JPR INFO .com
Journal of Pharma Research

Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

Porous Microsphere and its Significances

Geeta* Charan Singh[1], Tarun Virmani[2], Reshu Virmani[3]
[1]CBS College of Pharmacy & Technology, Village-Chandpur, Faridabad, Haryana, INDIA; [2]MVN University, Palwal, Haryana, INDIA.
[3]Spectrum Institute of Pharmaceutical Sciences and Research, Greater Noida, U.P, INDIA.

Received on: 10-05-2015; Revised and Accepted on: 21-05-2015

ABSTRACT

Over the past few years, the large porous particle technology has been habituated for a number of biopharmaceuticals and conventional therapeutic agents, including insulin, testosterone, estradiol, deslorelin, tobramycin, ciprofloxacin and paraaminosalicylic acid. Porous microspheres have more attention in the last two decades for their large applications in many fields, such as carriers for drugs, absorption and desorption of substances, pulmonary drug delivery, and tissue regeneration.

Keywords: *Pulmonary drug delivery, negative surface charge, desorption, tissue regeneration, porous particle technology, hydrophilic Macromolecules.*

INTRODUCTION

Small progress was made until the 1990s when porous microspheres were imposed as suitable materials for potential applications including as carriers for drugs, high speed chromatography, cell delivery, and tissue regeneration as a supporting frame work [1].

The large porous particle technology has been wonted for a number of biopharmaceuticals and conventional therapeutic agents, including insulin, testosterone, estradiol, deslorelin, tobramycin, ciprofloxacin and para-aminosalicylic acid [2].

Microspheres are conceptual carriers for delivery of the drug in both oral and parental routes of administration. Porous microspheres have been evolved for not only sustaining the drug release profile but have also been used to meliorate the amount of drug release [3]. Increased binding capacity connected with higher polymer acid values. With certain polymers, rhBMP-2 adsorption was declined or inhibited at high protein concentration, but protein loading could be improved reiterative by increasing the protein solution:PLGA (volume:mass) ratio or by reiterative soaking [4]. Greater immersion has been centered on the development of porous materials as controlled drug delivery matrices because of retaining several alternatives features such as stable uniform porous structure, high surface area, tunable pore sizes with narrow distribution and well defined surface properties [5]. Drug release from the porous carrier may be complete within 10 min or be incomplete after several hours or days. Solvent polarity and surface properties play an major role in the adsorption and release from the porous carriers [5].

In general, the drug release from microspheres are deliberated to occur both by degradation of the polymer matrix and by simple diffusion of the drug molecules. It has been unveiled that various factors affect the feature of drug release, such as the size and structure of the microsphere, porosity, chemistry, degradability, and molar mass of the polymer material, and pH value of the medium [1]. Furthermore, pH-sensitive release technique has been improved [6]. The traditional use of totally porous silica particles as support material for preparing columns for high-performance liquid chromatography (HPLC) has recently been undergoing serious changes. The reincarnation of superficially porous (often called Fused-Core®, core shell or porous shell) particles has rapidly resulted in the routine use of these materials because of superior performance for separating both small molecules. For separating small molecules, superficially porous particles with pores in the 80–100 Å range appear enough for such solutes to enter the pore structure without obstructed pierce which would depreciate column efficiency. Larger molecules require larger pores for entry, and Fused-Core particles with 160 Å have been made available for dissociating compounds such as peptides. Superficially porous particles with 200–400 Å pores have been wonted for separating proteins and other larger molecules [7].

***Corresponding author:**
Geeta Charan Singh
CBS College of Pharmacy & Technology,
Village-Chandpur, Faridabad, Haryana, INDIA.
**E-Mail: geetasorout@gmail.com*

Material for preparing porous microsphere:

Various types of pores like open, closed, transport and blind pores in the porous solid permit them to adsorb drugs and release them in a more reproducible and predictable manner. Micro-scale interconnected pores produced through salt-leaching, gas foaming, lyophilization , and sphere templating have shown to be productive in allowing for cellular infiltration and, subsequent, increased framework vascularization. Several different techniques have been developed to create open pore structures using degradable polymers. More recently, Washburn et al. published a co-polymer extrusion technique using two immiscible polymers, where one is water-soluble. In this study, a new scaffold fabrication technique is developed where this polymer blend extrusion method is combined with gas foaming to create scaffolds with optimal pore size distribution. Compared with polymer leaching techniques used to create porous structures, this method uses a water-soluble polymer, poly(ethylene oxide) (PEO), which does not require potentially toxic organic solvents for dissolution. Additionally, PEO itself is non-toxic to cells; therefore residual polymer should not affect cell viability [17].

Very recently, poly (lactic-co-glycolic acid)(PLGA)-based microspheres and nanoparticles have been used for oral and nasal delivery of unfractionated heparin and Low molecular weight heparins (LMWH,) although not for pulmonary delivery of LMWH [2].

In the case of hydrophobic polymers that undergo surface erosion, degradation occurs at the implant surface with insignificant decrease in the molecular weight of the bulk material. The matrix becomes smaller but maintains its original geometric shape as a function of degradation time until the structure is completely eroded as indicated in Scheme 1b. Thus, the surface-eroding polymers also fail to form porous structures during the degradation process and also require material prefabrication into 3D interconnected porous structures for tissue regeneration. In addition, biodegradable polyphosphazene-PLAGA blends exhibit several distinct advantages.

Food and Drug Administration has approved several products comprised of PLAGA for a variety of biomedical applications. The synthetic flexibility of polyphosphazene allows us to design specific side group chemistry that enables both inter- and

intramolecular interactions such as hydrogen bonding. The degradation mode and pattern of the polymer can also be tuned efficiently by incorporating different side groups.For example, amino acid ester side groups confer hydrolytic instability to the polymer while addition of phenyl phenoxy side groups increases its hydrophobicity [18].

Liquid penetration into and its subsequent flow through such porous materials depends on both the molecular and the bulk property of the liquid and the geometric and surface property of the porous medium [5].

Methods for preparation of porous microsphere:

Emulsion solvent evaporation:

At first, PLLA microspheres (smaller than 105 μm) were prepared employing an emulsion solvent evaporation technology. Briefly, a PLLA solution (5 g in 250 mL dichloromethane) was dropped into 1.6 L methanol under stirring. The mixture was stirred for 18 h (1000 rpm) at room temperature to evaporate most of the organic solvent. Afterwards, deionized water was added to replace the residual organic solvent. After 3 times decantation and water replacement, the mixture was lyophilized. PLLA microspheres with diameters smaller than 105 μm were obtained by sieving [19].

w/o emulsion thermal cross-linking method Preparation of egg albumin microspheres Egg albumin microspheres of DH were prepared by the w/o emulsion thermal cross-linking method with minor modification. Hundred ml of light paraffin oil was placed in a glass beaker and mixed with 0.4% w/v span 60 solution by stirring and heating at 70°C for solubilization. The mixture was allowed to cool at room temperature. Add 10 ml of egg albumin aqueous solution of a different drug to polymer ratio ((1.0:1.0, 1.0:1.5 and 1.0:2.0) drop wise (various concentrations 5% w/v, 7.5% w/v, 10% w/v, and 15% w/v) to the different using a 22-gauge hypodermic syringe into an external phase. Light paraffin was stirred at 600 rpm for 10 min with the help of a magnetic stirrer (Remi equipment, 5 l capacity, Mumbai, India). A w/o emulsion was formed. The temperature of the oil bath was raised to 95°C {as preliminary study was carried out at four different temperature levels (30°C, 60°C, 80°C and at 95°C), indicating small, spherical highest percentage yielding microspheres with moderate aggregation at 95°C} and stirring was continued until microspheres were completely dehydrated. Microspheres were then separated by decantation and washed six times with 20 ml of petroleum ether for 2 min at 700 rpm to remove traces of oil. Finally, microspheres were washed three times with 60 zz ml of distilled water for 2 min at 700 rpm and dried at room temperature (at 25°C ± 0.5°C, 60% RH) for 24 h. After drying, a fine yellow free flowing powder was obtained that was stored in desiccators at room temperature [20].

Suspension polymerization:

Suspension polymerization is also called pearl, bead or granular polymerization [15]. In suspension polymerization, the monomer is 'insoluble' in the continuous phase, but in practice may have slight solubility (e.g. styrene in water) [15]. In suspension polymerization, initiation occurs within the monomerrich droplets and with greater than one radical per droplet at any time [19]. The presence of multiple radicals per droplet results in termination kinetics that are similar to those observed in solution polymerization. Essentially, a solution polymerization occurs in each suspended monomer-rich droplet, although with better heat transfer due to the large total surface area.

Pharmaceutical Characterization of porous microsphere:

Particle size analysis and morphology of porous microsphere Microspheres were characterized for their morphology, size, zeta potential, tapped density, and aerodynamic diameter. The morphology of the formulations was studied under a scanning electron microscope. The samples for SEM were prepared on a conductive, double-sided adhesive tape and then sputter-coated with gold under argon.Particle size measurement was carried out by the optical microscopy method. The prepared microspheres were subjected for particle size analysis. Microspheres were suspended in liquid paraffin and particle size was measured [2, 8].

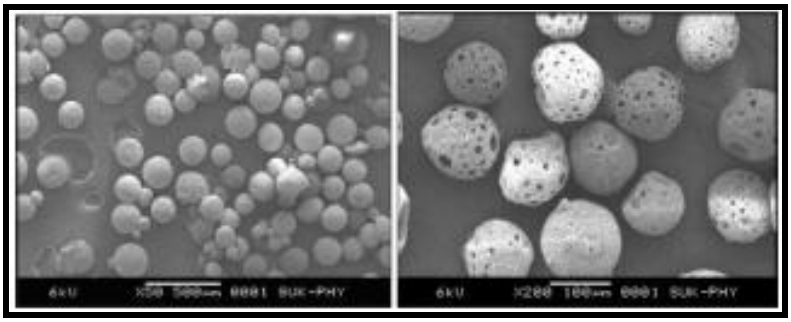

Fig. 1: SEM image of porous microsphere [9]

Pore size of porous microsphere:

The word pore comes from the Greek word 'popos', which means passage. This indicates the role of a pore acting as a passage between the external and the internal surfaces of a solid, allowing material, to pass into, through or out of the solid. Porosity is the collective term for these pores and their distribution in the structure of the solid. Based on the pore size the porosity is classified as microporosity, mesoporosity and macroporosity as given in table 1 [10].

Table No. 1: Classification of porous material/carriers for drug delivery [10]

Types of pores	Pore dimension	Pore formation
Microporous	Less than 2 nm	Formed as a result of imperfect stacking of constituent
Mesoporous	Width between 2 to 50nm	Result of major defects in the structure
Macroporous	Width greater than 50 nm	Formed as a result of major Latticestructure defects like racks, fissure and etching channels.

As pore size plays an essential part in the porous microspheres, some efforts have been made to regulate the pore size, but there's still no universal method to deal with this problem. Large porous particles (~10-15 μm) have demonstrated effective lung deposition and enhanced lung residence as a result of their large diameter and reduced clearance by macrophages in comparison to small microparticles (~1-5 μm) [13]. In many studies, pore size was controlled to some degree by choosing suitable porogens or by adjusting their concentrations. Only a few studies have tried to discover a universal technology. Cheng et al employed CO2 bubbles as templates and precisely adjusted the system pressure. Their carbonated hydroxyapatite microspheres' pore sizes could be well regulated over a wide range from the microscale to the nanoscale. Their results suggested that the gathering and growth of the CO2 bubbles generated the formations of the porous structure, and with the increase of system pressure, the surface of the microsphere got denser and the flakes, which assembled the porous structure, became smaller [11].

Application of porous microspheres:

1. Tissue engineering, which utilizes biodegradable scaffolds, cells, and cell factors to construct three-dimensional (3D)

engineered tissues for in vivo implantation, provides a promising remedy for the treatment of tissue defect and has been largely developed in recent years.

2. suboptimal pore size of the microspheres and poor encapsulation efficiency of many drugs remain major impediments to the widespread use of large porous PLGA microspheres as carriers for inhaled long-acting formulations.
3. control of recombinant human bone morphogenetic protein 2 (rhBMP-2) delivery is chievable by selection of PLGA microsphere carriers.
4. Micro-scale interconnected pores produced through salt-leaching [2, 3], gas foaming [4–6], lyophilization [7–10], and sphere templating [11–14] have shown to be effective in allowing for cellular infiltration and, subsequent, enhanced scaffold vascularization.
5. In addition to the structural characteristics of the scaffold, the effective local delivery of angiogenic factors, including VEGF and PDGF, are necessary to promote blood vessel formation. For tissue regeneration, localized gene delivery can promote the expression of tissue inductive factors to guide tissue formation. Local gene delivery via hydrogel scaffolds has been studied for nearly a decade primarily through the encapsulation of naked DNA during hydrogel formation [5, 15–19]. Although naked DNA achieves gene expression and guided regeneration in vivo [5, 15], limitations with low gene transfer efficiency and rapid diffusion of the DNA from the hydrogel scaffold motivated the use of DNA nanoparticles instead of naked DNA [16].

CONCLUSION

Porous microsphere have been largely studied in few years for their advantages in tissue regeneration, pulmonary drug delivery, bifurcation of substances nad in recombinant technology. the great features are the porous structure, large area for drug incorporation, and less in density.

However, some problem is also present in the benefit of porous microsphere. The methods to prepare porous microsphere are not absolute.the pore size fabricate a large difference in the absorption and desorption of substance.

Future aspect:

The drug release can be controlled by increasing and decreasing the pore size, amount of drug incorporated in the porous microspheres can be increased by changing the pore structure.

REFERENCES:

1. Yunpeng Cai, 1. Y., & cai. (Published online **2013** March 15). Porous microsphere and its applications, *Int. J. Nanomed.*, 10.2147/IJN.S41271.
2. Amit Rawat, 1. Q. Inhalable Large Porous Microspheres of Low Molecular Weight Heparin: In Vitro and In Vivo Evaluation, *J. Control Release*, **2009**; 128(3): 224–232.
3. Bhise, M. CarbamazepineLoaded Porous Microspheres for ShortTerm Sustained Drug Delivery, *J. Young Pharm.*, **2010**; 2(1): 7-14.
4. J. A. Porous bone morphogenetic protein-2 microspheres: Polymer binding and in vitro release, AAPS PharmSciTech., **2001**; 2(3): 66–72.
5. Pathak, G. A. Porous Carriers for Controlled/Modulated Drug Delivery, Ind. J. Pharm. Sci., **2009**; 71(6): 599–607.
6. Joseph J. DeStefano, S. A. Performance characteristics of new superficially porous particles[star], J. Chromatogr, **2012**; 1258: 76–83.
7. Bhise, M. R. Carbamazepine-Loaded Porous Microspheres for Short-Term Sustained Drug Delivery, J Young Pharm., **2010**; 2(1): 7–14.
8. Satish Balakrishna Bhise A. Formulation and In Vitro Evaluation of Rifampicin Loaded Porous Microspheres, Sci. Pharm., **2010**; 78(2): 291-302.
9. Cai, Y. Y. Porous microsphere and applications, Int. J. Nanomedicine, **2013**; 8: 1111–1120.
10. Takashi Sasaki K. Morphology and Release Kinetics of Protein-Loaded Porous Poly(L-Lactic Acid) Spheres Prepared by FreezeDrying Technique, ISRN Pharm., **2011**; 490-567.
11. Matthew M. Arnold, 1. E. NanoCipro Encapsulation in Monodisperse Large Porous PLGA Microparticles, J. Control Release., **2007**; 121(1-2): 100–109.
12. Ram K. Jha, S. T. Bioadhesive Microspheres for Bioavailability Enhancement of Raloxifene Hydrochloride: Formulation and Pharmacokinetic Evaluation. AAPS Pharm. Sci. Tech., **2011**; 12(2): 650-657.
13. Mitra Jelvehgari, a. D. Preparation and Determination of DrugPolymer Interaction and In-vitro Release of Mefenamic Acid Microspheres Made of CelluloseAcetate Phthalate and/or Ethylcellulose Polymers, Iran J. Pharm. Res., **2011**; 10(3): 457–467.
14. Talar Tokatlian C. Design and Characterization of Micro-Porous Hyaluronic Acid Hydrogels for in vitro Gene Transfer to mMSCs, Acta Biomater, **2012**; 8(11): 3921–3931. .
15. C.E. Petrie Aronin J. Osteogenic differentiation of dura mater stem cells cultured in vitro on three-dimensional porous scaffolds of poly(e-caprolactone) fabricated via co-extrusion and gas foaming, Acta Biomater, **2008**; 4(5): 1187–1197.
16. Dr. Meng Deng, D. L. In Situ Porous Structures: A Unique Polymer Erosion Mechanism in Biodegradable Dipeptide-basedPolyphosphazene and Polyester Blends Producing Matrices for Regenerative Engineering, Adv. Funct. Mater., **2010**; 20(17): 2743–2957.
17. N Pandya, M. P. J. Young Pharm., **2011**; 3(2): 97–104.
18. TP Shailesh, P. V. Preparation and in vitro Evaluation of Ethylcellulose Coated Egg Albumin Microspheres of Diltiazem Hydrochloride, J. Young Pharm., **2010**; 2(1): 27-34.
19. Elbert, D. L. Liquid-liquid two phase systems for the production of porous hydrogels and hydrogel microspheres for biomedical applications: A tutorial review, Acta Biomater., **2010**; 7(1): 31–56.
20. Cancan Xu, W. L. Porous Collagen Scaffold Reinforced with Surfaced Activated PLLA Nanoparticles, Scientific World Journal, **2012**.

How to cite this article:

Geeta Charan Singh et al.,: Porous Microsphere and its Significances, J. Pharm. Res., 2015; 4(5): 217-219.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil