Published in final edited form as:

Curr Pharm Des. 2016 ; 22(17): 2463–2469.

Large Porous Hollow Particles: Lightweight Champions of Pulmonary Drug Delivery

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Abstract

The deep lungs provide an efficient pathway for drugs to transport into the systemic circulation, as the extremely large surface area and thin epithelial membrane enable rapid drug transport to the blood stream. To penetrate into the deep lungs, aerosol particles with aerodynamic diameters of 1–3 μm are optimal. Large porous hollow particles (LPHPs) can achieve this aerodynamic size range through enhanced porosity within the particles (typically $< 0.4 \text{ g/cm}^3$), which aerodynamically balances the large particle size ($> 5 \mu\text{m}$, up to $30 \mu\text{m}$). The physical properties of these particles provide some key advantages compared to their small, nonporous counterparts through enhanced dispersibility, efficient deep lung deposition, and avoidance of phagocytic clearance. This review highlights the potential of LPHPs in pulmonary delivery of systemic drugs, with a focus on their critical attributes and key formulation aspects. In addition, three examples of LPHPs under development are presented to emphasize the potential of this technology to treat systemic diseases.

Keywords

PulmoSpheres; nanoparticle aggregates; porosity; dispersibility; aerodynamic diameter; systemic circulation

1. Introduction

While the delivery of drugs by inhalation has become a mainstay in the treatment of respiratory disease [1–3], the last decade has seen significant advances in the use of the lungs as a portal of drugs to the systemic circulation [4, 5]. The complex nature of the airways, though, makes it difficult to deposit aerosols in the lung periphery or alveolar region of the lungs [6]. For systemic delivery, this represents the primary site for drug transfer to the blood circulation. When aerosol particles do deposit in the alveoli, immune cells called alveolar macrophages often efficiently phagocytose and clear the particles from the lungs, thus not allowing the drug sufficient time to travel across the alveolar membrane. Therefore, significant research has gone into the engineering of particles with optimized

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properties for pulmonary delivery of systemic drugs [7]. Large porous hollow particles (LPHPs) are a promising aerosol platform because of their enhanced dispersibility, ability to deposit in the lung periphery, and tendency to avoid the natural clearance mechanisms of the lungs. LPHPs are large ($>5\text{ }\mu\text{m}$, up to $30\text{ }\mu\text{m}$), low density (typically $<0.4\text{ g/cm}^3$) aerosol particles delivered to the respiratory tract typically via dry powder inhalers. These particles are known by a variety of different names such as large porous particles (LPPs), large hollow particles and porous nanoparticle aggregate particles (PNAPs). But in all cases, the basic design principle is the same: to lower the density of the particles such that the geometric diameter can be significantly larger, while maintaining a low aerodynamic diameter. These properties lead to efficient delivery of various pharmaceutical drugs to the lung periphery, facilitating delivery to the systemic circulation.

2. Key Features of Large Porous Hollow Particles

2.1. Aerodynamic Diameter

LPHPs are designed to take advantage of basic aerodynamic principles for efficient delivery to the lungs, even reaching the deepest regions of the lungs. The most important parameter that determines the deposition pattern of aerosol particles in the respiratory tract is the mass median aerodynamic diameter. The theoretical mass mean aerodynamic diameter of a spherical particle can be estimated from its mass-mean geometric diameter (d_g) and mean particle mass density (ρ_p): $d_{aero} = d_g * \rho_p^{0.5} / \rho_o^{0.5}$, where $\rho_o = 1\text{ g/cm}^3$ [8]. Therefore the aerodynamic diameter of a particle “corresponds to the diameter of a [water droplet falling] under gravity with the same velocity” [9]. For nonspherical particles, a shape factor, χ , is added: $d_{aero} = d_g * (\rho_p / \chi)^{0.5}$. LPHPs take advantage of this basic concept to lower the density of the particles such that the geometric diameter can be significantly larger, while maintaining a low aerodynamic diameter. From an aerodynamic standpoint, a $1\text{ }\mu\text{m}$ particle with a density of 1 g/cm^3 (i.e. the density of a water droplet) has an equivalent aerodynamic diameter to a spherical $5\text{ }\mu\text{m}$ particle with a density of 0.04 g/cm^3 or a $10\text{ }\mu\text{m}$ particle with a density of 0.01 g/cm^3 . The high porosity can be attained by various particle forms: particles with a large internal porous structure [10, 11], hollow particles [12], thin-walled hollow particles that collapse into crumpled-paper particles [9], and agglomerates of nanoparticles [13] (Figure 1). No matter their form, the unique advantages that can be achieved due to the large size and low density of LPHPs are the same: high dispersibility from an inhaler, enhanced deposition in the lungs upon inhalation, and reduced clearance by phagocytosis when compared to smaller, denser particles.

2.2. Dispersibility

LPHPs, by virtue of their large size, are more easily deagglomerated and dispersed from an inhaler device than smaller particles [15]. For particles that are cohesive and have average diameters smaller than about $15\text{--}20\text{ }\mu\text{m}$, van der Waals forces of cohesion are proportional to the diameter of the particles (d), while the force to break particle agglomerates by shear, as would be experienced in a dry powder inhaler (DPI), scales with the d^2 [16–19]. Thus the viscous force generated during shear increases with particle diameter faster than the cohesion force and it is easier to separate larger particles from the agglomerate. In terms of pulmonary drug delivery, this means a smaller inhalation flow rate is required to generate

enough shear to break apart the agglomerates so that they can be dispersed and deposited in the lungs. Since most DPIs in common use are breath activated, this is particularly important in patient populations that are unable to achieve high inhalation flow rates, such as those with chronic lung disease. Enhanced dispersibility is reflected in the uniformity of the emitted dose (ED) and fine particle dose [20]. For LPHP formulations, EDs in the range of 80–98% have been achieved, though lower ED values are also reported [9, 21–23]. The upper end of this range represents, as noted by Venbever *et al.* [9], “a strikingly high ED value” compared to ED values obtained from typical aerosol products. Even in one human study, the reported ED of LPHPs was high (~90%) and reproducible [24]. Beyond particle physical characteristics, dispersibility from a passive dry powder inhaler is often dependent on patient inhalation flow rate. However, LPHPs have been observed to exhibit equivalent dispersibility over a wide range of dispersion pressures [25], suggesting that LPHPs can be formulated to emit from an inhaler independent of flow rate. Flow rate independence has been observed in at least one in vivo study in humans, where inhalation flow rates between 12 and 86 L/min resulted in similar ED and lung deposition [21]. The enhanced dispersibility of LPHPs can also eliminate the need for an inert carrier such as lactose [23].

2.3. Deposition Efficiency

For delivery to the systemic circulation, the highly vascularized alveolar region of the lungs is the target, requiring particle aerodynamic diameter to be optimized to between 1 and 3 μm for sufficient deposition. Particles in this “respirable” range of aerodynamic diameters flow more easily with the inhalation air stream and can navigate the twists and turns of the complex lung airways. Several studies have compared the deposition efficiency of LPHPs to nonporous or micronized particles via cascade impaction, an in vitro system for estimating potential deposition in the lungs based on particle aerodynamic diameter. Edwards *et al.* [26] demonstrated that large porous particles achieved significantly higher respirable fractions (50%) compared to nonporous particles (21%) when their aerodynamic diameters were nearly identical. Other groups have followed on this initial work, often citing a doubling or tripling of the fine particle fraction (FPF) achieved with porous particles compared to nonporous formulations, as well as an increase in the mass fraction predicted to reach the lung periphery [27–29]. These results are exciting for a number of reasons. First, enhancing the respirable fraction of an aerosol decreases oropharyngeal deposition, which can limit side effects. Second, most published impaction studies of LPHP formulations have used low-tech inhalers, which lower the cost of treatment and are more likely to be used for developing world treatment. Finally, the wide range of formulations prepared as LPHPs, in terms of both drug compounds and excipients, points to the versatility of the platform in drug delivery. To this last point, Dellamary *et al.* [11] reported that cromolyn hollow porous PulmoSpheres exhibited a FPF of 68% compared with 24% for micronized cromolyn particles. In this case the particles were emitted from a metered dose inhaler using an HFA propellant, demonstrating versatility even beyond the dry powder aerosol space.

While impactors are useful tools for predicting deposition in the lungs, the ultimate test of lung deposition is obtained from in vivo studies. The deposition efficiency of various peptide-containing LPHP formulations has been determined in rodents. After aerosolization of PLGA-BSA porous particles into mice, Lee *et al.* demonstrated a two-fold higher

deposition efficiency for the porous particle formulation compared to the nonporous particles of the same geometric size (2.9 μm). Similar results have been observed when comparing porous and nonporous particles of the same aerodynamic diameter as well. Edwards *et al.* [26] demonstrated that only 21% of nonporous PLA particles deposited in the bronchoalveolar spaces, whereas 54% of porous PLAL-Lys particles reached this region of the lungs. Using confocal microscopy to characterize lung deposition in rats, Ungaro *et al.* [10] determined that large porous PLGA-cyclodextrin formulation containing FITC-insulin were able to deposit in the alveoli, the target region for systemic delivery of peptides. In humans, reported deposition efficiencies have been significantly higher (59.0 and 37.3%, Figure 2) compared to other published studies (13 to 35% at the time of the study) [24].

Phagocytic Clearance—Phagocytosis by alveolar macrophages in the lungs is most significant for particles with geometric diameters of 1–2 μm and significantly decreases when particle size increases above 3 μm or decreases to the nano-size range [30, 31]. In comparison to their nonporous counterparts, LPHPs, by virtue of their size alone, exhibit little to no uptake by macrophages [26, 27, 32, 33]. Edwards *et al.* [26] demonstrated a 27% reduction in phagocytosis of porous particles immediately after inhalation by rats compared to nonporous particles (30% of phagocytic cells contained nonporous particles vs. 8% of phagocytic cells contained porous particles, determined after bronchoalveolar lavage). After 48 h, phagocytic cells contained more nonporous particles (18% contained three or more particles) than porous particles (4% contained three or more particles). Similar observations were made by Yang *et al.* [33] who observed that nonporous PLGA particles were “avidly taken up in less than 10 min” by mouse macrophages and that every macrophage contained multiple particles after 1.5 h, whereas highly porous large particles ($d_g = 18 \mu\text{m}$) were not taken up by macrophages. This avoidance of phagocytic clearance allows the particles to remain in the alveoli longer, which is advantageous for systemic delivery of slowly absorbing drugs and controlled release systems. However, if the particles are too large (i.e. larger than the macrophage itself), macrophage attachment and repeated attempts to internalize the particles may result in incomplete or frustrated phagocytosis [34–37]. If phagocytes fail to engulf the particles, they may release toxic pre-inflammatory mediators that can cause significant damage to the lung tissue.

Phagocytic clearance is dependent on additional factors beyond size, including particle aspect ratio (longer rod shaped particles lead to more frustrated phagocytosis than shorter rods or spherical particles) [34, 37] and particle chemistry (uptake of particles can be either enhanced or reduced by altering the particle chemistry). Bot *et al.* [32] developed hIgG-loaded PulmoSpheres ($d_g = 7 \mu\text{m}$) to enhance immune activity and observed a significant increase in macrophage loading with an increase in the IgG content of the particles, with <0.1% of cells containing empty particles and up to 25% containing IgG-loaded particles. On the other hand, significant reduction in phagocytic uptake has been observed by incorporating native lung surfactant components such as DPPC into the particle formulation [38, 39]. With larger sized particles the effects of particle chemistry on phagocytic uptake might not be as prominent as the effect of particle size, though this remains an area where further research is needed.

2.5. Flexibility in Formulation of Large Porous Hollow Particles

LPHPs are formulated using strategies that create void spaces in the particles to generate the porous or hollow structure, resulting in a lower density. These strategies include most common particle formation processes, such as spray drying, spray freeze drying, and double emulsions, under proper conditions. In addition, various excipients such as shell forming agents, porogens, and osmogens have been evaluated for their ability to generate the porous or hollow structures within LPHPs. These agents can provide more control over the porous structure, and in some cases, better control over particle size and higher drug encapsulation efficiency. A brief discussion of excipients to generate porosity in LPHPs is provided here.

Shell-forming agents are compounds that sequester at a droplet interface, forming a shell upon droplet drying. If the shell is strong enough, the particles can remain as spheres with hollow interiors. If the shell is too fragile, it can collapse upon droplet drying, forming crumpled-paper particles. Leucine and trileucine are examples of shell-forming agents that have been added to spray dried formulations as the compounds accumulate at the air-water interface of the droplets due to their distinct hydrophilic and lipophilic regions [40], significantly reducing the density of spray-dried powders [41]. Surfactants such as dipalmitoylphosphatidylcholine (DPPC) have been used because of their preference for a water-oil interface and low aqueous solubility. As an example, with a water-ethanol co-solvent system the saturation of DPPC can be controlled by controlling the water-ethanol ratio. When the DPPC solution is spray dried, the heating of the droplets causes preferential evaporation of ethanol and changes the water-ethanol ratio, leading to DPPC saturation at the droplet surface. This results in the formation of a DPPC shell on the droplet surface, which upon complete drying, leads to a porous or hollow particle structure [42]. Generation of particles by the same method but with the removal of the DPPC from the formulation led to an increase in the particle density and decrease in the particle size [43]. The use of surfactants in formulations destined for the lungs is advantageous as various surfactants are naturally occurring in the lungs, including DPPC, and surfactant replacement therapy is an approved treatment for premature babies to prevent respiratory distress. DPPC also has the potential to achieve sustained drug release in the lungs due to its low aqueous solubility and can limit macrophage uptake of particles [44].

Porogens are a broad class of compounds that can induce a porous structure through their removal during particle formulation (Figure 3). For example, salts can be incorporated into particle formulations that leach out and leave behind pores [45]. Another strategy is to create a foam-like particle morphology using porogens. A prominent example in this category is PulmoSpheres™, which are produced by spray drying an emulsion containing a volatile blowing agent perfluorooctylbromide (PFOB) in the dispersed phase [46]. The fluorocarbon-in-water emulsion is stabilized with a phospholipid, typically a phosphatidylcholine, and the fluorocarbon is volatilized during drying, leaving behind pores [32, 47]. PulmoSpheres are unique in that once the powder is produced, it is typically resuspended in non-aqueous propellant for delivery via an MDI. Other gas-foaming agents investigated include volatile salts such as ammonium carbonate and ammonium bicarbonate. Volatile salts are versatile pore-forming agents as they can be dissolved in water, incorporated in the dispersed phase of a water-in-oil emulsion, or added as a micronized solid to an organic solvent [48]. These

salts break down into gases (ammonia, carbon dioxide and water vapor) at temperatures between 36–60°C, forming a porous matrix as the gases escape [22, 41]. These techniques often produce fairly irregular pore structures and the particle size increases with an increase in porogen concentration.

Osmogens placed in the internal aqueous phase of an emulsion cause water influx from the external aqueous phase during solvent evaporation, which swells the particles and results in high porosity. Like porogens, the porosity can be tuned by changing the concentration of the osmotic agent. Compounds that have been included in LPHP formulations to induce osmotic swelling include salts, albumin, and polycations such as polyethyleneimine (PEI) [49]. In some formulations, albumin and DPPC are used together in the formation of LPHPs to obtain optimum particle characteristics [48, 50]. Osmotic agents have the benefit that they can generate highly porous structures while maintaining particle size (Figure 3) [45].

2.6. Dosing Limitations with Large Porous Hollow Particles

The low mass density of LPHPs results in a low drug mass-to-volume ratio in the powder. In addition, due to the large size of the particles, the mass of powder that can be placed into a capsule or blister pack is significantly smaller than for denser particles. Thus, a larger number of inhalations may be required to achieve a sufficient dose in the lungs, which may make the LPHP formulation unsuitable for diseases or drug combinations that require very large mass loading for effective treatment.

3. Applications of Large Porous Hollow Particles in Pulmonary Delivery of Systemic Drugs

LPHPs are being investigated in a wide variety of applications for systemic diseases and disorders. Three examples of pulmonary delivery of systemic drugs using LPHPs as the carrier are highlighted below (Table 1). These examples depict the wide range of drug compounds that can be delivered, including both small and large molecules, as well as hydrophobic and hydrophilic molecules.

3.1. Thrombosis

Thrombosis is a disorder characterized by formation of a blood clot inside a blood vessel, resulting in obstruction of blood flow through the vasculature [51]. Traditional strategies for managing thrombosis include the use of immunosuppressive agents such as corticosteroids to reduce the immune response to inflammation of the blood vessels, and use of anticoagulants such as heparin and warfarin to dissolve the clots [51]. The anticoagulation therapy involves the initial use of low molecular weight heparin (LMWH) or unfractionated heparin (UFH), followed by the vitamin K antagonist warfarin [52]. Heparin is usually administered intravenously or subcutaneously to avoid problems caused by interpatient variability because of its polydispersity and polyanionic nature. The I.V. and S.C. administration of heparin is accompanied by a number of side effects such as local irritation at the site of injection and ulceration, resulting in poor patient compliance [53]. Orally administered warfarin avoids some of these side effects, but displays inconsistent dose response and is affected by dietary changes [54]. These limitations have necessitated

investigations into finding an alternate, non-invasive route for delivering these drugs to the systemic circulation.

Qi *et al.* investigated the pharmacokinetic and pharmacodynamics effects of pulmonary delivery of heparin-loaded porous particles on both *in vitro* and *in vivo* models. Studies carried out on *in vitro* Calu-3 cells as well as *in vivo* tissue sections showed that low molecular weight heparin (LMWH) caused temporary, reversible opening of the tight junctions in the lung epithelium. This resulted in more efficient delivery of LMWH and heparin, smaller onset of action time ($t_{\max}$ of 40 min compared to 2–4 h for S.C. administration), and $C_{\max}$ similar to that for S.C. administration (0.9 $\mu\text{g/mL}$ vs. 1.1 $\mu\text{g/mL}$). Repeated administration of inhaled heparin gave a stable pharmacokinetic performance in terms of $t_{\max}$, $C_{\max}$ and bioavailability, and did not result in any observable side effects [53]. It is important to note that while their results are promising, the safety in use of chemicals that alter tight junctions is a concern as alteration of tight junctions has been associated with progressive lung disease [55, 56]. Patel *et al.* investigated heparin-loaded large porous particles made of polyethylene glycol - poly(lactide-co-glycolide) (PEG-PLGA) for improved heparin delivery by pulmonary route. These particles also demonstrate high drug entrapment, greater extent of drug release and reduced uptake by alveolar macrophages. The LPPs displayed elimination half-life of about 19 h as compared to 4 h by the S.C. route, enabling longer term heparin delivery with fewer doses required [57]. Overall, these studies highlight the potential of LPPs to deliver the drug across the alveolar membrane into the systemic circulation and achieve pharmacokinetic characteristics similar to or better than the currently utilized delivery systems.

3.2. Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that initially infects the human lungs, and after initial infection, distributes to other body systems including the central nervous system (CNS), abdomen, kidneys, bones, and joints [58]. Thus, complete treatment of TB often requires addressing both the pulmonary and extrapulmonary sites [59]. The main objective of the anti-tubercular treatment regimen is complete eradication of the bacteria [60]. Current therapeutic strategies requires oral administration of a cocktail of bactericidal agents over a minimum period of six to nine months [61]. The long duration of the treatment regimen, along with the financial burden and undesirable side effects, cause many patients to discontinue the chemotherapy, resulting in incomplete treatment and the development of drug resistance in the organism [58, 62]. Multi-drug resistant (MDR) strains of *M. tuberculosis* are resistant to most of the first-line bactericidal agents, necessitating a prolonged regimen of second-line antibiotics which display low efficacy and a high degree of toxicity.

Given its ability to target high drug concentrations to the lungs and the systemic circulation, a more effective approach to TB treatment may be to deliver antimicrobials via the pulmonary route. Direct pulmonary delivery can reduce the administered dose and accelerate the onset of action, leading to reduced costs and treatment periods, thus improving patient compliance. In addition, small molecule drugs used for TB treatment can be rapidly absorbed across the alveolar lung epithelium into the systemic bloodstream, thereby

facilitating eradication of bacteria in the extrapulmonary organs. Garcia-Contreras *et al.* compared the pharmacokinetic profile of pulmonary administration of rifampicin (RIF) large porous particles (IRPPs) with I.V. and oral administration of rifampicin in guinea pigs (doses of 20, 10 and 40 mg/kg of body weight, respectively). RIF from IRPPs displayed faster absorption in the plasma compared to the oral RIF and an onset of action similar to I.V. ($t_{\max}$ for IRPP was 1.33 ± 0.41 h and for the oral route 1.88 ± 0.25 h). IRPPs sustained higher RIF concentrations above the minimum inhibitory concentration (MIC) in the lungs compared to the other formulations and achieved systemic concentrations of RIF similar to the oral formulation at half the dose of the latter [63]. In another study, Tsapis *et al.* administered para-aminosalicylic acid (PAS) large porous particles (LPPs) to lungs of rats and observed greater local and systemic concentrations of PAS following administration of lower doses of PAS-LPPs compared to oral administration of PAS [64]. Studies in guinea pigs using the second-line drug capreomycin-loaded large porous particles and capreomycin administered I.V. and I.M. showed comparable plasma concentrations for all the formulations 2 to 6 h after administration, in spite of the lower pulmonary dose. Capreomycin was cleared at a lower rate when administered by pulmonary route compared to I.V. or I.M. route [65]. Therefore, pulmonary administration of TB antibiotics has been shown to sustain local and systemic concentrations at sufficient levels to fight the infection in both the pulmonary and extrapulmonary organs.

3.3. Human growth hormone deficiency

Human growth hormone (GH) is a 191-amino acid protein that is secreted by the somatotrophic cells of the pituitary gland, and is used for the treatment of pituitary dwarfism in children, adult growth hormone deficiency, Turner syndrome, and chronic renal insufficiency [66]. Current therapies used for treating growth hormone deficiency require subcutaneous or intramuscular injections of GH administered daily or three times a week. However, these therapies have several drawbacks such as short half-life of GH, renal toxicity and poor patient compliance due to frequent, painful injections, and high healthcare costs. Hence, a non-invasive, sustained release formulation could improve the effectiveness of GH therapy [66, 67]. Aerosol formulations of GH have been under development since the late 1980's, including both pre-clinical work and clinical trials [68, 69], but none have yet made it to the market and few sustained release formulations have been tested.

Inhaled large porous particles have the potential to act as depots for the sustained release of GH across the alveolar membrane into the systemic circulation. Kim *et al.* [70] studied porous, biodegradable polymeric microspheres whose pores were loaded with GH then closed at the surface to provide sustained release of GH over a period of one month. Bosquillon *et al.* [71] investigated the efficiency of GH dry powder consisting of porous particles in pulmonary delivery and the role of excipients in enhancing absorption across the alveolar membrane. *In vivo* pharmacokinetic studies conducted in rats showed faster GH absorption in the systemic circulation from the dry porous particles containing DPPC as an excipient ($t_{\max} = 23$ min) compared to S.C. administration ($t_{\max} = 64$ min) and spray-instillation of GH solution ($t_{\max} = 51$ min). GH-loaded porous particles also resulted in higher $C_{\max}$ values (234 ng/mL) compared to S.C. administration (55 ng/mL) and spray-instilled GH (46 ng/mL). In 2003, Alkermes and Lilly announced results from a Phase I

clinical trial, which included concentration-time profiles of inhaled GH similar to those from S.C. administration and the ability to deliver high doses to participants with no adverse effects. These results are promising and lend optimism that development of LPHPs for systemic delivery is clinically feasible.

4. Conclusions

Large porous hollow particles are a versatile platform for the pulmonary delivery of a wide range of drugs that can be transported from the lung spaces to the systemic circulation. These particles show tremendous promise in the treatment of a number of systemic diseases and disorders, providing efficient pulmonary deposition to the deep lungs and limited clearance for potential therapeutic success.

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Figure 1.

SEM micrographs exhibiting various forms of LPHPs: **(Top left)** Cross-section of a particle with high internal porosity (x 1600 magnification), reproduced from [14] with permission of The Royal Society of Chemistry. **(Top right)** cross-section of a large hollow particle (scale bar = 10 μm), reprinted from [12] with permission from Elsevier. **(Bottom left)** crumpled-paper particles composed of 90% leucine and 10% dipalmitoylphosphatidylcholine (DPPC) spray dried using the Niro Mobile Minor spray dryer. **(Bottom right)** a porous nanoparticle agglomerate, reproduced with permission from Tsapis *et al.* [13].

Figure 2. In vivo lung deposition image obtained by γ -scintigraphy for one subject. A) 3 μm MMAD LPHPs, B) 5 μm MMAD LPHPs. Reprinted from [24] with permission from Elsevier.

Figure 3. Schematic description for preparation of porous microspheres by A) salt leaching, B) gas foaming, and C) osmosis induction methods. Schematic adapted from [45].

Table 1

Studies of pulmonary delivery of systemic drug loaded LPHPs.

Therapeutic Agent	LPHP type	Formulation	Technique	Types of studies	Reference
Capreomycin	Porous	Leucine	Spray drying	<i>In vitro</i> deposition and <i>in vivo</i> guinea pig studies	[22] [54]
Diphtheria vaccine	Porous nanoparticle aggregate	PLGA	Double-emulsion solvent evaporation	<i>In vivo</i> guinea pig studies	[72]
Heparin	Porous	DPPC	Spray drying	<i>In vivo</i> rat and rabbit studies	[44]
Heparin	Porous	PEG-PLGA	Double-emulsion solvent evaporation	<i>In vitro</i> simulated lung fluid and <i>in vivo</i> rat studies	[46]
Human growth hormone	Porous	Pluronic F127 - PLGA	Emulsion solvent evaporation	<i>In vitro</i> release studies	[59]
Human growth hormone	Porous	Lactose - DPPC	Spray drying	<i>In vivo</i> rat studies	[60]
Insulin	Porous	PLGA	Double-emulsion solvent evaporation	<i>In vitro</i> deposition and <i>in vivo</i> rat studies	[26]
Insulin	Porous	PLGA - Cyclodextrin	Double-emulsion solvent evaporation	<i>In vivo</i> rat studies	[3]
Insulin	Porous	HSA - DPPC	Spray drying	<i>In vitro</i> deposition and <i>in vivo</i> rat studies	[9]
Para-aminosalicylic acid	Porous	DPPC	Spray drying	<i>In vitro</i> deposition and <i>in vivo</i> rat studies	[53]
Rifampicin	Porous	Leucine	Spray drying	<i>In vitro</i> deposition and <i>in vivo</i> guinea pig studies	[15] [52]
Testosterone	Porous	PLGA and PLAL-Lys	Double-emulsion solvent evaporation	<i>In vitro</i> deposition and <i>in vivo</i> rat studies	[26]