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Formulation and Evaluation of Vancomycin Loaded Microsphere for the Treatment of Septic Arthritis

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Abstract

Appropriate delivery of drug to the sites is crucial via conventional drug delivery system. A controlled and sustained release system microsphere loaded with vancomycin was developed by using porous and pH-responsive poly(lactic-co-glycolic acid) (PLGA). The microspheres, developed through the W/O/W double-emulsion evaporation method, comprised a PLGA-based shell and a core containing Vancomycin.To promote colon targeting of the systems was directly coated with poly(methacrylic acid-co-methyl methacrylate) (Eudragit-S100). The optimized preparation conditions for PLGA–Eudragit–Van microspheres were investigated and characterized, and it demonstrated as a porous microstructures with regular shape and uniform size and the characteristic of controlled drug release, The results of the study showedits further utilization for the treatment of septic arthritis.

Keywords:Polylactic-co-glycolic acid,Targeted drug delivery system, Eudragit-S100, Septic Arthritis

Introduction

Septic arthritis is a painful joint infection and a detrimental RA condition. The disease is caused by the direct introduction or invasion of pathogens (Staphylococcus aureus) migrating from another part of the body via the bloodstream. The pathogenesis of this disease is based on the interaction with the host's immune system and the attachment of pathogens. The infestation of bacteria in the joint space destroys the joint within a few days. Risk factors for septic arthritis include previous rheumatic diseases, low socioeconomic status, leg ulcers, diabetes, previous surgery, alcohol abuse, viral infections, and use of corticosteroids.

Rheumatoid arthritis (RA) is an autoimmune disease. In 2002, the prevalence rate was between 0.5% and 1% of the population. RA primarily affects the lining of the synovial joints and can lead to progressive disability, premature death, and socioeconomic distress. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limitation of range of motion. Early diagnosis is considered a key improvement index for the most desirable outcomes (i.e., less joint destruction, less radiographic progression, no functional impairment, and remission without disease-modifying antirheumatic drugs (DMARDs)) as well as

cost-effectiveness. The first 12 weeks after the onset of early symptoms is considered the optimal therapeutic window. Poorly controlled or severe disease is at risk of developing extra-articular manifestations such as keratitis, pulmonary granulomas (rheumatoid nodules), pericarditis/pleurisy, small-vessel vasculitis, septic arthritis, and other symptoms.

Although there is currently no cure for RA, the treatment strategy aims to accelerate diagnosis and quickly achieve low disease activity state (LDAS). There are many composite scales that measure disease activity, such as the Disease Activity Score using 28 joints (DAS-28), the Simplified Disease Activity Assessment Index (SDAI), and the Clinical Disease Assessment Index (CDAI). To achieve complete suppression of disease activity (clinical remission), rheumatologists must continually and accurately monitor disease activity and adjust treatment regimen accordingly.

A worse form of RA, septic arthritis is a painful joint infection that can result from germs getting into your bloodstream from another part of your body. Septic arthritis results from direct introduction or invasion of pathogens. The pathogenesis of this disease is based on the interaction with the host's immune system and the attachment of pathogens. The infestation of bacteria in the joint space destroys the joint within a few days. The most common bacterium that causes joint infection is Staphylococcus aureus. Risk factors for septic arthritis include previous rheumatic diseases, low socioeconomic status, leg ulcers, diabetes, previous surgery, alcohol abuse, viral infections, and use of corticosteroids. Antibiotics are the main drugs used to treat septic arthritis. However, the choice is based on the likelihood that the organisms will develop septic arthritis. There are more and more rheumatism patients. Chronic steroid use is one of the most important predisposing factors. The clinical picture of septic arthritis differs in immunocompromised patients from that in patients with rheumatoid arthritis

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases. The colon specific drug delivery system (CSDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability and finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers, great sensitivity to absorption enhancers, reduced digestive enzymatic activity and the presence of large amounts of enzymes for polysaccharides (e.g. β-D-glucosidase, β-D-galactosidase, amylase, pectinase, dextranase, etc.), which are secreted by a large number and variety of colonic bacteria. An interesting approach for colon-specific drug delivery is based on the use of polysaccharides (e.g. pectin, dextran, inulin, etc.) specifically degraded by colonic bacteria (enzymatically controlled delivery systems). Pectin is an anionic polysaccharide present in the

cell wall of most plants, consisting mainly of D-galacturonic acid and its methyl ester linked via αglycosidic bonds.

Microspheres

Microspheres is spherical multiparticulated novel drug delivery systems with a diameter of 1–1000 μm composed of biodegradable proteins or polymers with particle size <200μm. Various techniques are used to prepare microspheres that provide multiple options to enhance the efficacy of a drug with reduced toxicity.

Biodegradable polymers are frequently used for the development of microsphere matrixes such as polylactic acid and copolymer of lactic acid and glycolic acid. Apart from them, there is an extensive range of microspheres prepared from albumin, albumin dextran sulphate, and fibrinogen. Administration of medication via microparticulate systems is advantageous because microspheres can be ingested or injected; they can be tailored for desired release profiles and used for site-specific delivery of drugs and in some cases can even provide organ-targeted release. So far, a series of phytomedicines such as rutin, camptothecin, zedoary oil, tetrandrine, quercetin and Cynara scolymus extract have been successfully exploited through this delivery system. In addition, reports on immune microsphere and magnetic microsphere are also common in recent years. Immune microsphere possesses immune competence because the antibody and antigen were coated or adsorbed on the polymer microspheres

There are two types of microspheres: monolithic-type (matrix-type) and reservoir-type (capsular). The capsular type of microspheres is also called microcapsule. Microspheres are able to incorporate a wide range of different drugs, they are biocompatible and can be prepared from biodegradable particles. Prolonged release of acyclovir was achieved by its encapsulation within poly(d,l-lactide-co-glycolide) enabling reduction of the dose of acyclovir. Also, there are attempts to use microspheres as delivery systems for vaccines in order to sustain immunological challenge

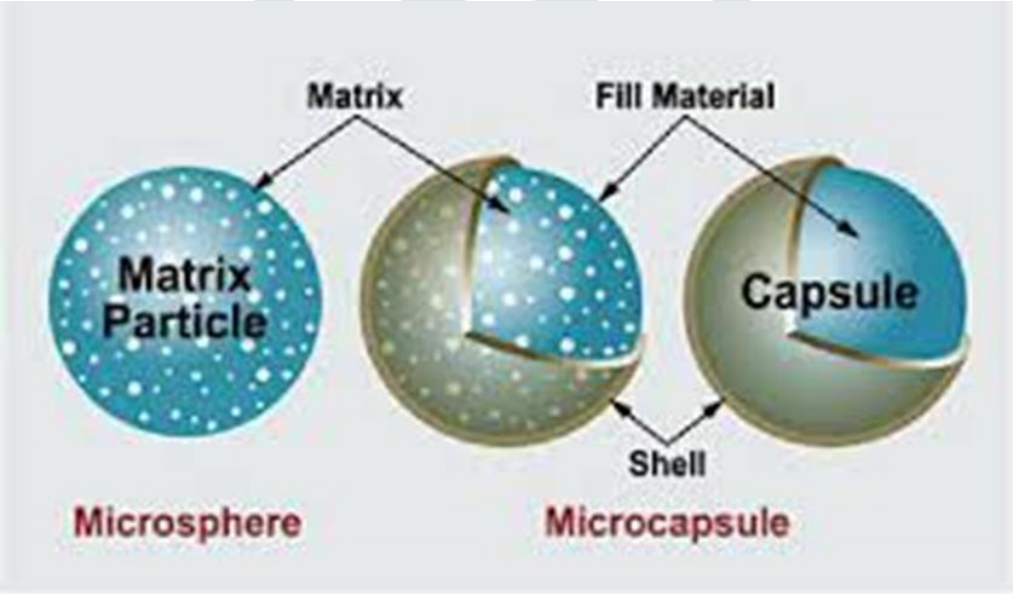

Figure 1: Microsphere and Microcapsule

Types of Microspheres:

a- Polymeric Microsphere
b- Bio adhesive Microsphere
c- Magnetic Microsphere
d- Floating Microsphere
e- Radioactive Microsphere

Materials Used in the Preparation of Microsphere:

Polymers are mainly use for the preparation of microsphere.

They are classified into two types:

1.Natural Polymers: Natural polymers are obtained from different sources like a) Carbohydrates b) Proteins c) Chemically modified Carbohydrates Carbohydrates: Agarose, Carrageenan, Chitosan, Starch Proteins: Albumin, Collagen and Gelatin Chemically modified carbohydrates: Poly dextran, Poly starch

2. Synthetic Polymers: It is divided into two types.

a) Biodegradable polymers b) Non-biodegradable polymers

a) Biodegradable polymers: Lactides, glycolides& their copolymers, Poly anhydrides, poly alkyl cyano acrylates

b) Non-biodegradable polymers: Poly methyl methacrylate (PMMA), glycidyl methacrylate, acrolein, epoxy polymers.

Method of Preparation

The laboratory-scale nanoparticle preparation methods can be classified as:

1. Solvent evaporation method
2. Single emulsion techniques
3. Double emulsion techniques
4. Phase separation coacervation technique
5. Spray drying
6. Solvent extraction

Drug Profile:

Generic Name: Vancomycin HCl

Brand Name: Firvanq

Class: Glycopeptide Antibiotics

IUPACName: C66H76Cl3N9O24

Molar Mass: 1,449.3 g/mol

Half-life: 7.8 h.

Clearance:2.64 l/h

Structure:

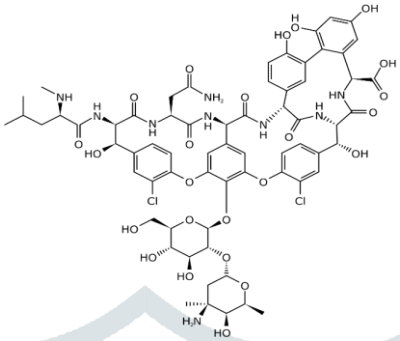

Figure 2: Molecular structure of Vancomycin

About Drug: Vancomycin is a tricyclic glycopeptide antibiotic, available in dosage forms IV, oral (poorly absorbed). VANCO is an amphoteric molecule containing three phenolic groups (pKa1 = 10.6; pKa2 = 10.3; pKa3 = 9.4), a carboxyl group (pKa4 = 2.5) and two amino groups (pKa5 = 8.6; pKa6 = 6.8) [14] and active against a large number ofmultiresistant Gram-positive bacteria. It is preferred first-line therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection. The major side effects of drug includes diarrhoeahearing loss, kidney problems, low potassium level

Mechanism of Action: The bactericidal action of vancomycin inhibits of cell-wall biosynthesisalters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi.

Figure 3: Marketed formulation of Vancomycin

Conclusion: The microsphere of Vancomycin was successfully developed. Van and Eudragit can be loaded into PLGA under optimal process conditions to create PLGA–Eudragit–Van microspheres.The other drug release

and morphological factorsof the microspheres were systematically evaluated. The release of drug against the standard strain of S. aureus was successful.

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