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Review Article

Microsphere-Based Drug Delivery to Alveolar Macrophages - a Review

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ABSTRACT

The lungs have a large surface area and high permeability, hence pulmonary delivery systems provide both local and systemic therapeutic effects. Pulmonary delivery system has been selected by many researchers because the route of administration is not invasive, has low metabolic activity, controlled environment for systemic absorption and avoids first pass metabolism. Alveolar macrophages are the first defense in the lung tissue to fight airborne pollutant, other foreign particle and pathogen by phagocytosis mechanism. Alveolar macrophages play an important role in the process of activation of the adaptive immunity including in inflammation and cancer diseases. Drug targeting to alveolar macrophages can achieve improvement in efficacy of therapeutic treatment for medical conditions including tumor, cancer, inflammation and infection. Respiratory infection-causing bacteria such as tuberculosis and pneumonia are able to survive in alveolar macrophages and they turn macrophages become a reservoir. This presents the challenge of making macrophages as targets in pulmonary delivery system because most of drugs do not reach the macrophages level effectively. To achieve this goal, the use of carrier particles in either micro-sized or nano-sized technology is the right choice. This review focuses on the influences of various physicochemical properties of microspheres carrier include particle size, aerosolisation property, morphology surface charge, surface properties and hydrophilicity on their uptake by alveolar macrophages either enhance macrophages uptake or decrease macrophages uptake. Making macrophage a target of treatment especially for infectious diseases is a promising strategy to improve the efficacy of treatment although in its development there are still many challenges.

Keywords: Microspheres, Inhalation, Alveolar macrophage, Macrophage uptake, Physicochemical properties.

Introduction

Lungs have a complex but coordinated system to eliminate inhaled pathogenic and pollutant particles. Pulmonary contact with pathogenic particles has the potential to cause respiratory disturbances, so the process of eliminating foreign particles must be ensured to continue functioning normally. Pulmonary delivery system becomes the choice of drug delivery, for example in the provision of inhaled antibiotics aimed at several diseases such as tuberculosis and pneumonia. This delivery route is also intended for the treatment of pulmonary hypertension[1] and the administration of paclitaxel and doxurobicin in the treatment of lung cancer.[2] In several studies that have been carried out, inhalation delivery system is also intended to have a systemic effect, for example insulin delivery,[3] delivery of anti-nerve growth factor hormone,[4] and antithrombotic therapy.[5] Lungs' natural defense mechanism to fight pollutants and potentially pathogenic particles is a complex system and involves several processes such as mucociliary cleansing, the release of anti-pathogenic endogenous proteins, and the presence of leukocyte responses that occur in the lungs.[6] Alveolar macrophages are the first defense responsible for the process of fusion and elimination of pathogenic particles and pollutants that enter through the respiratory system. Alveolar macrophages have immunoglobulin, mannose, and some special receptors responsible for the phagocytosis process of inhaled foreign particles. Several studies have shown that in certain circumstances, there is a change in the cleaning function and phagocyto[3] by alveolar macrophages that can initiate the emergence of several diseases such as asthma, cancer, atherosclerosis, idiopathic pulmonary fibrosis, and infection.[7-10] In certain cases, it is [3]o found that some bacteria like Toxoplasma gondii and several species of Leishmania, Mycobacterium tuberculosis, and Listeria monocytogenes are able to survive and avoid the mechanism of phagocytosis by macrophages.[11]

Passive targeted system to deliver several drugs made in the nano system or microparticles to target infected macrophages becomes the right choice to handle several cases of infection caused by some of these bacteria. Furthermore, an active targeting system can also be carried out by giving selective ligands to the drug carrier particles. The success of inhalation delivery to achieve the target of alveolar macrophages depends on the optimization in terms of pharmaceutics, such as the design of drug release and the increase in drug residence time in the target area. At present, preparation formulated for inhalation purpose tends to be in the forms of liquid mist and particles given as dry powder. These formulation tend to form particulates which when recognized by alveolar macrophages are phagocytosed. When formulating a preparation with the aim of targeting macrophages is necessary to understand what conditions are needed to facilitate particle uptake by macrophages with the aim of increasing

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the residence time of drugs in macrophages to formulation approaches that will determine the characteristics obtained by macrophages which also affect particle uptake by macrophages.The following section will explain the use of microspheres with various forming polymers for 14 eted purposes on alveolar macrophages with the aim of increasing drug residence time in the lung area and increasing drug uptake by alveolar macrophages.

11 rospheres system is an ideal system for targeted delivery in phagocytic cells such as macrophages and dendritic cells. In vitro 45 in vivo tests administration of hepatitis C vaccine microspheres can trigger a mediation of immune cell response by inducing CD8+ T cells expression and increasing the number of CD8+ T cells in mice significantly.[12] Furthermore, microspheres without drugs can stimulate innate immunity which will trigger bacillary killing in macrophages. The use of certain polymers with certain polysaccharide and carbohydrate groups in the microsphere system at the same time can act as ligands that are easily recognized by respires on macrophages. Drug release profiles from microspheres that are easy to modify are also what make this system widely developed. Drug release from microspheres is controlled by two factors, namely drug dissolved from the polymer or the micro spherical polymer matrix degradation process. In this case, the use of polymers plays a fairly large role.

Targeted Delivery System on Alveolar Macrophages

Pulmonary delivery systems provides many advantages compared to conventional delivery systems, one of which is the rapid onset of work and is able to deliver drugs locally to the target, minimizing drug dosage so as to reduce the toxic effects of drugs and increase the index of drug therapy.[13] The lungs have a short diffusion pathway from the respiratory tract to the systemic circulation and an increase in blood flow makes the lung the pathway for drug entry into the systemic pathway.

The upper airway is covered by thin mucus that serves to protect the tissue and capture and clean the particles that pass through it. In the deeper part there is an alveolar. Alveolar contains a variety of proteins and lipids that act as barriers to transport several molecules. Along with alveolar, the tight junction along epithelial cells also a 44 as a major barrier in the transport process. Protein transporters play an important role in the process of delivering drugs either throu 49 he mechanism of active absorption or passive diffusion, depending on the nature and structure of the drug delivered. Another important aspect in this area is the mechanism of clearance of molecules by macrophages which need to be considered in the process of transporting drugs to the lungs. Molecules that can cross the barrier will be inhaled by cells and absorbed into the systemic circulation or can also un 27 o phagocytosis by macrophages. Drug molecules can be absorbed more efficiently from the lungs compared to other non-invasive routes. The mechanism of deposition and uptake of particles in the lungs is shown in Figure 1. 48

Furthermore, the process of deposition of particles in the lung including the uptake mechanism by macrophages is strongly influenced by particle size. Particles with a size of 1-3 μm will experience uptak 23 macrophages (with a diameter of each cell 15-22 μm) better than particles with a diameter of 6 μm, whereas particles with a s 2 of 0.26 μm are able to avoid phagocytosis.[13] Smaller particles will interact with non-phagocytic cells in the epithelium and initiate endocytosis regulated by clathrin-coated and caveola. Nano-scale particles are more likely to be delivered to the systemic circulation. Inspirational expansion and expulsion of pulmonary alveoli can trigger the opening and closing of the caveola. The opening process itself can reach sizes of 40 and 100 nm which can allow macromolecular components such as proteins to pass through the alveol 30 pillary barrier15. This shows the mechanism and location of deposition of particles in the lung differ depending on the size of the particle itself as illustrated in Figure 2.

Phagocytosis is the prima 4 mechanism for the process of taking particles by macrophages. Macrophages are one type of phagocytic cells that are responsible for cytokine secretion and help in delivering messages against the occurrence of pathogenic infections that will produce an immune response.[16] Macrophages produce antibacterial

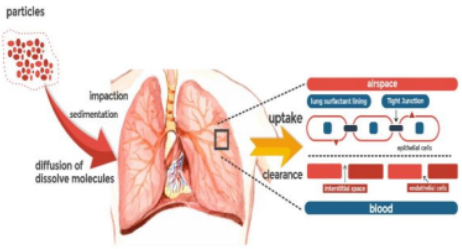

Figure 1: Mechanism of deposition and uptake of particles in the lungs.[14]

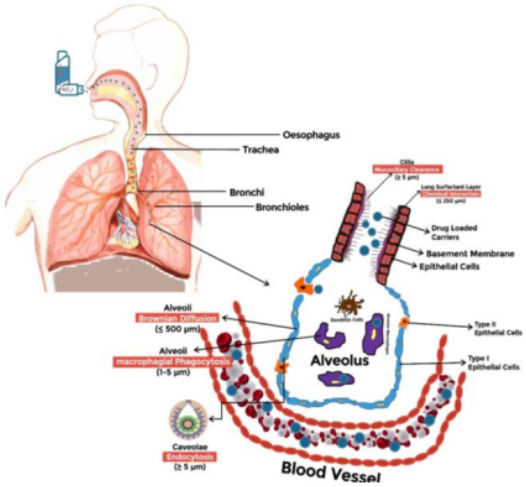

Figure 2: Relationship between particle size and route of distribution of particles, clearance mechanisms and absorption.[15]

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substances, such as nitric oxide and cationic proteins that contribute to the destruction of microorganisms.[17] In some cases, macrophages are not able to damage the components of pathogenic microorganisms because it is known that some of these microorganisms can avoid the fusion mechanism by lysosomes and phagosomes or by inhibiting the antimicrobial response in phagolysosomes. Not only have a survival strategy for macrophages, some bacteria also obtain some nutrients in the macrophages to carry out intracellular replication.[18] This phenomenon makes macrophages a target of treatment for several pathological conditions. Alveolar macrophages are the most dominant 4 rt in alveoli. The combination of alveolar macrophages with epithelial cells, dendritic cells, and lymphocyte T cells found in the 4 veoli provide a good defense in the respiratory tract through several receptors and cytokines/chemokines that can control the immune system to clear pathogens from the lungs.[19]

The targeting on macrophages can increase the efficacy of treatment in tumor genesis, inflammation and infection therapy. The delivery system for particulate drugs both nano or microparticles, liposomes, micelles, polymeric conjugates, and dendrimers has been used for drug delivery via the pulmonary route including to target alveolar macrophages. One of the microparticles used is microspheres. In addition to having particle size that allows entry into the respiratory system and inner lungs, microspheres also have a great tendency to be phagocytosed by macrophages, so as to increase drug influx in macrophages. The particulate system has also been formulated in such a way as to increase its specific side to bind to the target, provide

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sustained release, achieve deposition in the inner lung, and increase the bioavailability of the drug it carries. Although it is also well known that the lungs have a mucociliary cleansing mechanism, the possibility of particles to get trapped in the mucous layer and undergo phagocytosis by alveolar macrophages can eliminate drugs encapsulated in the particles or cut the residence time of the drug which has an impact on the limited efficacy of the drug. However, in some pathological conditions such as in inflammatory and infectious conditions, making macrophages as a target of treatment can increase the therapeutic effect. This depends on the purpose of therapy, whether aimed at increasing or avoiding the uptake by macrophages.[6]

Parameters of Microparticles Targeted on Alveolar Macrophage

To design particles so that they can enter the respiratory tract and reach pulmonary area that is rich in alveolar macrophages, there are several factors related to the nature of the particles that have to be considered.

Particle Size

In preparation intended for inhalation systems, particle size plays a role in determining the deposition mechanism and deposition location in the lungs. Particle size also determines the success of uptake by macrophages. Larger spherical polystyrene particles (3 μm) have been reported to be taken up more slowly compared to 1.5 μm sized particles, suggesting that higher energy requirement for membrane deformation of large particles could abate uptake.[20] This's relates to the activation of the complement pathway.[21] Particles of different sizes provoked different responses to macrophages. Larger particles tend to interact with tissues, while smaller particles (<200nm) tend to circulate on veins and flow along lymphatic, providing better antigen presentation.[22] Particle size also determines the path of endocytosis. In general, particles larger than 1 micron will be analyzed by phagocytosis and smaller particles of 0.2-1 micron through endocytosis.[23] Particles ranging from 1-3 µm are the most easily phagocytosed size by alveolar macrophages, whereas particles > 10 µm or <0.2 µm are able to escape phagocytosis.[24] Particles with a diameter of 1-6 µm show higher uptake compared to larger particles.[25] The effect of particle size on the deposition mechanism in the lungs the process of entry into macrophages are summarized in Table 1. The effect of particle size on the success of uptake by macrophags has been carried out on polystyrene microspheres with sizes of 0.2, 0.5, 1.0, 6.0 and 10 μm, respectively. The parameter of successful uptake of particles by macrophages is seen from the superoxide levels produced by macrophages, where the higher the superoxide levels produced indicates the more particles are uptake by macrophages. Particles with sizes 1.0 and 6.0 μm showed the highest levels of superoxide, followed by particles with sizes 0.5, 10.0 and 0.2 μm that had superoxide levels similar to those of bufer phosphate solution control.[29] Based on the research, it was concluded that there was an increase in particle uptake by macrophages for particles with sizes above 1 µm and below 6 µm. Similar research was also carried out by Hirota.30 PLGA-rifampicin microspheres was made with sizes 1.0, 3.0, 6.0 and 10 µm respectively. The number of particles successfully phagocytosed by macrophage depends heavily on the particle size of the microsphere. Microspheres measuring 3 and 6 µm are more effective than particles measuring 1 and 10 µm. From the results of this study it is also possible that particle size 3 - 6 µm is the right size to obtain optimum phagocytosis activity.[30] Some examples of particle size parameters successfully taken by particles by macrophages are summarized in Table 2.

Properties of Aerosolization

Particles with a size that is too small are likely to come out again with carbon dioxide in the expiration process, so besides having a small size, the particles must have a certain weight. This value is known as mass median aerodynamic diameter (MMAD). A good MMAD is 1-6 μm,[25] while another study reports MMAD ranges from 1-5 μm to be deposited in the lungs, but particles smaller than 3 μm are easier to reach the respiratory system.[35] To be able to target macrophages, the particles made must be ensured to be able to enter the respiratory tract particularly into the inner lungs, especially on the alveoli. Besides by synchronizing with the milling, ball milling, and spray drying techniques,[36, 37] to improve the aerosolization properties of a given particulate system in the form of dry powder inhalation (DPI), it also uses other excipients such as lactose and mannose with certain particle sizes. Du *et al.*[38] conducted an evaluation of the effects of lactose and granule lactose administration within a certain size to the aerosilization of salbutamol DPI. The size, rough or smooth surface of lactose, the density and flow properties of lactose as a carrier contribute to aerosol dispersion performance. In that study, it was concluded that redispersion decrease or increase not only related to particle size, but also other properties of the lactose used.[38]

The instruments used to evaluate the aerodynamic properties of particles include Twin Stage Impactor (TSI), Next Generator Impactor (NGI) and Anderson Cascade Impactor (ACI). TSI has 'throat' angle followed by two chambers to hold the particles (stage I and stage II). The first stage and 'throat' will hold larger particles, then finer particles will be accommodated on the second stage.31A number of particles successfully deposited on stage II on the instrument show the success of drug deposition stated in fine particle fraction (FPF). The airflow velocity used in TSI is generally 60 ± 5 L/min. The airflow velocity and vacuum regulation on the pump contained in the device will determine the location of particle deposition on the device. After the aspiration process, the TSI instrument is released and each chamber of the instrument is rinsed with phosphate buffer saline and then measured to obtain the number of drugs deposited on each stage quantitatively. This procedure is also carried out if measurements are carried out using NGI. Furthermore, the drug that is stored in the inhaler, capsules, and adapters is also cleaned and dissolved in the acetate buffer. The MMAD value is determined by looking at the deposition of particles at different stages on NGI.[24] The size and shape of the particle affects the fine particle fraction (FPF) value. The addition of leucine to microparticles is able to increase FPF 4.3 to 6.9 times higher than microparticles without leucine. Leucine was useful as a natural antiadherentamino acid to improve the deagglomeration of particles prepared using spray drying method.39 MMAD also evaluated using eight stages of ACI. Microspheres are inserted into the tool as many as 5-6 cycles with a flow rate of 28.3 L/min.[6] Carrier system includes polymeric liposomes, nanocarrier system with cyclodextrin or with the use of gelatin, micelles, dendrimers, and other various carrier systems such as microspheres and nanosphere also used to improve the flow properties of the drug. Microspheres are spherical particles of less than 200 μm of size which are used as a carrier system for delivery to various work targets in the body. Microspheres with the aim of inhalation must have an MMAD value of 3 μm to obtain optimal delivery in the lungs and can be captured by alveolar macrophages.[25]

Morphology

The shape of the particles affects the process of internalization or the process of avoidance of particles by macrophages. This geometry shape determines the initiation of contact with macrophages and the subsequent phagocystosis process. Macrophages internalize foreign particles through the process of phagocytosis, a process in which particles attach to macrophages and then engulfment by the plasma membrane. The process of attachment of particles with different geometries very dependent on the shape and size of the particles. Particles with different geometry shapes are able to provide at least one side to contact with macrophages and trigger phagocytosis. The shape of the particles influences the process of phagocytosis by macrophages, and furthermore, separately the shape of the particles influences the attachment and internalization of the particles. Particles with high attachmenet values will reduce the percent of particles internalized to macrophages. In oblate particle, it shows high attachment and internalization, so the number of particles phagocytosis is also high.41 The research was conducted on three particle forms, namely prolate ellipsoid (major axis 0.35 - 2.5 μm, minor axis 0.2 -2 μm), oblate ellipsoid (major axis 0.35 μm-2.5 μm, minor axis 0.2 - 2 μm) and spheres (radius: 0.26 - 1.8 μm). Research that has been done shows that particle shape also influences the internalization process or the avoidance process of particles by macrophages.[42] This geometry shape determines the initiation of

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contact with macrophages and the subsequent phagocytosis process. Tests carried out on particles with different shapes, namely spherical, , ellipse, to rectangular plates. The result is that the elongated particles t not to be taken by mouse peritoneal macrophages, while spherical particles tend to be more easily taken by macrophages. Furthermore, spherical particles tend to be able to avoid macrophages and increase anticancer activity.43 Effect of particle morphology on the number of particles that are phagocytes showed in Table 3.

rface Charge

It is known that macrophage cells have sialic acid on the surface, which makes the surface macrophage cells negatively charged.[44] This leads the researchers that the particle surface charge plays a role in determining the success of particle uptake by macrophages. The surface charge of a particle determines the stability and interaction of parti with phagocytic cells. Positive charged particles are widely used for intracellular delivery because of their ability to int t with cell membranes which mostly have negative charges. Positively charged nanoparticles, with many more positively moieties than amynoglicosides are tipically trapped in mucus.[45] So that they are able to increase uptake by cells and enhance immune responses. Hwang *et al*.[31] used hyaluronic acid to increase the uptake of microspheres by macrophage cells by up to two times. Hyaluronic acid has a negative charge, besides that the use of hyaluronic acid can increase the mucoadhesive properties of particles.[31] Hyaluronic acid itself is able to act as a ligand that is recognized by the CD44 protein, so the use of this material can increase the selectivity of CD44 receptors that are overexpressed in tissue that is inflamed.[46] Positively charged particles have a deficiency in acceptance related to toxicity because they can trigger the formation of ROS and induce apoptosis.[47] This makes the focus shift to negatively charged or uncharged particles that are more physiologically compatible. Particle composition in addition to affecting the physicochemical character also affects the process of particle recognition by macrophages. Some lipid groups such as phosphatidylserin and phosphatidylglycerol can be detected by macrophages because they have a negative charge. Particles made from functionalized alginates produce negatively charged particles.[48] Particles with a negative charge provide several advantages for reducing bioadesive with plasma proteins and decreasing the speed of particles to be taken up by non-specific cells. Particle charge and macrophage delivery can be seen in Table 4.

Surface Properties of Particles

Particle rigidity affects the ability of particles to be taken up by macrophages. Phagocytosis is a process that depends on actin which is affected by th rget's mechanical properties. Harder and stiffer polyacrylamide particles can be internalized into cells more efficiently than softer particles. Particle rigidity is generally responsible for the reception and interaction of particles with macrophages.[52] Although it has lower entrapment efficiency, porous particles will release the drug faster than nonporous particles. In the process of deposition in the lungs, an increase in porosity and a decrease in the density of microspheres close to the size of the particle geometry trigger a decrease in aerodynamic diameter. Meanwhile, in the uptake process by macrophages, spherical particles without pores or spherical particles with low pores are more effec in experiencing uptakes by macrophages.[53] The most no ous particles are deposited in the nasal cavity, while the porous particles are most deposited in the nasal cavity or bronc d there is the least deposited in the pharynx and trachea. Porous particles with a geometry diameter of 5 μm t o be deposited into the bronchial and alveolar regions, whereas particles with larger geometry tend to be left in the nasal cavity and trachea.[54] The difference in deposition properties between porous and unpredictable particles is influenced by differences in the degree of cohesiveness of each particle.[55] From various studies conducted, a conclusion is drawn that porous particles can be deposited more deeply on the inside, but tend to avoid phagocytosis by macrophages. Some examples of porous particles given by the inhalation route are presented in Table 5. Particle surfaces can be modified to increase uptake by macrophages by utilizing receptors on the surface of macrophages including Fc, manosil, galactosil, lipoprotein, and fibrinocetin receptors. Some examples of ligands used include peptides, antibody, and polysaccharide-based polymers. Polysaccharide based polymers are also used as ligands for delivery to macrophages. Carrageenan, a polymer with sulfated sugar groups other than fucoidan and ulvan, is used as a ligand for macr ge delivery.58 Several examples of other ligands used include bovine serum albumin and O-steroyl amylopectin (O-SAP) which are used in the manufacture of targeted in macrophages.[59] Receptors on macrophages can be targeted for active targeting so that further research is expected to develop specific ligands for various macrophage receptors for more efficient delivery. Use of ligands in particle surface is shown in Table 6.

Hydrophilicity

The lipophil hydrophilic nature of a particulate also affects the uptake of particles by macrophages. Particle coating with lipophilic material facilitates the process of particle recognition by macrophages, while coating with hydrophilic material such as polyethylene glycol (PEG) allows particles to survive the process of opsonization by serum proteins, inhibits hepatic clearance, and decreases the chance of particles to be recognized by macrophages. The use of appropriate polymers can affect the hydrophilic and lipophilic nature of particles and modulate their uptake by macrophages. Polymers such as poloxamer and poloxamine can make particles tend to be hydrophilic and prevent particles from being taken up by macrophages.[62] Surfactant protein in the lungs is included in collagen-lectin family surfa protein-A (SP-A) and surfactant protein-D (SP-D) which have specific receptors on the surface of macrophages. This protein can be used as an opsonin for targeted delivery on macrophages. In contrast, surfactant phospholipids which are a major component in pulmonary surfactants show inhibitory activity on particle uptake by macrophages.[63] Furthermore, coating the particles with DPPC that is the main lipid component in surfactants decreases the uptake of particles by cell macrophages NR8383.[64] Factors of physical and chemical characteristics that can reduce and increase particle uptake by macrophages are summarized in Table 7.

Polymer Characteristics as Factor for Macrophage Targeting

In general, microspheres are made by using polymers, both natural polymers such as ch san, gelatin, alginate, and carrageenan, as well as with synthetic polymers such as Poly-Lactic-co-Glycolic-Acid (PLGA), Poly Lactic Acid (PLA), and Poly-ε-Caprolacone (PEC). The chemical physical properties of the polymer determine how the drug is deposited in the lungs. Both synthetic and natural polymers, and hydrophilic and hydrophobic choices must be adapted to the purpose of development. For the target system in macrophages, hydrophobic polymers have a greater chance of being phagocytosed by macrophages, but polymers with polysaccharide groups such as chitosan, alginate, and carrageenan also have the ability to interact with human receptors and activate the phagocytic mechanism.[24] The choice of polymer affects many things for the drug delivery, where the polymer used determines drug release and drug accumulation on the target. This is because the polymer determines the shape and size and the charge of the particles or system produced. The shape, size, and load become the parameters that need to be considered in the inhalation delivery system. The concentration of the polymer used in making a system affects the pattern of drug release from the system. Microspheres consisting of 50% polymers give burst effect in the release test pared to over-the-counter drugs. This can be caused either by the chemical interaction between the drug and the polymer or because of the nature of the microspheres that form an amorphous particle.1 The use of polymers and crosslinker with different concentrations also affect the pattern of drug release from the system. Slower release is obtained by increasing the polymer ratio and crosslinker.[65] To obtain the microspheres system with controlled release also carried out with a combination of polymers. Kolesnyk[66] makes microspheres with a combination of alginate-kappa carrageenan with the use of CaCl2 as the crosslinker. The difference in the comparison of alginate to κ-carrageenan provides a different release profile.[66] Polymers characteristics as carrier for targeting macrophage as shown in Table 8.

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Table 1: Mechanisms of deposition and endocytosis pathways based on particle size

Particle SizeT (μm)	Deposition	Mechanism/ Endocytosis	Site of particle deposition in the lung	References
5 – 9 (slow inhalation)	Inertial impaction		Large airways include oropharynx, trachea and bronchi	15
3 – 6 (fast inhalation)	Inertial impaction		Large airways (trachea and bronchi)	
1 – 5	Gravitational sedimentation		Smaller airways	
<0.5	Brownian diffusion		Alveoli	
0.5 – 1	Brownian motion		Alveoli	
5 – 10	Impaction		Primary bronchi	26, 28
1 – 5	Sedimentation		Secondary bronchi	
1 – 3	Sedimentation		Bronchioles	
0.5 – 1	Brownian motion		Alveoli	
<0.2 – 1	Endocytosis		-	
<200	Clathrin-coated		-	26, 27
>500	Caveola mediated		-	
>1	Phagocytosis		-	
<0.2 – 1	Endocytosis		-	

Table 2: Example of particle size at the target of macrophage delivery

Delivery System	Drug	Particle Size (µm)	Particle Target	References
Polymeric Microparticles	Isoniazid	4.1 ± 0.57 µm	Phagocytosed particles and concentration of INH in macrophages increased 8.28 ± 0.3% compared to the administration of free INH of 1.74% ± 0.69	6
Microspheres	Rifampicin	1 – 6 µm	Particles are effectively phagocytosed by macrophages through the process of mediated scavenge receptors	25
Microspheres	Ofloxacin	2-5 µm	An increase of uptake of Microspheres with hyaluronates 1.7 times compared with microspheres without hyaluronates up to 2.1 times higher than free ofloxacin solutions	31
Microspheres	Ofloxacin	1 – 6 µm	Uptake of particles by macrophages increased up to 3.5 times compared with free ofloxacin	32
Microspheres	Isoniazid	3.54 ± 3.14µm	Particles undergo uptake by macrophages. Under fluorescent macrographs, microspheres are seen in the intracellular region and even the nucleus	33
Microspheres	Rifampicin	1-4 µm (~3 µm)	As compared with free rifampicin, microspheres significantly more rifampicin in PLGA MS was uptaken by macrphages at different time point.	34

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Table 3: Effect of particle morphology on the number of particles that are phagocytes

Particle Morphology	*Internalization (%)*	*Attachment (relative to spheres)*	*Phagocytoced (relative to spheres)*	References
Prolate ellipsoid	52%	3.8	0.6	41
Oblate ellipsoid	86%	2.5	2.7	
Spheres	70%	1	1	
	Diameter of Initial Spheres		***Particle attached per cell***	42
Spheres	0.5		1.7	
	1		2.1	
	3		3.0	
Rods	0.5		3.5	
	1		3.1	
	3		1.3	
Oblate ellipsoid	0.5		2.7	
	1		3.7	
	3		0.5	

Table 4: Relationship between particle charge and macrophage delivery

Delivery System	Drug	Charge	Target of macrophage	References
Microspheres	Lysine hydrochloride, manose	Negative	The presence of free amino acids makes the system negatively charged and can be used by macrophages. After 15 minutes of administration, the particles have reached the cytosol through the mechanism of endocytosis.	**33**
Solid lipid nanoparticle (SLN)	Mannose	Negative	Negatively charged particles increase cell uptake through a charged scavenger receptor. SLN increases the process of endocytosis by macrophages. Microparticles are detected in the cytoplasm.	49
Nanostructured lipid carrier	Tuftstin	Negative	Nanoparticles with tufstin petide components are significantly internalized compared to nanoparticles without tufstin.	50
Microspheres	Mannosylated gelatin	Positive	Mannosyltaed gelatin microsphere uptake by macrophages is higher than that of microspheres without mannosyltaed gelatin. This is related to the interaction of mannose groups with surface receptors on macrophages.	51

Table 5: Porous particle of inhalation delivery

Delivery System	Drug	Particle Porosity	Target Parameter	References
Microparticle	Lysozyme	Highly porous	Particles can be deposited in the trachea and inner lung. Particles with pores can avoid phagocytosis by macrophages, whereas particles without pores can quickly experience uptake by macrophages.	28
Microparticle	-	Porous particle (5 – 10 μm)	Porous particles with geometric diameters >3 μm are able to reach the lung alveli region (stage 6-8 in ACI) and are able to avoid phagocytosis. Even particles with a geometry diameter of 5 μm tend to be more able to reach the inner lung than particles with a geometry diameter of 10 μm.	54
Microspheres	L-lactic acid	Nonporous Microporous (0.2 – 2 nm)	Porous particles with a geometrical size of 5-10 μm with lower MMAD (<3 μm) have good aerosolization properties,	55

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		Mesoporous (2 – 50 nm) Macroporous (>50 nm)	are able to avoid phagocytosis and are deposited in the inner lung. Maximum uptake occurs in nonporous particles.	
Porous particle	Rifampicin	Porous size of 4 μm	In vivo test showed that rifampicin in the form of porous particle (PPs) is more effective for delivering drugs reaching the alveoli than in the form of free powder. PPs can avoid the mechanism of ckearence in the respiratory tract.	56
Particulate	Meloxicam	Large Porous Particle (LPPs) (>5 μm)	Large porous parts (LPPs) have a higher deposit fraction compared to nonporous particles despite having the same MMAD value (2.55 μm). In aerodynamic testing using ACI, LPPS has EF (Emmited Fraction) EF and (Fine Particle Fraction) FPF higher than nonporous particle >85.4% and >65.8%	57

Table 6: Use of ligand in particle surface

Delivery System	Drug	Ligand	Target Parameter	References
Nanostructured lipid carrier	Rifampicin	Peptide tuftstin	Selectively, tuftstin recognizes infected surface receptors of macrophages, thereby increasing uptake by macrophages. furthermore, tuftstin increases the antimicrobial activity of rifampicin	50
Microspheres	Isoniazid	Mannose	Microsphere with mannose selectively experiences Iupatke and can reach phagolisosome vesicles on macrophages. Formulasi can maintain therapeutic drug concentration use despite a decrease in clinical dose	51
Nanoparticle	Licoris	Mannose	Formulations with mannose have increased uptake due to the interaction between mannose and manosil receptors on macrophages.	60
Microparticle	Budesonide	Phospolipid 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), Dipalmitoylphosphatidylcholine (DPPC), Dipalmitoylphosphatidylglycerols (DPPG).	The use of phospholipids can increase macrophage uptake. Where in the same comparison DSPE is the most effective phospholipid, followed by DPPG and DPPC	61

Table 7: Particle characteristic factors that affect macrophage uptake

Parameter of particle	Characteristics of particles to increase uptake by macrophages	Characteristics of particles to reduce uptake by macrophages
Size	Particle sizes are 100-200 nm and 1-6 μm	Particles sizes are <1 µm and > 6 µm
Surface morphology	Spherical particles	Elongated, branched, and filamentous particles
Surface properties	Modified particle surface with mannose, SP-A and SP-D, O-SAP, maleylated bovine serum albumin (MBSA), and tuftsin	The particle surface is modified with PEG, poloxamer, and poloxamin.

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	Modified particle surface with mannose, SP-A and SP-D, O-SAP, (MBSA), and tuftsin	The particle surface is modified with PEG, poloxamer, and poloxamin.
Charge	Very positive or negative charged particles	Particles with a charge tend to be neutral
Rigidity	Rigid and non-porous particles	Fragile and porous particles
Hydrophilicity	Insoluble and hydrophobic particles	Dissolved and hydrophilic particles

Table 8: Polymer characteristics on targeted delivery of macrophages

Polymer	Role of polymers in the delivery of macrophages	References
PLGA	- Can be used for targeted delivery of macrophages even though macrophages do not have specific receptors for PLGA. - The introduction of PLGA particles by macrophages is determined by the proportion of lactic and glycolic acid in PLGA and the molecular weight of the copolymer used. - The degradation rate of the polymer is difficult to control. PLGA degradation causes changes in the lung environment to become more acidic which can interfere with the stability of peptides and proteins which will have an effect on its therapeutic effect.	2, 30, 32, 67, 68
PEC	PEC is hydrophobic polymer which is able to activate the phagocytic process of macrophages. PEC will produce particles with porosity that are good enough to be used by macrophages.	6, 69
PLA	- PLA is a hydrophobic polymer that is also capable of activating the process of phagocytosis by macrophages. - The different route of administration gives different immune expression which might influence the efficacy of drug delivery. - The lactate produced by PLA degradation also causes the lung area to become more acidic which will affect the stability of the particular drug it delivers.	41
Alginate	- Alginate is composed of manuronic acid which can be a specific ligand for TLR-2 and TLR-4 receptors found in infected macrophages. - Manuronic acid influences the inate immune response that is responsible for the activation process of the bactericidal effect on host cells. Manuronic acid also plays a role in increasing the activity of macrophage phagocytosis.	36, 53, 70, 71
Carragenan	The presence of sulfate in carrageenan makes this polymer negatively charged as an alternative to targeted systems in macrophages, where carrageenan will bind to CysD in the extracellular region of the cell. To increase the stability and efficiency of its entrapment, carrageenan is combined with other polymers such as chitosan and alginate.	58, 72, 73
Gelatine	Gelatine has low antigenic properties and has an active group that can bind to the human receptors on macrophages. Gelatine can be modified to increase the tendency of microparticles to be taken up by macrophages. The presence of a free -NH2 group on gelatin provides a side to be conjugated with mannose to deliver the drug more effectively.	51, 60, 74
Chitosan	- Positive charge of amino groups of chitosan can increase contact time between particles and negatively charged respiratory tract mucosa. - Chitosan with different molecular weights gives different cell uptake and trap efficiency. - Chitosan interacts with macrophage manosa receptors that trigger phagocytosis followed by degradation of lysozyme and N-acetyl-β-D-glucosamidase in phagosomes. - Chitosan able to activate macrophages by increasing the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and decreasing the release of anti-inflammatory cytokines IL-10.	32, 75, 76, 77

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Conclusion

To sum up, the various advantages of inhalation delivery system make many researchers compete to obtain an effective formulation by making various modifications both to the carrier system and to the excipient. Modifications are made to obtain an appropriate size for the inhalation process with good aerosolization properties and enhancement of drug loading carrier system and to obtain the desired release profile. Furthermore, alveolar macrophages are potential targets for more efficient drug delivery, especially for handling respiratory tract infections and diseases. The microspheres carrying system has been modified in such a way as to increase uptake 36 alveolar macrophages, either by utilizing a passive target system or by 28 ng ligands to the surface of the microspheres. The chemical and physical properties of particulate systems, such as particle size, shape, surface, charge, and other properties directly and indirectly contribute to the increase or decrease in particle uptake by macrophages. This goes back to the initia 31 rpose of providing therapy. This will have an impact on the pattern of drug distribution in the respiratory tract which will determine the point of drug accumulation in the respiratory system.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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