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Review: Application of Polysaccharide Polymer Combination in Microsphere Delivery System for Anti-Tuberculosis

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Abstract

Tuberculosis is still a health problem both in Indonesia and in the world and is one of the leading causes of death. Unfortunately, the first-line OAT therapy that is currently recommended in Indonesia has some limitations, namely requiring a long duration of treatment and starting to find cases of resistance in its use. *Drug Delivery System* is one of the solutions to this problem, as a formulation or system that is able to mediate the delivery of therapeutic substances in the body to increase therapeutic effects, reduce drug side effects, increase bioavailability and improve patient compliance. Purpose: Therefore, in this review we will review the polysaccharide polymers used as microsphere delivery systems as anti-tubeculosis treatment. The review of this article was made using the library research method obtained through Google Scholar, PubMed, Scopus, NCBI, Elsevier with the keywords "*Drug Delivery Pulmonary*", "Polysaccharide Polymer for Pulmonary", "*Chitosan Polymer", "Sodium Alginate Polymer", "Carrageenan Polymer", "Pectin Polymer*", "*Antibiotics Chitosan-Na.Alginate Pulmonary", "Antibiotics Chitosan-Pectin Antibiotics", "Antibiotics Na.Alginate – Pulmonary Carrageenan*", "*Antibiotics for Tuberculosis*", "*Drug Delivery for Anti Tuberculosis*". The use of polymer combination is an option in order to complement the shortcomings of each of the other polymers, then it can produce controlled-release drugs, which have the advantage of reducing the frequency of dosing, reducing drug side effects, increasing the level of patient compliance which can certainly be a solution for the development of anti-tuberculosis drugs.

Keywords: Microsphere, Polysaccharide, Combination, Anti-Tuberculosis

1. Introduction

Tuberculosis is an infectious disease caused by Mycobacterium Tuberculosis. Tuberculosis is still a health problem both in Indonesia and in the world and is one of the leading causes of death. It is a case that always increases every year. This disease is usually transmitted through air contaminated with *M. tuberculosis* bacteria released when people with tuberculosis cough. This bacterium is an acid-resistant gram-positive bacterium with very slow growth. In body tissues, these bacteria can be dormant, so that for tuberculosis healing therapy is carried out in the long term. Tuberculosis bacteria can spread through blood vessels or lymph nodes. Therefore, tuberculosis infection can infect almost all organs of the body such as: lungs, brain, kidneys, digestive tract, bones, and lymph nodes, although the most commonly affected organs are the lungs [1]. The use of anti-tuberculosis drugs (OAT) is one of the main components of efforts to control these problems. Unfortunately, the first-line OAT therapy that is currently recommended in Indonesia has some limitations, namely requiring a long duration of treatment and starting to find cases of resistance in its use.

Anti-Tuberculosis Drugs (OAT) currently used are pyrazinamide, isoniazid, and rifampicin. Several clinical studies have shown that some antimicrobials (macrolides, quinolones, betalactams) can be used as OAT. High-dose drug administration is carried out because only a small portion of the total drug dose can reach the lungs after oral administration [1]. Rifampicin, isoniazid, and pyrazinamide are well absorbed by the digestive system and each drug has a short biological half-life of about 2-5 hours, 3.1 ± 1.1 hours and 9-10 hours respectively [2]. The short biological half-life of the drug causes patients to take the drug continuously, increasing the risk of unwanted side effects. The main side effects of these drugs are hepatotoxicity, nausea, hearing loss, nephrotoxicity, hyperuricemia, tingling, red urine, no appetite, joint pain and not a few found resistance to the use of these drugs as a result of the patient's non-compliance in taking the drug. To reduce the side effects of taking drugs with high doses and short half-lives of drugs, the development of controlled-release dosage forms is more beneficial.

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Because this drug carrier system can increase the effectiveness of therapy and to reduce side effects, plasma concentration and reduce dose and controlled dose frequency. Drug carrier systems can be synthesized using polymers by encapsulation method. Drug Delivery System (DDS) is defined as a formulation or system capable of mediating the delivery of therapeutic substances in the body to increase therapeutic effects, reduce drug side effects, increase bioavailability and improve patient compliance [3]. Targeted drug delivery to the lungs has evolved into one of the most researched systemic or local drug delivery approaches. This route also allows for more specific drug deposition at high concentrations in the diseased lung thereby reducing the overall amount of drug administered to the patient (10-20% of the amount orally), as well as increasing local drug activity and reducing systemic side effects [4]. Microspheres are substances or compounds that have free-flowing properties (powder). Microspheres are composed of proteins or synthetic polymers that are biodegradable and ideally have a particle size of 1-1000μm and ideally have a particle size of less than 200μm. Microspheres can be made through various types of materials such as glass, polymers, and ceramic microspheres. Microspheres play an important role in increasing the bioavailability of conventional drugs and minimizing side effects [5]. Polymers have been used in drug delivery for many decades, such as serving as bulking agents or as materials intended to swell upon contact with gastrointestinal media, leading to drug release. Scientists have frequently turned in recent years to polymers and oligomers to enable creation of systems that can overcome aqueous solubility limitations and achieve effective drug delivery. The use of polymer microspheres as carriers of active substances makes it possible to achieve controlled or sustained release [6]. Therefore, this review will reported the polysaccharide polymer used as a microsphere delivery system as an anti-tuberculosis treatment, especially for targeted lung delivery.

2. Methods

The making of this article review is using the library research method obtained by using research journals, journal reviews, and scientific articles. The journals found were national and international journals published online from various web journals, namely Google Scholar, PubMed, Scopus, NCBI, Elsevier with 90 articles and 54 selected articles. In this study, a search was conducted for research journals published from 2000 – 2023.

3. Polysaccharide as microsphere delivery system

A microsphere is a spherical or spherical particle made of a polymer containing a core material, wherein the core material is dispersed and adsorbed in the polymer matrix. Core materials can be solids or liquids in the form of organic or inorganic compounds The advantages of microspheres include being able to deliver drugs at certain organ or target sites or tissues with small drug concentrations, providing protection for unstable drugs before and after administration, being able to improve the action of drugs in vivo, pharmacokinetic profiles, tissue distribution and cellular interactions of drugs, increasing absorption and bioavailability of drugs due to their small particle size, reducing side effects of drugs both systemic and local [7]. Polymers are key ingredients for manufacturing, drug protection and increased bioavailability.

Polysaccharides are polymer raw materials that are suitable for use as non-ionic polymeric surfactants. This is because polysaccharides have the advantage of abundant availability in nature and are renewable, biodegradable, non-toxic, and contain hydroxyl groups and aromatic compounds that can be added with hydrophobic groups and hydrophilic groups in the polymer section [8]. Polysaccharide polymers exhibit biocompatibility, biodegradability, high relative abundance and low cost, making them indispensable as matrices for active agent carriers and maintaining the stability of active substances [9]. Below is a polysaccharide polymer that is often used in microsphere delivery systems. The chemical structures of all investigated polysaccharide polymers are illustrated in table 1.

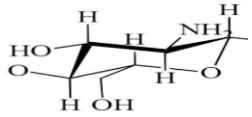
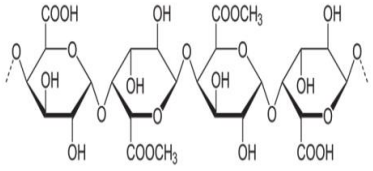
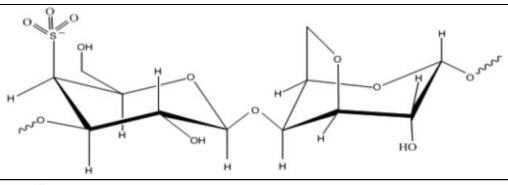
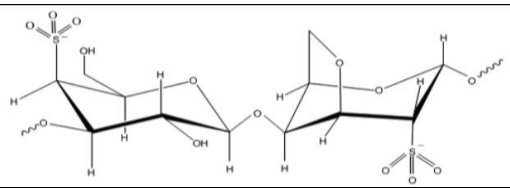
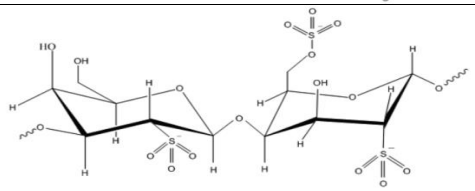
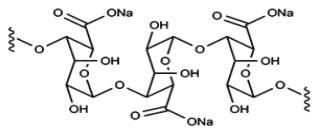
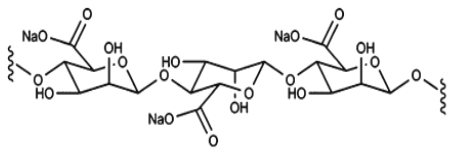
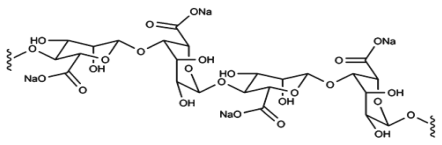
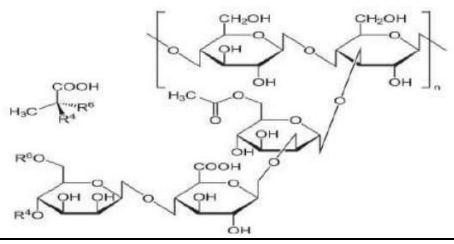
3.1 Chitosan

Chitosan, b-(1-4) linked 2-amino-2-deoxy-b-D-glucopyranose, is an N-deacetylated derivative of chitin obtained by transforming the acetamide groups into primary amino groups [10]. Chitosan is white, odorless, and tasteless with very low immunogenicity and toxicity [15]. The high positive charge density confers mucoadhesive properties, making chitosan an ideal polymer for drug delivery in mucosal tissue. [16] Chitosan can also help tissue healing, and interacts well with human cells [17]. It can be found on the skin of white shrimp. The skin of white shrimp contains 15.68% chitosan [18]. Chitosan is a natural polysaccharide derived from chitin, is biocompatible, specific biological activity [15].

3.2 Pectin

Pectin is a complex polysaccharide found in the middle lamellae on the plant cell wall. Generally, commercial pectin is extracted from orange peel and apple pulp under slightly acidic conditions [19]. The structure of pectin varies depending on the type of raw material, the location of the raw material growth, and the extraction conditions [20]. Pectin is one of the polysaccharide polymers that has been studied generally in the food and pharmaceutical industries for the protection and controlled release of active substances (drugs and vitamins), due to its excellent biocompactability, pH sensitivity, biodegradability, and non-toxicity [21]. The pectin in orange peels is about 25-30%, in ampelous pulp 10-15% [22], and more recent report on extraction and characterisation of pectin from banana peels it ranges from 0.9% [23].

Table 1.: Chemical Structure of Polysaccharide Polymers

Polymers	Chemical Structure	References
Chitosan		10
Pectin		11
K-carrageenan		12
i-carrageenan		12
λ-carrageenan		12
Sodium Alginate G sequence		13
Sodium Alginate M sequence		13
Sodium Alginate MG sequence		13
Xanthan gum		14

3.3 Carrageenan

Carrageenan is a natural polysaccharide composed of galactose and 3.6 anhydrogalactose complexes, is anionic and has the ability to form gels. It is generally sourced from red seaweeds of the genera Euchema, Chondrus, Iridaea, and Gigartina. Carrageenan has many functions, including as a bulking agent, thickening, stabilizing, and gelling agent, so it is widely used in the food industry. The pharmaceutical industry also benefited greatly from this polysaccharide due to its high compatibility and good viscosity during the tablet granulation process, making it one of the best excipient agents for tablets [24]. K-carrageenan is extracted from algal (Kappaphycus alvarezii), i-carrageenan is obtained from Eucheuma denticulatum, and λ-carrageenan: extracts from Gigartina and Chondrus genera [25]

3.4 Sodium Alginate

Sodium alginate is a biocompatible polymer with very low toxicity. This is the main advantage that makes alginate one of the biopolymers with the widest biomedical application. One of the most common applications of alginate is its use as an excipient in drug delivery systems, i.e. as a stabilizing agent and controlled drug release in various pharmaceutical formulations. Sodium alginate is mainly used in the pharmaceutical industry and can be used for the purpose of prolonging drug release [26]. Sodium alginate is present in the cell wall of Phaeophyceae with levels reaching 40% of the total dry weight [27].

3.5 Xanthan gum

Xanthan gum is produced by a natural microbial fermentation process that converts glucose to produce this product. It has unique characteristics so that it is included in a multifunctional excipient. In addition, xanthan gum is also known to be resistant to enzymatic degradation and shows synergistic interactions with other hydrocolloids. Xanthan gum can be synthesized by Xanthomonas campestris [28]. Formulations with polymers produce controlled-release drugs that have the advantage of reducing the frequency of dosing, decreasing drug side effects, increasing patient compliance levels, decreasing fluctuations, and prolonging the duration of drug action, and ensuring that pharmacokinetic and pharmacodynamic responses can be reproducible and predicted. In addition, the polymer can also be modified in such a way as to be a targeted drug delivery system to specific organs. Mixtures of various natural or synthetic polymers can mutually correct the deficiencies of each other's physicochemical characteristics and can produce new characteristics in the mixture. The biopolymer used must have an opposite charge, so that it can form a flexible matrix to adsorb drugs with wider properties, for example a combination of chitosan-alginate or chitosan-carrageenan that can be used as a matrix of various drugs with more general properties because the adsorption takes place physically.

In the selection of polymers to form a microsphere system, there are several things to consider such as the solubility of the polymer, and the benefits described in table 2. In addition, it is very important to pay attention to the binding and release mechanism between polysaccharide polymer combinations. The binding and release mechanism of this polymer combination can be seen in table 3.

Table 2: Solubility and Utilization of Polysaccharide Polymers

Polymers	Solubility	Utilization
Chitosan	• Insoluble in water, alkaline solvents, phosphoric acid, sulfuric acid and some organic solvents [18,29] • Soluble in organic acid solutions such as formic acid, acetic acid, tartaric acid, and citric acid at pH ± 6.5	Inhibits tumor cells, antimicrobial activity, regenerative properties. Chitosan is also used in drug delivery applications as an absorption enhancer, mucoadhesive polymer, and for gene delivery applications [30]
Pectin	• Pectin with high methoxyl content is soluble in cold water, pectin with low methoxyl content is soluble in alkaline or oxalate solution. • Pectin is insoluble in acetone and alcohol [31]	pectin acts as an adhesive, texture-forming and cell membrane [32]
Carrageenan	Easily hydrolyzed in an acidic and stable solution in an alkaline atmosphere [33]	As a gel-making agent, thickener and stabilizer [33]
Sodium alginate	• Practically insoluble in ethanol (95%), ethers, chloroform, ethanol-water mixtures (ethanol content greater than 30%), other organic solvents, and acidic solutions with pH less than 3 • Soluble in water and forming a viscous colloidal solution [34]	• Alginate can function as a suspending agent, emulsifier, stabilizer, binder, thickened, film former, coating agent, gelling agent, syneresis inhibitor, crystalization inhibitor and encapsulating agent [34] • Helps in cleaning up heavy metal and radioactive pollution in the food consumed [27]
Xanthan gum	Water-soluble, stable under acidic and alkaline conditions and stable at various temperatures [28]	• As a tablet excipient to increase or decrease the release rate of the drug [14]

Table 3: Polymer Bonding and Release Mechanism of Polymer Combinsai

Polymers	Inter-Polymer Bonding	Discharge Mechanism
Chitosan-Na.Alginate with CaCl2 crosslinker	Alginates can interact with chitosan through the formation of polyelectrolyte complexes. Sodium alginate is reacted with CaCl2, then there will be an exchange of Na+ ions from sodium alginate with Ca2+ from calcium chloride solution so that it will form a hydrogel with an egg box model. Then when the calcium alginate formed is reacted with chitosan, the carboxyl group (COO-) (anion) in the alginate will bind to the amino group (NH3+) (cation) in chitosan [35]	When the microcapsule is exposed to neutral pH, the anionic alginate in the Ca-alginate-chitosan complex can be replaced by hydroxyl ions and chitosan can lose its charge resulting in the disintegration of the matrix and the encapsulated drug released into the surrounding fluid [36].
Chitosan-Pectin	Polycationic chitosan interacts with pectin (anionic) to form a polyelectrolyte complex, which is an association complex formed between polyions with opposite charges due to electrostatic interactions between the charged polyions [7]. The negative charge of the pectin carboxylate group can bind ionically to the positive charge of the chitosan amine group [37]	Drug release affected by drug diffusion through polymer matrix pores. The enzyme degrades the pectin on the matrix and breaks its polymer chain, causing more pores to form on the surface of the matrix and making the matrix more permeable for drug release.
Na.Alginate – Carrageenan	Alginates can form hydrogen bonds with carrageenan through molecular interactions through carboxyl, hydroxyl and ether groups. The formation of cross-links between alginate and carrageenan polymer chains by CaCl2 leads to the formation of stronger bonds and results in less space between polymer chains [38]	The release of drugs from the alginate matrix occurs due to the exchange of ions between Ca2+ as cross-linkers with the Na+ group which will be bound to the -co- group of the alginate guluronate block which causes damage to the "egg-box" structure so that the active ingredients can be released from the matrix [39]. Meanwhile, the mechanism of drug release from carrageenan occurs due to the replacement of the group that binds sulfate, causing damage to the bond in thecoil-helix structure [40]
Chitosan-Xanthan gum	Forms polyelectrolyte complexes through ionic bonds between poditive-charged and negatively-charged -$NH3^{+and}$ -coo- [41]	N/A
Na.Alginate-Pectin	Sodium alginate can form strong complexes with other neutral polyelectrolytes, such as pectin by forming interconnected chains and forming hydrogels with the addition of divalent cations such as Ca2+ that can improve the mechanical properties of alginate [42]	N/A

Table 4 : Antibiotic Applications - Polymer Combinations for Treatment of Anti-Tuberculosis

Polymers	Polymer Combination Objectives	Active substance	Research Results
Chitosan-Na.Alginate	• The solubility of chitosan at low pH can be prevented by alginate tissue because alginate does not dissolve under low pH conditions. The possibility of alginate breaking down at higher pHs is prevented by chitosan, which is stable at higher pH ranges [46] • The chitosan-alginate complex is beneficial in improving the stability of the drug in biological fluids [47] • The use of double coating of chitosan-sodium alginate can reduce porosity and increase the stability produced [48] • Na alginate - chitosan based microcapsules used for the controlled release. Alginate improves the basic structure of chitosan with the formation of polyelectrolyte complexes [36,49]	Pyrazinamide	• There is an increase in the value of encapsulation efficiency along with an increase in alginate concentration • Particle size in the range of 68.06 nm to 295.40 nm, the distribution of particle sizes is uneven [46]
		Isoniazid	• Spherical shape with particle size below 7 µm • It was found that the polymer system can control drug release [56]
		Isoniazid	• Shows a spherical shape with a smooth surface • Positive zeta-potential values at maximal and minimal concentrations of chitosan • Drug content and yield showed high values compared to free isoniazid. Drug content reached 90.3% • *Swelling index* was high at pH 7.4 compared to pH 1.2 [57]

Chitosan-Pectin	• Increasing the bioavalability and residence time of preparations [50] • The polyelectrolyte complex between chitosan and anionic polymers enhances the ability to inhibit drug release [37]	Vancomycin	• Pectin-chitosan polymers have been shown to reduce and control vancomycin release [54]
Na.Alginate – Carrageenan	• Can improve swelling index and entrapment efficiency of formulated microsphere systems [51] • Maintaining elasticity and swelling index so that it is not fragile [52] • The addition of carrageenan polymers can minimize the burst effect of alginate polymers so that the release of active ingredients can occur in a controlled manner [40]	Ciprofloxacin	• Spherical shape and has a flat surface morphology • Particle size from 1.24 ± 0.006 – 1.72 ± 0.137 µm • There is an increase in drug loading, an increase in entrapment efficiency and a decrease in the value of recovery/*yield* along with an increase in polymer concentration [57]
		Etionamide	The minimum inhibitory concentration (MIC) oftrapped etionamide is much higher than free etionamide because of the slow release of the drug [62]
Chitosan-Xanthan gum	• Chitosan is very soluble in acidic solutions so that it cannot withstand the release of drugs, so chitosan is combined with xanthan gum. Xanthan gum not only slows the release of the drug and results in a time-independent drug release kinetics, but also results in constant plasma levels of the drug [53] • The chitosan microencapsulation coating formed with the addition of gum guar has better rheological properties [54,55]	Rifampicin	• Shows a highly ordered spherical shape with a smooth, *compact* surface • Average particle size 1.9 - 2.6 µm • The average entrapment efficiency is quite high (70% -83%) • High stability to vesicle aggregation and fusion • Increasing the resistance of the matrix to aerosolization, resulting in a formulation capable of delivering higher amounts of drugs to lower levels of impinger [59]
		Ciprofloxacin	• The absorption efficiency was found to increase with an increase in drug concentration reaching about 93.8 ±2.1% • In vitro release studies showed a steady increase in cumulative drug release (96.1±1.8% to 150 minutes) • Cytotoxicity showed no cell toxicity, highest cell viability 97 ±0.5% at a concentration of 50 µg/mL • Ciprofloxacin with a polymer matrix showed its ability to inhibit gram-positive and negative bacteria with a higher inhibitory zone diameter than free ciprofloxacin [60]
Na.Alginate-Pectin	Microcapsules containing only alginate do not sufficiently produce better drug encapsulation so that the addition of pectin with low methoxy to the polymer matrix can increase the efficiency of encapsulation [61]	N/A	N/A

Targeted drug delivery to the lungs has evolved into one of the most researched systemic or local drug delivery approaches. The use of drug delivery systems for the treatment of lung diseases is increasing due to their potential for localized topical therapy in the lungs. This route also allows for more specific drug deposition at high concentrations in the diseased lung thereby reducing the overall amount of drug administered to the patient (10-20% of the amount orally), as well as increasing local drug activity and reducing systemic side effects and first-line metabolism [4,43]. Another advantage is that the same therapeutic effects can be achieved at much lower doses than those obtained through oral administration without the influence of any conditions that can reduce patient compliance, such as poor pain. Drug substances ranging from small molecules to large peptide molecules can be delivered for inhalation formulations [44]. Pulmosphere is a hollow porous particle with low particle density <0.1 gram / ml and excellent redispersibility, made by supercritical fluid condensation technology [45]. The use of polymer combinations is necessary to fulfill the shortcomings of each polymer used such as enhancing solubility, increasing bioavailability, improving encapsulation efficiency and providing a more controlled drug release thus providing better treatment effectiveness. Table 4 summarizes the various combinations of polysaccharide polymers with antibiotics used for the treatment of tuberculosis.

4. Current and Future Development

Microsphere delivery systems, which use polymers as the formers, are an effective and promising technique for drug therapeutic applications to improve drug solubility and targeting ability to the desired site. Microsphere delivery systems generally exhibit long half-life, high stability, low immunogenicity, and specific targeting. In the future, approaches using

computational methods that provide detailed information on molecular interactions, physicochemical properties of drugs, and carriers are also needed.

5. Conclusion

The pulmonary drug delivery system for the treatment of tuberculosis has several advantages such as better targeting of infected alveolar macrophages, rapid onset of action due to large surface area, increased bioavailability of the drug in the targeted area, better average residence time and lower dosing frequency, good tolerance with biodegradable excipients, then the treatment approach without the use of needles so that it is non-invasive for self-administration and becomes a viable route for the administration of relatively large amounts of the drug.

6. Conflicts of Interest

There are no conflicts to declare.

7. Funding sources

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