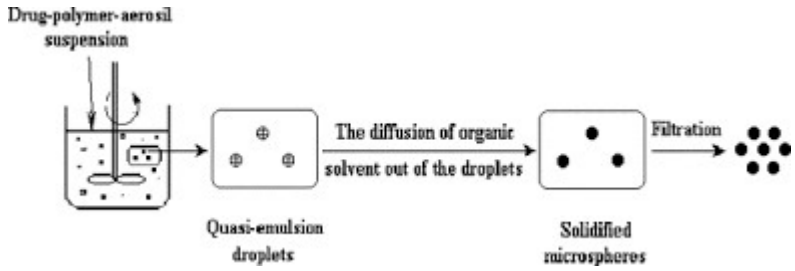

Fig.14:Quassi Emulsion Solvent Diffusion [24]

Physicochemical Evaluation:

i) Characterization

A crucial phenomenon that aids in the development of an effective carrier for the transport of proteins, drugs, or antigens is the characterisation of the microparticulate carrier. Different microstructures can be seen in these microspheres. The release and stability of the carrier are controlled by these microstructures.

Particle Size and Shape

Scanning electron microscopy (SEM) and conventional light microscopy (LM) are the two most popular techniques for observing microparticles (SEM). Both methods can be used to analyse the external structure and form of microparticles. When it comes to double-walled microspheres, LM offers control over the coating parameters. The architecture of the microspheres may be seen before and after coating, and the difference can be observed and quantified microscopically. SEM has greater resolution than LM, in contrast. SEM enables surface examinations of microspheres, and following cross-sectioning of particles, it also enables examination of double walled systems. The structure of multiple walled microspheres is characterised using conflocalfluorescence microscopy. Other than instrumental methods, which can be utilised for the characterisation include laser light scattering and multiple size coulter counters.

Analysis Electron Spectroscopy for Chemical:

The electron spectroscopy for chemical analysis can be used to determine the microspheres' surface chemistry (ESCA). The ESCA method offers a way to ascertain the surface's atomic make-up. You can assess the surfacial degradation of the biodegradable microspheres using the spectra produced using ECSA.

Attenuated total reflectance Fourier Transform-
Infrared Spectroscopy:

The deterioration of the carrier system's polymeric matrix is assessed using FT-IR. Measurements of alternating total reflectance are used to analyse the microspheres' surface (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATRFTIR provides information about the surface composition of the microspheres depending upon manufacturing procedures and conditions.

Density Determination:

Using a multi volume pycnometer, the density of the microspheres may be determined. The multi volume pycnometer is filled with a cup of precisely weighed sample. The chamber is filled with

helium, which is then given time to expand at a constant pressure. As a result of this expansion, the pressure inside the chamber decreases. Two successive readings of pressure reduction at various beginning pressures are reported. The volume of the microsphere carrier and, consequently, its density, are calculated from two pressure readings.

Isoelectric Point:

The micro electrophoresis is a device that measures the electrophoretic mobility of microspheres and uses that information to calculate the isoelectric point. The time of particle travel over a distance of 1 mm is used to compute the mean velocity at various Ph values ranging from 3 to 10. This information can be used to estimate the particle's electrical mobility. The microspheres' ion-absorbing properties, ionisable behaviour, or surface-contained charge can all influence their electrophoretic mobility.

Surface Carboxylic Acid Residue:

Radioactive glycine is used to measure the surface carboxylic acid residue. The c14-glycine ethyl ester hydro chloride reacts with the microspheres to produce the radioactive glycine conjugates. The water-soluble condensing compound 1- ethyl-3 (3-dimethyl amino propyl) carbidiimide is used to connect the glycine residue (EDAC). Then, a liquid scintillation counter is used to determine the conjugate's radioactivity. Thus, it is possible to compare and correlate the carboxylic acid residue. For either hydrophobic or hydrophilic microspheres, as well as any other derivatized kind, the free carboxylic acid residue can be determined.

APPLICATIONS IN DRUG DELIVERY

1. **OPHTHALMIC DRUG DELIVERY SYSTEM**

   The polymers that are employed in ophthalmic drug delivery systems demonstrate favourable biological behaviour, including bioadhesion, permeability-enhancing qualities, and physicochemical characteristics. Ophthalmic Chitosan Gels lengthen the precorneal medication residence period by increasing adherence to the mucus that coats the conjunctiva and corneal surface of the eye.

2. **Gene delivery**

Viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems are a few examples of gene delivery mechanisms. Because they are extremely effective and have a diverse variety of cell targets, viral vectors are ideal for delivering genes. However, they have immunological reactions and carcinogenic consequences when utilised in vivo. Non-viral delivery techniques are being developed for gene therapy to get around the drawbacks of viral vectors. The benefits of a non-viral delivery system include ease of preparation, cell and tissue targeting, a reduced immune response, unrestricted plasmid size, and highly repeatable manufacture on a large scale. For applications involving the transfer of genes, polymer has been employed as a DNA carrier. In addition, polymer's adhesion and transport qualities in the GI tract make it a potential candidate for use as an oral gene carrier.

3. **Intratumoral and local drug delivery**

   Strategies for local and intratumoral medication administration have gained popularity

recently as a possible treatment option for cancer. Polymer films were created in order to deliver paclitaxel at the tumour location in a therapeutically effective concentration. The amount of paclitaxel that could be put into flexible, translucent films was 31% (w/w). According to the study, polymer films containing paclitaxels were produced using a casting method with high loading efficiencies, maintaining the chemical integrity of the molecules throughout the process.

4. **Oral drug delivery**

In rabbits, the potential of diazepam-containing polymer films for oral medication delivery was studied. The findings suggested that an effective dose form comparable to existing tablet dosage forms could be a film made of a 1:0.5 drug-polymer mixture. As an alternative to pharmaceutical tablets, the ability of polymer to form films may allow for its usage in the development of film dosage forms. The primary amine groups' reactivity and the polymer's sensitivity to pH make it a special polymer for applications involving oral medication administration.

5. **Nasal drug delivery**

An excellent location for bioadhesive drug delivery devices is the nasal mucosa. When in contact with the nasal mucosa, polymer-based drug delivery systems such microspheres, liposomes, and gels have been shown to have high bioadhesive properties and quickly swell, improving the bioavailability and residence time of the medications to the nasal route. For nasal sustained release of vancomycin hydrochloride, a number of polymer salts, including chitosan lactate, chitosan aspartate, chitosan glutamate, and chitosan hydrochloride, are suitable choices. A protective systemic and local immune response against Diphtheria Toxoid with increased IgG production is produced after nasal administration of Diphtheria Toxoid combined with chitosan microparticles. In comparison to parenteral delivery of the vaccine, nasal formulations have significantly increased serum IgG responses that are similar to secretory IgA levels.

6. **Buccal drug delivery**

Because it includes muco/bioadhesive chlorhexidine diacetate, polymer is a great polymer to employ for buccal distribution because it prolongs the drug's release in the buccal cavity, enhancing its antibacterial effectiveness. Drug-free polymer microparticles nevertheless exhibit antibacterial properties because of the polymer. The buccal bilayered devices (bilaminated films, palavered tablets) with or without anionic crosslinking polymers (polycarbophil, sodium alginate, gellan gum) have promising potential for use in controlled delivery in the oral cavity. These devices use a combination of drugs (nifedipine and propranolol hydrochloride) and chitosan.

7. **Gastrointestinal drug delivery**

When added to acidic and neutral environments, polymer granules with interior voids created by deacidification are buoyant and allow a controlled release of the medication prednisolone. Melatonin was delivered in floating hollow microcapsules with a gastroretentive, controlled-release mechanism. These microcapsules considerably slow down the release of the medication, with release lasting 1.75 to 6.7 hours in simulated gastric juice. The majority of mucoadhesive microcapsules, such as metoclopramide and glipizide-loaded chitosan

microspheres, are maintained in the stomach for more than 10 hours.

8. **Peroral drug delivery**

A presystemic metabolism of peptides can be significantly reduced by polymer and the majority of its derivatives, which significantly improves the bioavailability of several perorally administered peptide medications like buserelin, calcitonin, and insulin. Chitosan that hasn't been changed increases the penetration of peptide medicines. By immobilising enzyme inhibitors on the polymer, peptides incorporated in polymers can be protected from being broken down by intestine peptidases. By adding chitosanglyceryl mono-oleate, the mucoadhesive property of polymer gel can be increased by three to seven times. Drug release from the gel was regulated by matrix diffusion. When taken as beads contained in a chitosan matrix, nifedipine releases its medication more slowly than when taken as granules.

9. **Vaginal drug delivery**

Polymer, modified by the introduction of
thioglycolic acid to the primary amino groups properties and can act as an absorption enhancer. Buccal tablets based on chitosan microspheres containing

10. Transdermal drug delivery

The ability of polymer to create films is strong. The membrane thickness and cross-linking of the film have an impact on the drug release from the devices. In-situ preparation of chitosan-alginate polyelectrolyte complex in beads and microspheres has been done for potential use in packaging, controlled release systems, and wound dressings. For the treatment of local inflammation, polymer gel beads are a promising biocompatible and biodegradable delivery system for medications like prednisolone, which exhibited sustained release action that increased therapeutic efficacy. It was discovered that the sort of membrane being employed affected how quickly the medicine was released. For regulated drug distribution and release kinetics, a chitosan hydrogel and membrane combination containing the local anaesthetic lidocaine hydrochloride works well.

11. **Colonic drug delivery**

Insulin has been delivered specifically to the colon via polymer. The enteric coating (Hydroxy propyl methyl cellulose phthalate) on the chitosan capsules contained, in addition to insulin, many other absorption enhancers and enzyme inhibitors. It was discovered that the colonic region was where capsules specifically dissolved. It was proposed that this disintegration was caused by either the presence of bacterial enzymes that can degrade the polymer or the lower pH in the ascending colon compared to the terminal ileum.

12. **Multiparticulate delivery system**

Chitosan pellets were created by H.Steckel and F. Mindermann-Nogly utilising the extrusion/spheronization method. From 0% to 70% of microcrystalline cellulose was utilised as an ingredient. With various powder to liquid ratios, the powder mixture was extruded using water to dilute the acetic acid. The study demonstrated that using demineralized water as the granulating fluid, chitosan pellets with a maximum of 50% (m/m) could be manufactured. Using diluted acetic acid for the granulation process would enhance the bulk fraction of chitosan in the pallets to 100%.

13. **Targeting drug delivery**-

The idea of site-specific medication targeting is a well-established belief. It's getting all the attention.

The drug's strategy and particular response with its receptor determine how effective it is as a treatment. The vaccination is a crucial component of the delivery system for antimicrobial protection. The majority of parenteral vaccinations, including the diphtheria and tetanus shots, have been compressed into biodegradable polymeric microspheres.

14. **Buccal and sublingual drug delivery-**

The buccal mucosa may naturally have low molecular weight, great potency, and a long biological half-life for peptide drug delivery. In order to circumvent hepatic first-pass metabolism, spray-drying technology was used to create mucoadhesive microspheres of venlafaxine with linseed mucilage as a muco-adhesive component for buccal distribution [19].

15**. Nasal Drug Delivery-**

It has been proven that polymer-based drug delivery systems such microspheres, liposomes, and gels have high bio adhesive properties. When in contact with the nasal mucosa, it easily expands, enhancing the bioavailability and duration of the medications' residence time in the nasal route. such as albumin, dextran, and starch Other applications: There are several further applications. For membrane-based technology in flow cytometry, microbiology, and cell biology, fluorescent microspheres can be used [6].

In microspheres, natural excipients are often used [21]. Natural excipients are being used in innovative drug delivery methods, according to numerous recent studies [22–24].

CONCLUSION

Microspheres are a better drug delivery method than other types, according to the current review research. In the coming days, this microsphere novel drug delivery system will demonstrate greater efficacy in the treatment of cancer or any other disease, such as one that is related to the lungs, the heart, or the nervous system. This microsphere formulation will also demonstrate greater potency and greater in vivo efficacy. This formulation primarily ensures the safety of the active pharmaceutical component and other formulation excipients.

REFERENCES

1. Chien YW. Novel Drug Delivery Systems- Fundamentals, Development Concepts. Biomedical Assessment, Marcel Dekker, New York, pg.no. 1.

2. Chaudhari A, Jadhav RK, Kadam JV An overview:Microspheres as a nasal drug delivery system. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5(1).

3. Vyas S.P., Khar R.K. Targeted and Controlled Drug Delivery, Novel Carrier Systems, first reprint 2004, pg.no. 418, 419, 420, 423, 424, 444-454.

4. Jain N.K. Controlled and Novel Drug Delivery, 2004; 236-237,21.

5. www.pharmainfo.net/reviews/bioadhesive_microspheres_review, 24th2010 Patel J.K., Patel R.P., Amin A.F., Patel M.M., 2006; 4(6).

6. Nira.R.P, Dhargash A.P, Praful.D.B, Vikaram.P, Darshan.M. Microsphere as a novel drug delivery,Int.J.ofpharma& life sci.(IJPLS) aug 2011; 2(8): 992-997.

7. Kavita Kunchu, Raje Veera Ashwani et al. Albumin Microspheres: A Unique system as drug delivery carriers for non steroidal anti-inflammatory drugs. 2010;5(2):12.

8. Kalyan Shweta, Sharma Parmod Kumar et al. Recent Advancement In Chitosan Best Formulation

And Its Pharmaceutical Application. Pelagia Research Library. 2010;1(3):195-210.
9. Dr. Fishers Microsphere Selection Bangs laboratories inc, Tech Notes 201 A, 1-4 Available from URL http://www.bangslabs.com/sites/def ault/files/bangs/do cs/pdf/201A.pdf
10. Corrigan l. Owen and Healy Marie Anne. Surfactants in Pharmaceutical Products and Systems "Encyclopedia
of Pharmaceutical Technology" 3rd edition, 2003 volume 1, edited by James Swarbrick Informa healthcare Inc. P.NO – 3590
11. Saravana Kumar K, et. al., A Review on Microsphere for Novel drug delivery System, Journal of Pharmacy Research, 2012,5(1), Page 420-424.
12. Venkatesan PC, Manavalan R, and Valliappan K, Selection of better method for the preparation of microspheres by applying Analytic Hierarchy Process. J. Pharm. Sci. and Res. 2009; Vol.1 (3): P-64-78.
13. Harsh Bansal, et. al., Microsphere: Methods of Prepration and Applications; a Comparative Study, International Journal of Pharmaceutical Sciences Review and Research, 2011, 10(1); Article-012.
14. Patrick B. O'Donnell, et. al., Preparation of microspheres by the solvent evaporation technique, Advanced Drug Delivery Reviews 28 (1997) Page 25–42.
15. Tibor Renkecz, et. al., Preparation of Molecularly Imprinted Microspheres by Precipitation Polymerization, Methods in Molecular Biology, 2017, 1575, Page 341-352.
16. Xinghang Ma, et. al., Stability Study of Drugloaded Proteinoid Microsphere Formulations during Freeze-drying, Iournal of Drug Targeting, 1994, 2, Page 9-21.
17 . Shweta Saini, et. al., Microspheres as Controlled Drug Delivery System: An Updated Review, international journal of pharmaceutical science and research,4, 2018, 1760-1768.
18. Chaturvedi G and Saha RN. A Review on Microsphere Technology And Its Application. Birla institute of technology and sciences. 2009:56-58.
19. Gholap SB, Banarjee SK, Gaikwad DD, Jadhav SL and Thorat RM. Hollow microsphere: a review, International Journal of Pharmaceutical Sciences Review and Research. ,2010;1:10-15.
20. Agusundaram M, Madhu Sudana Chetty et al. Microsphere As A Novel Drug Delivery System A Review.
International Journal of ChemTech Research. 2009;1(3):526-534.
21. Sudha Mani T and Naveen Kumar K. At preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery International Journal Of Pharma Research And Development. 2010;2(8):120-121.
22. Thanoo BC, Sunny MC and Jayakrishnan A. Cross-linked chitosan microspheres: Preparation and evaluation as a matrix for the controlled release of pharmaceuticals. J Pharm Pharmacol. 1992;44:283-286.
23. Bahadur S, Sahu U, Sahu D, Sahu G, Roy A. Review on natural gums and mucilage and their application as excipient. Journal of Applied Pharmaceutical Research, 5 (4): 13 – 21 (2017)
24. Bahadur S, Chanda R, Roy A, Choudhury A, Das S, Saha S. Preparation and evaluation of mucoadhesive microcapsules of captopril for oral controlled release. Research Journal of Pharmacy and Technology, 1(2): 100 – 105 (2008)