Vol 5|Issue 3| 2015 |232-237.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

REVIEW ON A NOVEL APPROACH: MICROSPHERES DRUG DELIVERY SYSTEM

Vadigoppula Jyothi[1], T. Sri Krishna[1], Ranjtih Reddy Kondeti[2]

[1]Department of Pharmaceutics, Narayana College of Pharmacy, Chinthareddy Palem, Nellore, Andhra Pradesh, India.
[2]Emergent laboratories, Ameerpet, Hyderabad, Andhra Pradesh, India.

ABSTRACT

There are various approaches in the drug delivering to the target site in a sustained controlled release. One such approach is using microspheres as carriers for drugs which are also known as micro particles. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000µm. The range of Techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs. The size or average diameter of prepared microspheres were recognized and characterized by scanning electron microscopic methods. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 12 hrs .The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment for more than12 hrs.

Key words: Microspheres, prolonged release, buoyancy, gastric environment.

INTRODUCTION

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1-1000µm). Microspheres are sometimes referred to as micro particles. Microspheres can be manufactured from various natural and synthetic materials. [1] Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are. Polyethylene and polystyrene microspheres are two most common types of polymer microspheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm^3[1].

CHARACTERISTICS

The different characteristics of microspheres [2] are shown in table: 1and advantages and disadvantages are described below

Advantages

1. Microspheres provide constant and prolonged therapeutic effect.
2. Reduces the dosing frequency and there by improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release [3]

Disadvantages

Some of the disadvantages were found to be as follows

1. The modified release from the formulations.
2. The release rate of the controlled release dosage form

*Corresponding Author **Ranjith Reddy Kondeti** E mail: info@emergentlabs.in

may vary from a variety of factors like food and the rate of transit though gut.
3. Differences in the release rate from one dose to another.
4. Dosage forms of this kind should not be crushed or chewed.

Types of Microspheres

- Bio-adhesive microspheres
- Magnetic microspheres
- Floating microspheres
- Radioactive microspheres
- Polymeric microspheres
- Biodegradable polymeric microspheres
- Synthetic polymeric microspheres

Bio-adhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water 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 types of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. The effects of different polymers on bioadhesive microspheres4, 5, 6, 7 are mentioned in Table 2.

Magnetic microspheres

This kind of delivery system is very much important which targets 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 from magnetic field [8].

Therapeutic Magnetic Microspheres

These are used to deliver chemotherapeutic agents in liver tumors. The incorporated materials that are used for magnetic microspheres are chitosan, dextran etc [9].

Diagnostic microspheres

Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming anodize particles supra magnetic iron oxides [8].

Floating microspheres

Floating system was first described by Davis in 1968. Floating drug delivery systems (FDDS) has a bulk density less than gastric fluids and so remains buoyant in the stomach for a prolonged period without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system and the residual system is emptied from the stomach. This results in an increased Gastric Residence Time (GRT) and a better control of the fluctuations in plasma drug concentration [10].

Radioactive microspheres

Radio remobilization 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 tumor of interest. So all these conditions radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues [11].

Polymeric microspheres

The different types of polymeric microspheres are classified as follows; they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

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 most important drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release. Therefore they provide wide range of application in microsphere based treatement [12].

Synthetic polymeric microspheres

The synthetic polymeric microspheres [10-15] are widely used in clinical application and 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 [7]. Different kinds of polymers used for microspheres are given in table 3.

Method of Preparation

The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release ,method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are [16].

Emulsion solvent evaporation technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of pvp as emulsifying agent. The above prepared mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with de-mineralized water and desiccated at room temperature for 24 hrs [7].

Emulsion cross linking method

In this method drug was dissolved in aqueous gelatin solution which was previously heated for 1 hr at 40^0C. The solution was added drop wise to liquid paraffin by stirring the mixture at 1500 rpm for 10 min at 35oC, results in w/o emulsion then further stirring is done for 10 min at 15^0C. Thus the prepared microspheres were washed respectively three times with acetone and isopropyl alcohol and then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween-80 at 37ºC for 10min to block unreacted glutaraldehyde [6].

Spray Drying

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as Dichloromethane, Acetone, etc. The solid form drug 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 from which the solvent evaporate 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. The major advantages of process are feasibility of operation under aseptic conditions this process is rapid. In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as leads to the formation of porous micro particles shown in below Figure 1.

Hydroxyl appetite (HAP) microspheres in sphere morphology

HAP used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from cosolvencing and helped them to stay individual droplets. While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres [18].

Solvent extraction

Solvent evaporation method[17] is used for the preparation of micro particles, involves for the Removal of the organic phase by extraction of the organic solvent. This method involves Water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

EVALUATION PARAMETERS

Physicochemical Evaluation Characterization

The characterization of the micro particulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. The microspheres have different microstructures. These microstructures determine the release and the stability of the carrier.

Particle size analyzers

Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of Tween 80, to Prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer [19].

Optical microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was carried out under 450x (10x eye piece and 45x objective) and100 particles were calculated [4].

Electron spectroscopy for chemical analysis:

The surface chemistry of the microspheres can be determined by using the electron spectroscopy for chemical analysis (ESCA). ESCA provides a means for the determination of the atomic composition of the surface. The spectra obtained using ECSA can be used to determine the surfacial degradation of the biodegradable microspheres.

Swelling index

This process is used for Characterization of sodium alginate microspheres which was performed with swelling index technique. Different solution(100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37^0 C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper [20].

Density determination

The density of the microspheres can be measured by using a multivolume pycnometer. Accurately weighed sample in a cup is placed into the multivolume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and the density of the microsphere carrier is determined.

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic

property is specific to solid and affected by the Presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 20^0C a minute of deposition of microspheres.

Stability studies

The microspheres are placed in a screw capped container and were stored in following conditions.

1. Ambient humid condition
2. Room temperature (27+/-2 0C)
3. Oven temperature (40+/-2 0C)
4. Refrigerator (5 0C -80C).

It was carried out of a 60 days and the drug content of the microsphere was analysed [21].

***In vitro-In vivo* correlations**

Correlations between in-vitro dissolution rates and the rate and extent of availability as determined by blood concentration or urinary excretion of drug or metabolites are referred to as "*in vitro-in vivo* correlations". Such correlations are useful to develop product specifications with bioavailability

Dissolution apparatus

Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using both rotating elements, paddle 25, 26, 27 and basket 28, 29. Dissolution medium used for these studies varied from 100-500 ml and speed of rotation from 50-100 rpm

RECENT ADVANCEMENT IN MICROSPHERES

Increase stability of drug

Chitosan polymer is used to increase the stability of the drug in which the drug is complexed with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass through sieve no.16 and make a granules is completely stable at different condition.

Dental Medicine

Chitosan have been recognized to prevent wound healing to attain an aesthetically valid Skin surface, and to prevent excess scar formation. In dental medicine, chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis.

Wound healing properties

Chitosan acetate films, which were tough and protective, had the advantage of good oxygen permeability, high water absorptivity and slow enzymatic degradation.

FUTURE CHALLENGES

The microspheres look bright future challenges particularly in the area of medicinal field because it has wide spectrum of application in molecular biology, eg: microsphere based genotyping platform is used to detect six single nucleotide polymorphism, yittrium-90 microspheres is used to prevent tumour after liver transplantation and it's advanced way in delivery of vaccines and proteins. In future by combining various other strategies, microspheres will find the central place. In novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

Table 1. Microsphere property

S. No	Property	Consideration
1	Size	Diameter Uniformity/distribution
2	Composition	Density, Refractive index Hydrophobicity/ Hydrophilicity Nonspecific binding Auto fluorescence
3	Surface chemistry	Reactive groups Level of functionalization Charge
4	Special properties	Visible dye/fluorophore Super-paramagnetic

Table 2. The effect of different polymers on bio-adhesive microspheres

Drug	Route of administration	Bio-adhesive polymers use	Applications
Clonazepam	Nasal	Gelatin-Chitosan	Higher concentration of drug is achieved in brain.
Gentamicin	Nasal	DSM+LPC	Combination of these polymers improves nasal absorption.
Insulin	Nasal	DSM+LPC	Helps to deliver insulin via nasal route
Human growth Hormone (hGH)	Nasal	DSM+LPC	Improves absorption.
Propanalol, Hcl	Nasal	Chitosan- Gelatin	Controlled blood level profile, increased bioavailability of drug
Aceclofenac	GI	Eudragit (S100,RL100,RS100)	Controlled release of drug is achieved.
Furosemide	GI	AD-MMS (PGEFs)	Bioavailability increases higher, AUC and absorption also increases

Table 3. Various types of polymers and their application

Polymer	Mechanism
Modified starch, HPMC, Carpool 974P	Slow release of drug
Ethyl cellulose	Controlled release for longer period of time.
PLGA, Chitosan	Vaccine delivery
PLA, PLGA, Starch cyanoacrylate etc(PEG-) liposomes	Drug delivery without toxic side effects
Magnetic polystyrene microspheres	Specific cell labeling
Polymer resins such as Agarosepolyacroline, sephadex	Affinity chromatography
Chitosan coated PlGA microspheres	Targeted drug delivery

Fig 1. Spray drying method for preparation of microspheres

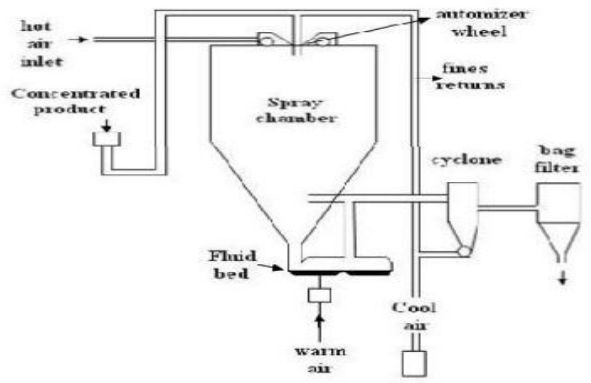
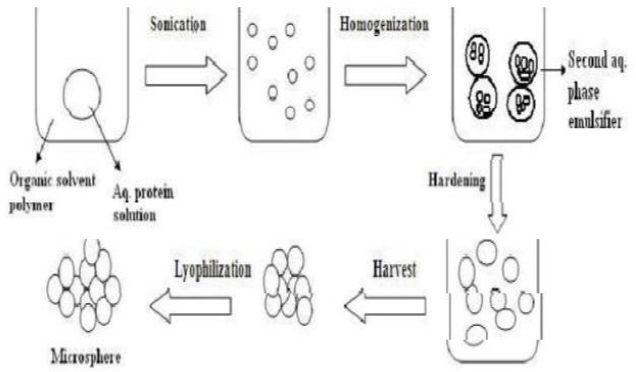


Fig 2. Solvent Extraction Method



CONCLUSION

This paper explains how the microspheres are better choice of drug delivery system. It has the advantage of target specificity and better patient compliance. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Hollow microsphere promises to be potential approach for gastric retention. Its applications are not only used for delivering drugs but also for imaging tumours, detecting bimolecular interaction etc. So, in future microspheres will have an important role to play in the advancement of medicinal field.

REFERENCES

1. Chaturvedi G and Saha RN. A Review on Microsphere Technology and Its Application. *Birla institute of technology and sciences*, 2009, 56-58.
2. Dr. Fishers Microsphere Selection Bangs laboratories inc, *Tech Notes*, 201, 1-4.
3. Ashvini Veera Raje, Kunchu Kavitha, Ganesh Nanjan Sockan. Albumin Microspheres: A Unique system drug delivery carriers for non steroidal anti inflammatory drugs. *Indian Journal of pharmaceutical Sciences*, 5(2), 2010, 12.
4. Shaji J, Poddar A, Iyer S. Brain-Targeted Nasal Clonazepam Microspheres, *Indian Journal of pharmaceutical Sciences*, 71(6), 2009, 715–718.
5. www.pharmainfo.net/reviews/bioadhesivemicrospheres-review
6. Dandagi MP, Masthiolimath SV, Gadad PA, Iliger RS. Mucoadhesive Microspheres of Propanalol HCl for Nasal Delivery. *Indian Journal of pharmaceutical Sciences*, 69(3), 2009, 402-407.
7. Trivedi P, Verma AML, Garud N. Preparation and Characterization of Aclofenac Microspheres. *Asian Journal of Pharmaceutics*, 2(2), 2008, 110-115.
8. Shanthi NC, Gupta R, Mahato KA. Traditional and Emerging Applications of Microspheres: A Review. *International Journal of Pharm Tech Research*, 2(1), 2010, 675-681.
9. Li SP, Kowalski CR, Feld KM, Grim WM. Recent Advances in Microencapsulation Technology and Equipment. *Drug Dev Ind Pharm*, 14, 1988, 353-376.
10. Najmuddin M, Ahmed A, Shelar S, Patel V, Khan T. Floating Microspheres Of Ketoprofen: Formulation and Evaluation. *International Journal Of Pharmacy and Pharmaceutical sciences*, 2(2), 2010, 83-87.
11. Hafeli U. Physics and Chemistry Basic of Biotechnology. Focus on biotechnology. Review. *Radioactive Microspheres for Medical Application*, 7, 2002, 213-248.
12. Yadav AV, Mote HH. Development of Biodegradable Starch Microspheres for Intranasal Delivery. *Indian Journal of pharmaceutical Sciences*, 70(2), 2008, 170-174.
13. Chowdary KPR, Koteshwara RN, Malathi K. Ethyl Cellulose Microspheres of Glipizide: Characterization, InVitro and In Vivo Evaluation. *Indian Journal of pharmaceutical Sciences*, 66(4), 2004, 412- 416.

14. Surini S, Anggriani V, Anwar E. Study of Mucoadhesive Microspheres Based on Pre-gelatinsed Cassava Starch Succinate as a New Carrier for Drug Delivery. *J.Med.Sci*, 9(6), 2009, 249-256.
15. Fischer S, Foreg C, Merkle PH, Gander B. Chitosan Coated Plga-Microspheres-A Modular System for Targetting Drug Delivery. *European Cells and Materials*, 7, 2004, 11-12.
16. Ghulam M, Mahmood A, Naveed A, Fatima RA. Comparative study of various microencapsulation techniques. Effect of polymer viscosity on microcapsule characteristics. *Pak.J.Sci*, 22(3), 2009, 291-300.
17. Parmar H, Bakliwal, Sunil *et al*., Different Method of Evaluation of Mucoadhesive Microsphere. *International Journal of Applied Biology and Pharmaceutical Technology*, 1(3), 2010, 1164-1165.
18. Pradesh TS, Sunny CM, Varma KH, Ramesh P. Preparation of micro structured hydroxyapatite microspheres using oil in water emulsion. *Bull Matter.Sci*, 28(5), 2005, 383-390.
19. Kannan K, Karar KP, Manavalan R. Formulation and Evaluation of Sustained Release Microspheres of Acetazolamide by Solvent Evaporation Technique. *J.Pharm.Sci & Res*, 1(1), 2009, 36-39.
20. Soni LM, Kumar M, Namdeo PK. Sodium alginate Microspheres for extending drug release: formulation and in vitro evaluation. *International Journal of Drug Delivery*, 2(1), 2010, 64-68.
21. Tamizharsi S, Rathi CJ, Rathi. Formulation and Evaluation of Pentoxyfylline-Loaded Poly (ε-caprolactone) Microspheres. *Indian Journal of pharmaceutical Sciences*, 70(3), 2008, 333-337.