Tuberculosis, a disease of the respiratory system caused by *Mycobacterium tuberculosis*, is currently of worldwide concern. Rifamycin antibiotics are used as therapy in the treatment of tuberculosis. Rifamycin antibiotics include rifampicin, rifabutin and rifapentine. Oral use of anti-Tb drugs is still common and effective, but because long-term use of antibiotics affects patient compliance, increases side effects of the drug, and increases drug resistance, a delivery system that can overcome these problems is needed. One of them uses dry powder inhalation (DPI) formulations. Natural polymers, especially polysaccharides, have various advantages, such as biodegradability, biocompatibility and non-toxicity. This review discusses the use of rifamycin microparticle tuberculosis inhalation using polysaccharide polymers and reviews relevant *in-vitro* and *in-vivo* studies. The use of natural polymers, especially polysaccharides, is expected to increase the efficiency of TB therapy by reducing drug doses and systemic side effects and increasing direct drug delivery to infected organs.

**Keywords:** Rifamycin, Inhalation, Natural polymer, Microparticle, *In-vivo.*

**ABSTRACT**

Tuberculosis (TB) is one of the urgent global health problems. TB therapy involves the use of antibiotics, but unwanted side effects often accompany the treatment of TB with high doses and long periods of time. In an effort to increase the effectiveness of TB treatment and reduce side effects, direct drug delivery to the lungs is the focus of research. One of the approaches used is the development of drug delivery systems that use natural polymers in dry powder inhalation (DPI) formulations. Natural polymers, especially polysaccharides, have various advantages, such as biodegradability, biocompatibility and non-toxicity. This review discusses the use of rifamycin microparticle tuberculosis inhalation using polysaccharide polymers and reviews relevant *in-vitro* and *in-vivo* studies. The use of natural polymers, especially polysaccharides, is expected to increase the efficiency of TB therapy by reducing drug doses and systemic side effects and increasing direct drug delivery to infected organs.

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**Source of support:** Nil.

**Conflict of interest:** None

**INTRODUCTION**

Tuberculosis, a disease of the respiratory system caused by *Mycobacterium tuberculosis*, is currently of worldwide concern. Rifamycin antibiotics are used as therapy in the treatment of tuberculosis. Rifamycin antibiotics include rifampicin, rifabutin and rifapentine. Oral use of anti-Tb drugs is still common and effective, but because long-term use of antibiotics affects patient compliance, increases side effects of the drug, and increases drug resistance, a delivery system that can overcome these problems is needed. One of them uses a delivery system that is directly in the lungs (inhalation).

Inhalation rifamycin may have potential in the treatment of pulmonary TB because the lung is the site of entry for mycobacteria and lung lesions predominate. There are several different types of inhalers, including nebulizers, metered dose inhalers (pMDI) and dry powder inhalers (DPI). The inhaler requires particulate carriers to control drug release, ensure selective drug targeting to the desired location in the lungs, and offer enhanced interaction with biomolecules both on cell surfaces and within cells due to their size being comparable to biological entities. At present, carriers for therapeutic molecules are mostly produced using natural polymers. Natural polymers have many advantages, including biodegradability, mechanical and economic properties, good biocompatibility properties, controlled enzyme degradation, interaction specifically with several biomolecules, and simple modification capabilities that can provide flexibility in drug delivery. This review discusses the use of rifamycin microparticle tuberculosis inhalation using polysaccharide polymers and reviews relevant *in-vitro* and *in-vivo* studies.

**MATERIALS AND METHOD**

This review was obtained from articles with selected keywords of reputable online databases that were published between 2000 and 2023.

**RESULTS AND DISCUSSION**

**Natural Polysaccharide Polymers**

**Chitosan**

Chitosan is a natural polymer that has been widely used as a carrier in pulmonary drug delivery due to its non-toxic nature. It is a natural polymer derived from chitin, which is a biopolymer found in the exoskeletons of crustaceans and the cell walls of fungi. Chitosan has several advantageous properties, including biodegradability, biocompatibility, and non-toxicity. These properties make it an ideal carrier for inhaled drug delivery systems. In addition, chitosan can be modified to improve its solubility, stability, and targeting capabilities. The modified chitosan derivatives can be tailored to achieve optimal drug release and targeting efficiency.

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characteristics, friendly to biological materials, biodegradable, and proven to be enzymatically biodegradable by the body, including in organs such as the lungs, low toxicity and mucoadhesive properties.\textsuperscript{7, 8}

Sodium alginate

Alginate is a biodegradable polymer. The advantages of using alginate polymers are that they are non-toxic characteristics, have muco and bio-adhesive properties, are biodegradable and biocompatible in nature, and are economical.\textsuperscript{6} Alginate can be cross-linked in an aqueous solution with divalent cations (e.g., Ca\textsuperscript{2+}) for microsphere formation. This process has been shown to increase the viscosity flow rate and maintain drug release from within the microsphere system.\textsuperscript{9}

Pectin

Pectin is a type of polysaccharide obtained through an extraction process using water from orange peel or apple pulp. The main component of the pectin is a galactopyranosiluronic unit partially esterified with methanol.\textsuperscript{10}

Cellulose

Cellulose is a carbohydrate that consists of two recurring glucose units connected by β-1,4 glycosidic bonds. Cellulose strands form a crystalline arrangement through hydrogen bonds between molecules and within molecules.\textsuperscript{11}

Xanthan-gum

Xanthan gum (XG) is a natural polymer with excellent thermal stability, where the solution retains a uniform viscosity over a wide range of temperatures.\textsuperscript{12} It is also utilized in the modified release of bioactive molecules, particularly in aqueous solutions for in-situ gelling systems in drug delivery systems. Additionally, physical gellan hydrogels, prepared with different cations, are used for tablet, bead, and microsphere preparation. Moreover, interpenetrating polymer networks or cross-linked polymer networks based on gellan and other polysaccharides have been developed for drug delivery matrices.\textsuperscript{13}

Fucoidan

Fucoidan is a natural polysaccharide consisting of chemical units that have been reported to be specifically recognizable by alveolar macrophages of Mycobacterium. Fucoidan contains sulfated fucose and other sugars and can be recognized by the surface receptors of alveolar macrophages so as to deliver the drug directly to the target place.\textsuperscript{14}

Konjac glucomannan

Konjac glucomannan (KGM) is a natural macromolecular polysaccharide extracted from the konjac plant, which belongs to the Araceae plant family and is an herbaceous plant of the monocot class. Konjac glucomannan can be used as a polymer for targeted delivery systems, for example for tuberculosis therapy inhalation treatment systems using the spray drying method.\textsuperscript{15, 16}

Locust bean gum

Locust bean gum (LBG) is a non-starch polysaccharide consisting of galactose and mannose groups and is known as galactomannan. Locust bean gum has been developed in drug delivery systems, including tablets, capsules, granules, microspheres, gels, and polymer films. LBG-based polymers show a sustained release drug delivery system and have a mucoadhesive effect.\textsuperscript{17, 18}

Method of Producing Microparticles

Ionotropic gelation

Ionotropic gelation is based on the principle that cross-linking events of polymers with divalent cations, such as Ca\textsuperscript{2+}, form an insoluble gel. In the method of ionotropic gelation with aerosolization, a polymer solution is sprayed into a solution containing cross-linking agents to create microspheres, eliminating the need for organic solvents. Ionotropic gelation with aerosolization can encapsulate drugs and protect them from environmental factors. The process is easy fast, and the cost is relatively cheap.\textsuperscript{19}

Spray drying

Spray drying can produce particles suitable for the pulmonary administration route. In this method, micronized particles are crafted with precise aerosolization characteristics. By adjusting the formulation and processing parameters during spray drying, various properties of the product can be fine-tuned. This includes factors like powder yield, moisture content, and density, as well as particle attributes such as size distribution, shape, and crystalline structure. Consequently, spray drying facilitates the creation of particles highly suitable for aerosol

<table>
<thead>
<tr>
<th>Drugs</th>
<th>t1/2 (hours)</th>
<th>Cmax (mg/mL)</th>
<th>Protein binding</th>
<th>MIC (mg/mL)</th>
<th>Description</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>3–4</td>
<td>8–24</td>
<td>80</td>
<td>0.125–0.25</td>
<td>Increased doses of rifampicin are needed for short-term treatment.</td>
<td>35</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>- Rifabutin 50% is excreted through the kidneys in patients with renal disorders needing a dose reduction of up to 50%.</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Toxicity of rifabutin: uveitis &amp; cytopenias.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Rifabutin has a therapeutic index that is too narrow, so it needs a combination of other TB drugs.</td>
<td>35</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>62</td>
<td>0.3–0.9</td>
<td>85</td>
<td>0.03–0.06</td>
<td>- Rifampicin has t1/2, which is longer than rifampicin but has the antibacterial activity of mycobacterium tuberculosis, which is lower than rifampicin.</td>
<td>35</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>13–15</td>
<td>8–082-30</td>
<td>95</td>
<td>0.01–0.05</td>
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</tr>
</tbody>
</table>

Table 1: Characteristics of pharmacokinetic and pharmacodynamics of rifamycin groups\textsuperscript{35}
### Table 2: Methods of manufacture, characteristics and results of in vitro studies of rifamycin microparticles groups (rifampicin, rifabutin & rifapentin)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Polymers</th>
<th>Inhalers</th>
<th>Profiling Methods</th>
<th>Characteristics</th>
<th>In Vitro Study</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifabutin (RFB) &amp; isoniazid (INH)</td>
<td>Fucoidan</td>
<td>DPI</td>
<td>Spray drying</td>
<td>The microparticles have a slightly winding shape but a smooth surface D V50: 2.77 ± 0.03 µm MMAD: 3.64 ± 0.32 µm (RFB) &amp; 3.90 ± 0.01 µm (INH) ED: 1.10± 0.02 mg (RFB) &amp; 1.64 ± 0.23 mg (INH) FPD: 0.53 ± 0.01 mg (RFB) &amp; 0.82 ±0.02 mg (INH) FPF: 38.1 ± 1.8% (RFB) &amp; 38.0 ± 1.6% (INH)</td>
<td>This formulation showed no cytotoxic effect on lung epithelial cells (A549), although mild toxicity was observed in THP-1 cells that had differentiated into macrophages at the highest concentration tested (1 mg/mL). These microparticles show potential activity against mycobacteria (95% inhibit the growth of mycobacteria)</td>
<td>14</td>
</tr>
<tr>
<td>Rifabutin and isoniazid</td>
<td>Konjac glucomannan</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Microparticle size 1.23-1.39 µm Aerodynamic Diameter 1.02 &amp; 1.71 µm. RFB efficiency 92-104%. Drug loading RFB 4% &amp; INH 7.7% KGM/INH/RFB microparticles showed that 100% slower drug release was achieved in 450 minutes compared to microparticles without KGM.</td>
<td>The microparticles of rifabutin &amp; isoniazid KGM viability of Calu-3 cells remained at about 80% after exposure to the highest concentration, while A549 cells reached about 65%. The use of KGM without other additives (leucine &amp; mannitol) exerts a much milder effect, especially at the highest concentrations tested and longer exposure (24 hours, 1 mg/mL). KGM/INH/RFB microparticles showed no cell toxicity.</td>
<td>16</td>
</tr>
<tr>
<td>Ributin</td>
<td>Chitosan</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Zeta potential 18-38 mV Yield 81.2 – 97% EE 40 - 61 % (with ethanol) Drug content 61-64% PDI &lt;0.1</td>
<td>Using cells A549 &amp; raw 264.7) showed that security and drugs can enter cells efficiently. Concentration of antibiotic inhibition against Mycobacterium (≤ 0.25–16 mg/L). - F3 DPI is less toxic compared to rifampicin powder. - DPI F3 concentration 0.1 mg/ml, cell viability A549 (89.73%) higher than rifampicin powder (51.32%) -Chitosan-alginate increases the safety of rifampicin powder against lung cells.</td>
<td>32</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Chitosan Alginete</td>
<td>DPI</td>
<td>Spray drying</td>
<td>DPiS drug content: 3.227-12.153 mg/g EE DPiS (12.826% - 48.107%) Drug release in the lung (78.301% ± 1.332% in 2 hours) Macrophage drug release (41.355% ± 1.259% in 2 hours). Particle Aerodynamics: 11.4288 ± 1.259 µm</td>
<td>Rifampicin chitosan-alginate reduces Rifampicin cytotoxicity at high doses (24 hours).</td>
<td>37</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Chitosan</td>
<td>DPI</td>
<td>ionic gelation</td>
<td>Particle size 124.1 – 402.3 nm EE 72.00 ± 0.1% Chitosan-Rifampicin 90% release for 24 hours FPF: 33.27% ±0.87 MMAD 3.3±0.18 µm FPF: 33.27% ±0.87 MMAD 3.3±0.18 µm</td>
<td>80-90% viability of J774 macrophage cells seen for 6 and 12 hours Safe RFM-NPs compared to free RFMs.</td>
<td>38</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Chitosan-alginate</td>
<td>DPI</td>
<td>Ionic gelation</td>
<td>Particle size 324.0 ± 40.7 nm PDI 0.226 ± 0.30 zeta potential – 28.52 ± 0.47 mV No Rifampicin drug release for 24 hours Yield: 9.15–30.17% Particle size 1.146–3.403µm Loading efficiency: 45.51–89.83% Zeta potential: 18.1–29.4 µV Swelling index: 57.63–1682.9% Drug content 45–60% rifampicin Medication content 70–89% Rifabutin RifMiroparticle drug release 90% (12h) Drug release RFB Microparticles 90% (96h) MMAD: 5.45µm – 7.37 µm GSD: 1.6% - 1.96% FPF: 21.46% &amp; 29.97%</td>
<td>Cell viability &gt; 90% after 5 and 24 hours of incubation, Rifampsin chitosan-alginate reduces Rifampicin cytotoxicity at high doses (24 hours). Microparticle retrieval on U937 alveolar macrophage cells, allowing targeting of Mycobacterium tuberculosis within the macrophage. Microparticles deposited in the lungs based on ACI data Rif &amp; RFB drug chitosan microparticles are not toxic in the lung but need further toxicity testing.</td>
<td>39</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Chitosan</td>
<td>DPI</td>
<td>Ionotropic gelation</td>
<td>Spray drying</td>
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<tr>
<td>Drug Combination</td>
<td>Microparticle Type</td>
<td>Method</td>
<td>Performance &amp; Properties</td>
<td>Toxicity &amp; Efficacy</td>
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<tr>
<td>Rifampicin &amp; Chitosan &amp; Carrageenan</td>
<td>DPI</td>
<td>Powder aerosol performance using the next generation impactor and Turbospin as a suction device.</td>
<td>Particle size 1076 &amp; 1167 nm Zeta potential 28 &amp; 17 EE 70 &amp; 69% CP 65 &amp; 61 % 50% MMAD ~9 μm (uncoated liposome), MMAD ~2 μm (coated liposome)</td>
<td>In vitro toxicity studies using human alveolar epithelial cells A549. It does not cause significant cytotoxic activity during the first 4 hours of incubation (less than 15% of deaths) and slowly increases to about 30% after 48 hours.</td>
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<tr>
<td>Rifampicin Sodium alginate</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Yield:</td>
<td>- Increased antibacterial activity when β-cyclodextrin is present. - The bioavailability of rifampicin alginate microsphere administered via the Inhalation route is 6x greater than that of the oral route.</td>
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<tr>
<td>Rifampicin Carbohydrate (maltodextrin, mannitol &amp; leucine)</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Drug content 89.3% to 99.2% Particle Size 5.47–6.80 μm Yield 30.65 and 86.67% EF 78.42% (F4) &amp; 95.22% (F7) RF 40.12% (F4) - 65.41% (F7)</td>
<td>- Human alveolar epithelial cell toxicity A549 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin Chitosan Inhalation</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Particle size 4.87 and 5.21 μm Drug loading 18.33–32.37% EE 65.11–72.18% Aerodynamic diameter 1.89 μm – 2.47 μm Rifampicin microparticle clearance 60% in 12 hours FPF: 62.44% and 58.26% MMAD below 3 μm GSD: 2.01–2.62</td>
<td>- The concentration of the drug in the plasma can still be detected up to 72 hours after delivery through the respiratory tract of chitosan microparticles containing rifampicin.</td>
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<tr>
<td>Rifampicin chitosan-guar gum</td>
<td>DPI</td>
<td>Spray drying Ionotropic gelation</td>
<td>Particle size 875 – 1575 nm PDI 0.110–0.341 Yield 55.81% - 65.81% Aerodynamic diameter 1.17 μm–1.92 μm EE 52.43% - 70.81% Loading drug 23.33% - 42.48%</td>
<td>The cytotoxicity of DPI is lower compared to INH and free RIF. The antimicrobial activity of the guar gum formulation is increased from 12 hours to 24 hours.</td>
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</tr>
<tr>
<td>Rifabutin &amp; Isoniazid Locust bean gum</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Aerodynamic diameters 1.15–1.67 μm Efficiency 86.3-102.8% Drug loading 8.8– 10.3% INH Microparticle Removal (86% in 20 minutes). 100% release at 240 minutes. LBG: RFB 10:1 Microparticle Release (w/w) 80% 240 min</td>
<td>There is no cytotoxicity effect of locust bean gum INH microparticles, the toxicity effect occurs due to INH itself. Cytotoxic evaluation of lung epithelial cells (A549 cells) and macrophages (THP-1 cells) revealed toxic effects of rifabutin-containing microparticles at the highest concentrations.</td>
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</tr>
<tr>
<td>Rifabutin &amp; Isoniazid Konjac glucomannan</td>
<td>DPI</td>
<td>Spray drying</td>
<td>Aerodynamic diameter 3 μm, with the addition of a reduced particle size mannose (&gt;65% in 90 minutes) Geometric diameter 1.87–2.24 μm Drug loading 40–50% RFB association efficiency 66-74% &amp; INH 78% and 91% RFB drug loading 7-13% &amp; INH 3-6% MMAD: 3 μm FPF 55-60% GSD 2.5-3 μm</td>
<td>KGM microparticles show safety Drug release was characterized in artificial lung fluid with both drugs (RFB &amp; INH) exhibiting a biphasic profile with rapid release of 60% of drugs, followed by slower drug release within 24 hours.</td>
<td></td>
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</tbody>
</table>
Inhaled Polysaccharide Microparticle Containing Rifamycin Groups

delivery, capable of reaching deep lung regions without the need for a carrier system. The advantage of this method is the drying time of a droplet is only a fraction of a second, with fast evaporation avoiding droplet overheating. Another advantage is the resulting product exhibits a significant surface area and consistent, adjustable particle size. Inhalation

The inhalation route has many advantages, including large lung surface area so that drug absorption is fast due to high vascularization, avoiding the first-pass effect of metabolism in the liver, reduced drug doses, reduced systemic absorption and reduced drug side effects. This inhalation delivery system requires a small particle size and a good aerodynamic mass median diameter (MMAD) of between 1 to 5 µm to achieve effective lung deposition. Particles measuring 5 to 10 µm will be positioned in the primary bronchi, while particles measuring 1 to 5 µm will be positioned in the secondary bronchi and particles measuring 0.5 to 1 µm will be positioned in the alveoli. Particles smaller than 0.5 µm are likely to come back out with carbon dioxide in the exhalation process.

**Type of inhaler**

TB treatment requires a comprehensive approach, and inhalers have become one of the important devices in the treatment of this disease. The following are the types of inhalers, along with their advantages, disadvantages, and drug formulations. Nebulizers require a dispersal force in the form of gas jets or

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Polymers</th>
<th>Study in Vivo</th>
<th>Parameter in Vivo</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>Chitosan &amp; carrageenan</td>
<td>Microparticles containing rifampicin loaded liposome and rifampicin nonliposome significant cytotoxic activity during the first 4 hours of incubation (less than 15% mortality), and increased slowly to about 30% after 48 hours.</td>
<td>N/A</td>
<td>36</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Chitosan</td>
<td>DPI rifampicin t1/2 increased in the lungs (sustained release). The residence time of rifampicin DPI is updated to 24 hours.</td>
<td>RFM-NPs formulation is non-toxic and safe to use</td>
<td>38</td>
</tr>
<tr>
<td>Rifampicin &amp; rifabutin</td>
<td>Chitosan</td>
<td>Free administration of rifampicin and rifabutin to intra-tracheal rats resulted in severe peribroncholar infiltration by inflammatory cells accompanied by hyperplasia of the BALT and thickening of the interalveolar septum, which is a sign of severe toxicity.</td>
<td>Acute toxicity studies of microparticles in Sprague Dawley rats showed no significant evidence of adverse local effects in the lung. Pulmonary pathology, showing that there is no significant toxicity of microparticles prepared from Rif and RFB against thlungs</td>
<td>41</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Sodium alginate</td>
<td>Rifampicin is present in plasma 4 hours to 72 hours after the administration of rifampicin alginate microspheres.</td>
<td>In vivo studies in rats show that the delivery of rifampicin alginate microspheres by the inhalation route can increase the bioavailability of the drug, increase the concentration of the drug at the target site and decrease the toxicity of the drug.</td>
<td>42</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>HPMC &amp; lactose</td>
<td>A 50 mg DPI dose in humans results in a higher concentration of the drug in the lungs compared to a 600 mg human dose in circulating products. The DPI of rimaparin in the lung is 1/2 as long as the circulating rifampicin.</td>
<td>Histopathological examination of virtually undetectable toxicity of DPI compared to circulating formulations. In vivo pulmonary pharmacokinetic studies of DPI formulations in rats showed higher drug concentrations in the lungs compared to circulating formulations.</td>
<td>43</td>
</tr>
<tr>
<td>Rifampicin &amp; isoniaid</td>
<td>Chitosan &amp; guar gum</td>
<td>Drug deposits in the lungs were detected 4–8 hours.</td>
<td>Chitosan-guar gum (GCNP) formulation of lower cytotoxicity and better absorption of the drug by thlungs. The chitosan-guar gum (GCNP) formulation also resulted in a 5-fold reduction in the number of tuberculosis bacteria in the lungs compared to over-the-counter drugs.</td>
<td>45</td>
</tr>
<tr>
<td>Rifabutin &amp; isoniaid</td>
<td>Locust bean gum</td>
<td>The percentage of macrophages absorbing LBG microparticles was very high in both cases (99.6 ± 0.2% for 220 µg/cm² and 99.5 ± 0.4% for 50 µg/cm²). It shows the absence of effect from concentration and shows high affinity of macrophages to LBG microparticles.</td>
<td>Locust bean gum microparticles show a strong ability to be taken up by rat alveolar macrophages (percentage of phagocytosis &gt;94%).</td>
<td>46</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Sodium alginate</td>
<td>Rifapentine sodium alginate particles diluted in a physiological salt solution are administered directly to the foci of infection in the lungs of beagles. Sustained drug concentrations are maintained in the dose area in this lung tissue for up to 7 days, with concentrations several times higher than in plasma.</td>
<td>The specific targeting associated with bronchoscopy is not intended to kill all pulmonary bacilli, and will instead be used as a companion treatment for oral therapy.</td>
<td>48</td>
</tr>
</tbody>
</table>
In-vitro and in-vivo studies using polysaccharide polymers containing rifamycin microparticles by inhalation route show that the use of inhalation polysaccharide polymers can increase the residence time of the drug (rifamycin) in the lungs, which has the potential to increase therapeutic efficiency, increase bioavailability of the drug in the lungs and increase the effectiveness of drug delivery to the lungs and show low toxicity. In-vitro and in-vivo studies are shown in Tables 2 and 3.

Based on the in-vitro and in-vivo studies, the use of polysaccharide polymers can increase the bactericidal effect and reduce the development of resistant strains. Along with the growth of M. tuberculosis in mononuclear phagocytes in the host body, the insertion of antitubercular agents in polymers can be a powerful tool for specific targeting and accumulation in infected cells. In addition, these polymers can increase the penetration of hydrophobic antituberculosis/antimicrobial drugs and protect them from degradation or elimination before reaching infected tissues.

Current and future development
Inhalable microparticle polysaccharide polymers containing rifamycin groups represent a significant advancement in the treatment of tuberculosis, a highly prevalent and challenging infectious disease. Future perspective represents a promising approach to address the challenges associated with tuberculosis treatment, including drug resistance and patient non-compliance. However, further research and validation, particularly in clinical settings, are necessary to confirm the efficacy and safety of these innovative inhalable microparticles for tuberculosis therapy.

CONCLUSION
Various formulations with natural polysaccharide polymers in the rifamycin groups demonstrate low toxicity and effectiveness in delivering drugs to the lungs based on in-vitro and in-vivo evaluation. This is a positive development in an effort to control tuberculosis more effectively.

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