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Review Article

Microsphere- A Novel Drug Delivery System

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Abstract

Microspheres are characteristically free flowing powders having particle size ranging from 1-1000 µm consisting of proteins or synthetic polymers. Microspheres are used in drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and action at the specific site to predetermined rate. Microsphere are spherical in shape so, therapeutic efficacy of microspheres containing drug depends upon their characteristics that can be altered in required terms by altering materials, methods, polymers or techniques used. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Microsphere can be manufactured by various type of material such as glass, polymers, and ceramic microspheres. Microspheres are various types like Bioadhesive microspheres, Magnetic microspheres, Floating microspheres, radioactive microspheres, Polymeric microspheres, Biodegradable polymeric microspheres, Synthetic polymeric microspheres and are prepared by methods like Spray Drying, Solvent Evaporation, Single emulsion technique, Double emulsion technique, Phase separation coacervation technique, Spray drying and spray congealing, Solvent extraction, Quassi emulsion solvent diffusion. Microspheres have wide range of applications because of controlled and sustained release.

Keywords: microspheres, method of preparation, patents, recent advancement, marketing formulation

Introduction

Microspheres may be defined as microspheres are the substances or compounds which having free flowing property (powders).Microspheres are consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size from 1-1000µm. Microspheres are also called as microparticals. Microsphere can be manufactured by various type of material such as glass, polymers, and ceramic microspheres. They are used in different applications, their use depends on their material and particle size used in construction. Micro sphere are two types microcapsules and micrometrics, which are described as, micro-capsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall. And micrometrics in which entrapped substance is dispersed throughout the matrix (see figure 1). Microsphere plays an important role to improve bioavailability of conventional drugs and minimizing side effect [1, 2].

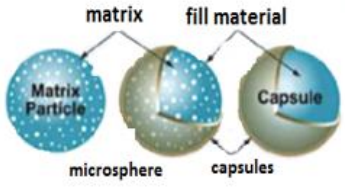

Figure 1. Types of microsphere

Advantage of microspheres

1. Particle size reduction enhances the solubility of the poorly soluble drug.
2. Microsphere provides constant and prolonged therapeutic effect.
3. Provide constant drug concentration in blood thereby increasing patent compliance.
4. Decrease dose and toxicity.
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery.
6. Reduce the dosing frequency and thereby improve the patient compliance.

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7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
8. Protects the GIT from irritant effects of the drug.
9. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
10. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects and also decrease the problems of repeated injections
11. Taste and odor masking.
12. Conversion of oils and other liquids to solids for easy of handling.
13. Protection of drugs against the environment (moisture, light etc.).
14. Improvement of flow of powders.
15. Aid or helps in the dispersion of water-insoluble substances in aqueous media [3].

Disadvantage of microsphere-

1. The costs of the materials and processing of the controlled release preparation, are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents [4].

Ideal properties of microspheres-

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale. υ Biocompatibility with a controllable biodegradability.
5. Susceptibility to chemical modification [3].

Benefits of microsphere in drug delivery system

Microspheres are used as controlled drug delivery systems for a variety of applications including chemotherapy, cardiovascular disease, hormone therapy, therapeutic protein delivery, and vaccine development.

Delivery of drugs through biodegradable microspheres has numerous applications compared to conventional delivery systems. While in conventional systems the drug is usually released shortly after delivery of drug and stops the working after a brief period of time, biodegradable polymer offers a way to provide sustained release over a longer time, thus eliminating the need for multiple doses and ensuring sustained and controlled drug delivery over weeks or months.

Use of biodegradable polymers minimizes the possibility of toxicity problems, but does produce by-products that must be tolerated without adverse reactions.

Applications of microspheres.

Localized delivery of drug: These are the product can be implied directly at the site where drug action is required (needed) and hence, systemic exposure of the drug can be reduced. This is becomes important especially for toxic drugs which are related to various systemic side effects (such as the chemotherapeutic drugs).

Sustained delivery of drugs: The drug in the form of encapsulated is released over extended periods and hence, reduce the need for multiple injections. This feature can improve patient compliance especially for drugs for chronic indications, requiring frequent injections (such as for deficiency of certain proteins).

Stabilization of the drug: The polymer can protect the drug from the physiological environment and hence improve its stability *in vivo*. This particular feature makes this technology attractive for the delivery of labile drugs such as proteins [3,4].

Types of Microspheres:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres
    i) Biodegradable polymeric microspheres
    ii) Synthetic polymeric microspheres

1. Bioadhesive microspheres:

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water-

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soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion. These kinds of microspheres shows a prolonged action time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action[5,6].

2. Magnetic microspheres:

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. The different types of

a. Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

b. Diagnostic microspheres, used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides[7,8].

3. 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, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Drug (ketoprofen) is given in the form of floating microspheres [9,10,11].

4. Radioactive microspheres:

Radio embolization therapy microspheres sized 10-30nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across. They are injected in the arteries that leads them to tumour of interest so all these conditions 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 [12,13].

5. Polymeric microspheres:

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres [13].

i) Biodegradable polymeric microspheres:

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive 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 ina 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. However they provide wide range of application in microsphere based treatment [14].

ii) Synthetic polymeric microspheres:

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[15].

Method of Preparation

1. Spray Drying
2. Solvent Evaporation
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technique
6. Spray drying and spray congealing
7. Solvent extraction
8. Quassi emulsion solvent diffusion [16,17,18].

1. Spray Drying

In Spray Drying technique, firstly the entire polymer are dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. and then the drug in the solid form is 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

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formation of the microspheres in a size range 1-100µm (figure 2). 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.

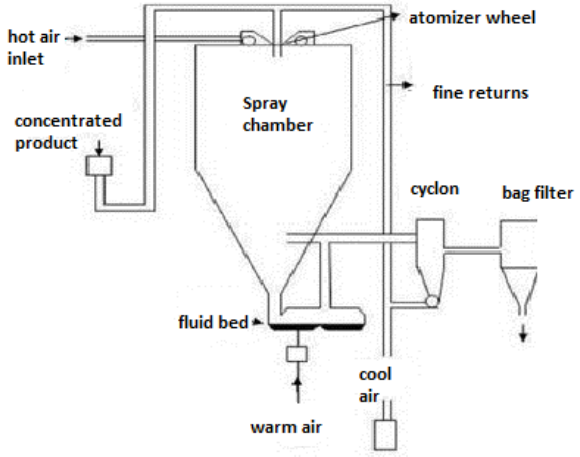

Figure 2. Spray drying technique

2. Solvent Evaporation:

This process are carried out in vehicles in this the two phases aqueous and organic phase that process called as emulsification i.e. o/w type emulsion after this the solvent evaporate and remains raw nanospheres of microspheres (figure 3).

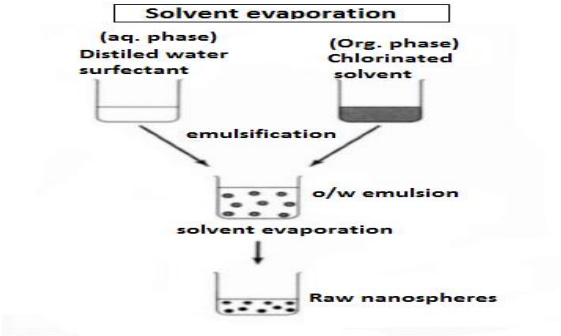

Figure 3. Solvent evaporation

3. Single emulsion technique:

In this technique aqueous solution of polymer are dispersed in organic phase oil/chloroform with continuous stirring this process called as sonification. After this microsphere can be prepared by two ways, first heat denaturation and chemical crosslinking and centrifuge the product and washing or finally separation to produce microspheres (figure 4)

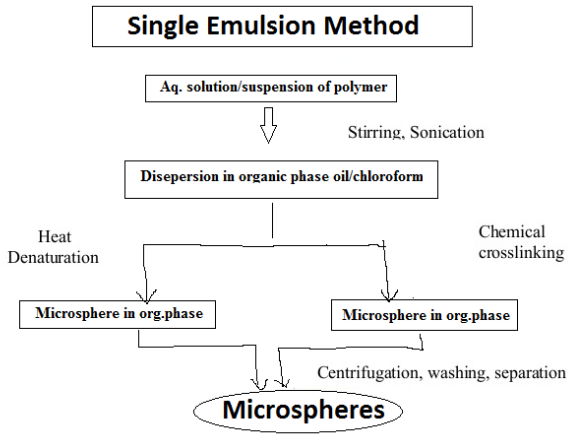

Figure 4. Single emulsion method

4. Double emulsion technique:

In this method aqueous solution of polymer and drug are dispersed in organic phase which produce first emulsion after addition of aq. Solution of PVA and make multi emulsion in solution separation, washing and drying to produce microspheres (figure 5).

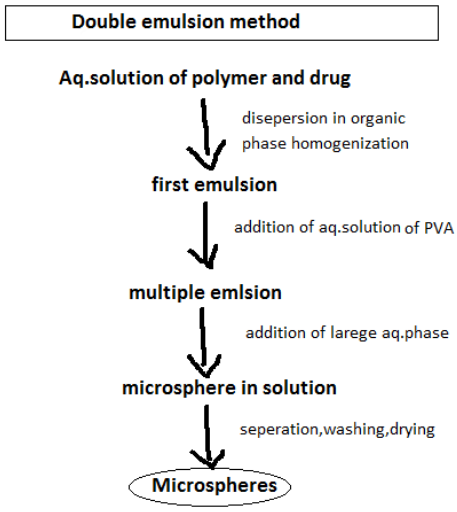

Figure 5. Double emulsion method

5. Phase separation coacervation technique;

In this technique aqueous/organic solution of drug dissolved in polymer solution that forms polymer rich globules or droplets and Harding in aqueous/organic phase, separation, of microspheres washing and then drying to pure form of microspheres (figure 6).

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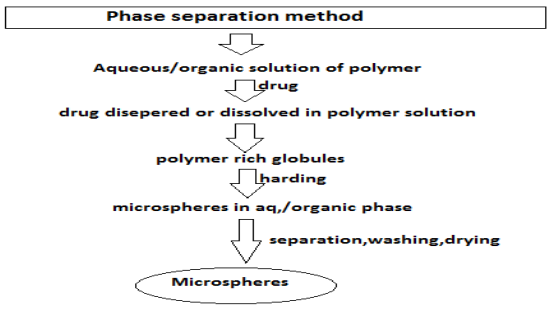

Figure 6. Phase separation method.

6. Spray drying and spray congealing:

Polymer dissolved in suitable volatile organic solvent such as acetone, chloroform, etc. dissolved in polymer solution under high speed homogenization atomized in stream of hot air and this lead to formation of small droplets and then solidifying and form of minute particles (figure 7).

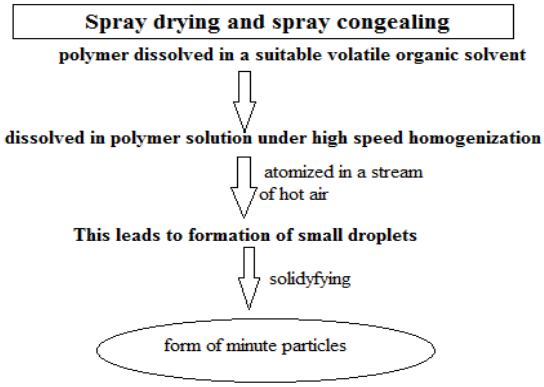

Figure 7. Spray drying and spray congealing.

7. Solvent extraction:

In the solvent extraction polymer and drug must be soluble in organic solvent which forms a solution that called aq. Phase and extract this solution with water missible organic solvent to produce microsphere in aqueous media (figure 8).

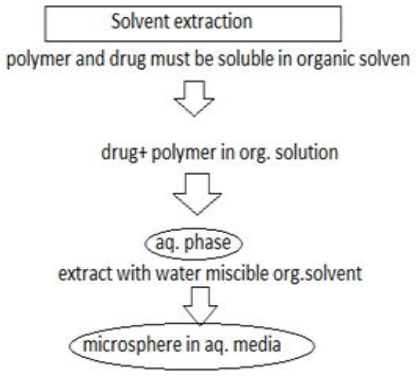

Figure 8. Solvent extraction.

8. Quassi emulsion solvent diffusion:

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 60.C 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 40° C.

Evaluation Parameters of Microsphere

1. Particle size and shape The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

2. Electron spectroscopy for chemical analysis: The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA)[19].

3. Density determination: The density of the microspheres can be measured by using a multi volume pycnometer [20].

4. Isoelectric point: The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined [21].

5. Angle of contact: The angle of contact is measured to determine the wetting property of a micro particulate carrier [22].

6. In vitro methods: Release studies for different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP / BP) [23].

7. Drug entrapment efficiency: Drug entrapment efficiency can be calculated using following equation, % Entrapment = Actual content/Theoretical content x 100.

8. Swelling index: The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) [24].

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Application of Microspheres

a. Vaccine delivery
b. Monoclonal antibodies
c. Imaging
d. Topical porous microsphere
e. Nasal drug delivery
f. Oral drug delivery
g. Targeting drug delivery
h. Gastroretentive controlled delivery system
i. Bio-medical application
j. Pharmaceutical application
k. Other applications are given in table no.1.

Table 1. Other applications of microspheres

Category	Drug	Use	Method	Result
NSAID	Acelofenac25	anti-inflammatory	By dissolving drug in polymer	Controlled release and minimize local side effect
Antibiotic	Amoxicillin26 Gentamicin27	for helicobacter pylori infection eliminating infection	Crosslinking double emulsion technique	Slow release rate Controlled release
Anti-inflammatory	Indomethacin28 Diclofennac29 Ketoprofen30	Anti-inflammatory …….. ……..	Co-matrix method Coacevation phase separation Multiple emulsion o/w/o	Decrease in release rate Suppress the release rate Modulate drug release
Cardiac agent	Nifedipine31,32 Propanolol31,32 Dilitazam33	Calcium channel blockers ……. Calcium channel blockers	Encapsulation Emulsification coacevation technique Controlled coacevation technique	More drug entrapment efficiency Enhance drug encapsulation efficiency Retard drug release
Steroidal	Progesterone34	Steroid	Crosslinking	Maintain plasma drug concentration
Antidiabatic agent	Insulin35	Antihyperglycemic	…..	Improve systemic absorption
Diuretics	Furosemide36	Diuretic	Crosslinking	Reduce affect of external variables
Anticancer	Fluoroucil37 Cisplatin38 Mitoxantrone Oxantrazol	For targeted delivery to treat cerebral tumors Antitumors activity Antitumor anticancer	Dry-in-oil w/o emulsion system crosslinking technique combined emulsion	Slow down of release rate of drug Reduse release rate Minimize drug toxicity & minimize therapeutic efficacy Enhance the delivery of drug in brain 100 times

Marketed formulation of microspheres: marketing formulation are given in table No.2

Table 2. Marketing formulation.

SN	Brand name	Drug	company	Treatment	Ref.
1	Protonix	Pantoprazole	Wyeth pharmaceutical inc.. Germany	Gastric ulcer	51
2	Lumason	Sulfur hexafluoride lipid microsphere	Bracco Diagnostics Inc	Diagnosis and Investigation	52
3	Altinac, Atralin, Avita, etc	Tretinoin	Janssen cilag pharmaceuticals inc..	Skin renew	53
4	Definity	Perflutren Lipid Microsphere		Ultrasound	54
5	Bellafill	dermal filler	Suneva Medical Inc.	Correction of Nasolabial Folds and Acne Scars	55
6	Optison	human albumin microspheres	GE healthcare as oslo, norway	ultrasound imaging procedures	56
7	Zilretta	Triamcinolone Acetonid	Flexion therapeutic inc.	inflammatory conditions(knee pain e.t.c)	57

Patent of microsphere: patent of microsphere are given in table no.3.

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Table 3. Patent of microspheres.

Patent no.	Filed	Date of patent	inventor	Work	Ref.
10195149	May 15, 2014	February 5,2019	Yi Mi Kim, Sun Kyung Lim, Mi Ran Park, Young Joon Park, Seung Hee Baek, Hyun Woo Shin	The present invention relates to a continuous process for preparing microspheres and microspheres prepared thereby, and in particular, a process for preparing microspheres	39
10201633	December 7, 2015	February 12,2019	Paul M.Weinberger, William D. Hill,George G Wicks	Glass composites for tissue augmentation,biomedical and cosmetic applications	40
9050843	June 9,2015	June 30, 2008	Franciscus gerardus henricus duijnhoven van, franciscus wilhemus maria gelissen,	Microsphere comprising a polymer core, a shell and an absorber	41
9944778	April 17,2018	October 16, 2013	Franciscus Wilhelmus Maria Gelissen, Franciscus Gerardus Henricus Van Duijnhoven	The present invention relates to microspheres and to their use, preferably as laser absorbing additive, and to a process for their production.	42
5017378	May 21, 1991	May 1,1989	Terry L. Turner, Stuart S. Howards	Intraorgan injection of biologically active compounds contained in slow-release microcapsules or microspheres	43
7931918	April 26, 2011	July 2, 2008	Barbara Pui Chan, Ming Cheuk Chan, Kwok Fai So.	Collagen-based microspheres and methods of preparation and uses.	44
8338428	December 25, 2012	March 15, 2012	Josiah Brown	Methods for administering aripiprazole	45
8334013	December 18, 2012	November 3, 2008	Dimiter N Petsev, Erin Derbins, Sergio Mendez, Shailendra Rathod, Nick Carroll, David A. Weitz	Mesoporous metal oxide microspheres and method for forming same	46
8728817	May 20, 2014	March 10, 2011	Roy Clinton Ogle, Edward A. Botchwey, III, Rebekah A. Neal	Compositions and methods for making and using laminin nanofibers	47
4452773	June 5, 1984	April 5, 1982	Robert S. Molday	Magnetic iron-dextran microspheres	48
7879304	February 1, 2011	January 16, 2008	Timothy L Ward, Jaime Bravo, Abhaya Datye, Gabriel Lopez, Hien Pham, Shailendra Rathod, Venkata Goparaju	Monodisperse mesoporous silica microspheres formed by evaporation-induced self-assembly of surfactant templates in aerosols	.49
6991779	January 31, 2006	January 17, 2003	Solomon S. Steiner, Cohava Gelber, Robert S. Feldstein, Roderike Pohl	Compositions for treatment or prevention of bioterrorism	50

Recent advancements of microspheres: Recent advancements of microspheres are given in Table No.4.

Table no. 4. Recent advancements of microspheres.

SN	Author	Recent work	Year	Reference
1	Zhang T, Sun W, Xue J, Chen J, Jiang Q, Mou L, Du H.	Podocytic infolding glomerulopathy (PIG) is a newly proposed disease	march 2019	58
2	Lu D, Li J, Lin C, Liao J, Feng Y, Ding Z, Li Z, Liu Q, Li H.	Microspheres, A High Performance Catalyst to Hydrolyze Ammonia Borane for Hydrogen Production.	march 2019	59
3	Braat AJAT, Kappadath SC, Ahmadzadehfar H, Stothers CL, Frilling A, Deroose CM, Flamen P, Brown DB, Sze DY, Mahvash A, Lam MGEH.	Radioembolization with Y Resin Microspheres of Neuroendocrine Liver Metastases	March 2019	60
4	Pan SD, Chen XH, Shen HY, Li XP, Cai MQ, Zhao YG, Jin MC	Rapid and effective sample cleanup based on graphene oxide-encapsulated core-shell magnetic microspheres for determination.	2019	61
5	Bastiaannet R, Kappadath SC, Kunnen B, Braat AJAT, Lam MGEH, de Jong HWAM.	The physics of radioembolization.	2018	62

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6	Baltatzis M, Siriwardena AK.	Liver Resection for Colorectal Hepatic Metastases after Systemic Chemotherapy and Selective Internal Radiation Therapy with Yttrium-90 Microspheres	2018	63
7	Delicque J, Guiu B, Boulin M, Schwanz H, Piron L, Cassinotto C.	Liver chemo-embolization of hepatocellular carcinoma using TANDEM microspheres	2018	64
8	Thakur S, Riyaz B, Patil A, Kaur A, Kapoor B, Mishra V.	Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis	2018	65
9	Zemánek J, Michálek T, Hurák Z.	Phase-shift feedback control for dielectrophoretic micromanipulation.	2018	66
10	Wong CY, Al-Salami H, Dass CR.	Microparticles, microcapsules and microspheres: A review of recent developments and prospects for oral delivery of insulin.	2018	67

Conclusion

The concept of microsphere drug delivery systems offers certain advantages over the conventional drug delivery systems such as controlled and sustained delivery. As well as microspheres also allow drug targeting to various systems such as ocular , intranasal , oral and IV route . Novel technologies like magnetic microspheres, immune-microspheres offer great advantages and uses than conventional technologies. Marketing preparation such as protonix, zilretta, lumson, definity etc. are famous preparation, therefore microsphere are offers great affinity to the preparation to make them efficient and enhance the therapeutic effect.

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Conflict of interest:

There are no conflict of interest.

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