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POLYMERIC NANOPARTICLES: A PROMISING TOOL FOR THE TREATMENT OF DYSLIPIDEMIA

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ABSTRACT

Polymeric nanoparticles (NPs) are a promising platform for drug delivery in various biomedical applications. These nanoparticles, ranging from 1 to 1000 nm, can contain active substances either surface-adsorbed onto the polymeric core or trapped inside it. Both nanocapsules and nanospheres, which are identified by their morphological structures, are referred to as nanoparticles. They are typically fabricated from biocompatible and biodegradable polymers like polylactic-co-glycolic acid (PLGA), chitosan, or PEG. The synthesis of polymeric nanoparticles involves techniques like solvent evaporation, emulsification/solvent diffusion, the inotropic gelation method, emulsification/reverse salting-out, and nanoprecipitation, allowing precise control over particle size, shape, and drug-loading capacity. Surface modifications with targeting ligands or stimulus-responsive moieties can enhance therapeutic efficacy while minimizing off-target effects. Polymeric nanoparticles offer advantages over conventional drug delivery systems, including prolonged circulation times, sustained drug release kinetics, and protection of encapsulated drugs from degradation. Dyslipidemia, characterized by abnormal lipid levels in the bloodstream, is a major risk factor for cardiovascular diseases. They offer a controlled and targeted delivery platform for simvastatin, a lipid-lowering agent, which faces challenges such as poor solubility and limited bioavailability. Review articles state that polymeric nanoparticles are loaded with simvastatin, highlighting their potential benefits in improving drug stability, solubility, and bioavailability. Review articles highlighted that *In vitro* studies showed sustained release of simvastatin over an extended period and minimal cytotoxicity to cells, In vivo pharmacokinetic and pharmacodynamic studies in animal models of dyslipidemia revealed enhanced drug bioavailability and lipid-lowering efficacy compared to free simvastatin.

Key words: Polymeric nanoparticles, Chitosan, Emulsification/solvent diffusion, Inotropic gelation method, Nanoprecipitation, Dyslipidemia, Simvastatin.

1 INTRODUCTION

1.1 Dyslipidemia

The imbalance of lipids, including triglycerides, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL-C), and cholesterol, is known as dyslipidemia. This disorder can be inherited, brought on by diet, or result from tobacco use. It may result in major side effects, like cardiovascular disease. The assessment and treatment of dyslipidemia are covered in this activity, which also emphasizes the importance of the interprofessional team in enhancing patient care.[1]

The intestines absorb lipids, such as triglycerides or cholesterol, which are then transported throughout the body by lipoproteins for the synthesis of bile acid, the production of steroids, and energy. Triglycerides, high-density lipoprotein (HDL), low-density lipoprotein cholesterol (LDL-C), and cholesterol all play major roles in these pathways. Dyslipidemia can result from an imbalance of any of these components, whether due to organic or nonorganic causes.[1]

Traditionally, they are identified by elevated blood levels of triglycerides, cholesterol, or both, along with elevated levels of related lipoprotein species. Increased atherosclerotic cardiovascular disease (ASCVD) risk is the most frequently reported clinical consequence of dyslipidemia. This condition is linked to elevated levels of total and low-density lipoprotein (LDL) cholesterol (C), triglycerides (TGs), and lipoprotein(a) (Lp(a)), as well as depressed levels of high-density lipoprotein (HDL)-C. Obesity and type 2 diabetes, in particular, are common secondary predisposing factors. Rare dyslipidemias are also linked to additional clinical outcomes, such as hepatosteatosis, pancreatitis with severe elevations in TGs, and deficiencies in fat-soluble vitamins in individuals whose production of apolipoprotein (apo) B-containing lipoproteins is genetically compromised. Research on dyslipidemias is a growing and active field. Recent studies have shed light on their genetic and molecular roots, described their role in the development of atherosclerosis, and clarified how pharmacologic treatments can reduce the risk of ASCVD in those who are affected. The range of management options available for dyslipidemias is also growing.[2]

Table 1: Classification based on total cholesterol, LDL, HDL, and Triglyceride [3-4]

Total cholesterol	
<200mg/Dl	Desirable
200-239mg/Dl	Borderline high
≥/240mg/Dl	High
LDL cholesterol	
<100mg/Dl	Optimal
100-129mg/Dl	Near or above optimal
130-159mg/Dl	Borderline high
160-189mg/Dl	High
≥/190md/Dl	Very high
HDL cholesterol	
<40mg/Dl	Low
≥/60mg/Dl	High
Triglycerides	
<150mg/Dl	Low
150-199mg/Dl	Borderline high
200-299mg/Dl	High
≥/500mg/Dl	Very high

2 PATHOGENEIS OF DYSLIPIDEMIA

Dyslipidemia contributes to the process of atherosclerosis, which results in cardiovascular disease. Dyslipidemia-related cholesterol is oxidized, which speeds up the description of endothelial selectin (E-selectin) and intercellular adhesion molecule (ICAM)-1 for monocyte adhesion. This, in turn, causes a sequence in monocyte influx and cytokine production. In order to further encourage the influx of monocytes, the monocytes differentiate into macrophages and produce the protein Monocyte Chemoattractant Protein (MCP)-1. Moreover, monocytes release oxidizing substances that promote the oxidation of cholesterol and synthesize cytokines like interleukin (IL)[6]. After absorbing oxidized cholesterol, macrophages develop into foam cells, which are then deposited on the blood vessel walls. This process leads to the development of plaque and atherosclerosis. Dyslipidemia increases the risk of atherosclerosis and cardiovascular disease in this way.

The extracellular matrix of the subendothelial space is thought to be the source of atherosclerotic lesions, where plasma low-density lipoprotein (LDL) is retained after passing through the endothelial cell layer. Once inside the artery wall, LDL undergoes non-enzymatic glycation and oxidation, which chemically alter it. The slightly oxidized LDL then draws monocytes into the artery wall.

Afterwards, these monocytes develop into macrophages, which raise LDL oxidation. An atherosclerotic plaque's fibrous cap, which shields the underlying core of lipids, collagen, calcium, and inflammatory cells like T lymphocytes, is the result of repeated damage and repair. In order to prevent plaque rupture and the ensuing coronary thrombosis, the fibrous plaque must be maintained.

Given that endothelial dysfunction and the induction of the vascular inflammatory response are closely linked to the increased generation of Reactive Oxygen Species (ROS), oxidative stress is considered to be one of the fundamental pathogenetic processes of atherosclerosis. Accelerated generation of ROS is linked to common conditions that are also recognized as cardiovascular risk factors that predispose to atherosclerosis, such as smoking, diabetes, high blood pressure, and hypercholesterolemia. Another name for atherosclerosis is an inflammatory condition of the medium and large arteries. Since cytokines are present at all stages of atherosclerosis, they have a significant impact on the pathophysiology of this condition. The pro-atherogenic cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) are produced by lymphocytes, natural killer cells, macrophages, and vascular smooth muscle cells. During the atherosclerotic process, TNF-α and IL-1 stimulate the description of cytokines, adhesion molecules, and the migration and mitogenesis of vascular smooth muscle and endothelial cells on the vascular wall.[5]

3 CLASSIFICATION OF DYSLIPIDEMIA

Additionally, subdivision may be based on biochemical alterations such as isolated elevated TC or TG, low isolated HDL cholesterol levels, and, finally, concurrently elevated TC and TG linked to low HDL cholesterol levels (mixed or combined).

Primary Dyslipidemia
Combined Dyslipidemia
Secondary Dyslipidemia

3.1 Primary Dyslipidemia

The term "primary dyslipidemia" (also known as "hyperlipidemias") refers to a diverse group of diseases marked by noticeably elevated levels of TG, LDL, or, less frequently, both.

3.1.1 Hypertriglyceridemia

3.1.2 Hypercholesterolemia

3.1.3 HDL decrease

3.2 Combined Dyslipidemia

Genetically complex combined familial hyperlipidemia, a prevalent form in pediatrics, is characterized by moderate to severe increased TG levels and low HDL levels. It is caused by genetic variations, polymorphism effects, and external stimuli.It affects 30% to 60% of adolescents associated with obesity. Diagnosis requires at least two first-degree family members with LDL or TG levels greater than p90.

3.3 Secondary Dyslipidemia

These are brought on by exogenous factors that alter lipid metabolism, and they are occasionally linked to genetic predisposition (genes with little effect on an individual basis). They can be categorized based on which of the following variations they promote:

3.3.1 Hypercholesterolemia

3.3.2 Hypertriglyceridemia

3.3.3 Low HDL levels. [6]

4 COMPLICATIONS OF DYSLIPIDEMIA

4.1 Atherosclerosis

Atherosclerosis is a common cardiovascular disease caused by the accumulation of fat, cholesterol, and calcium in arterial linings[7], resulting in fibrous plaques with cholesterol crystals, calcified outer layers, and an atheroma.

4.2 Coronary Artery Disease (CAD)

Coronary Artery Disease (CAD) is primarily caused by atherosclerosis, which restricts blood flow and oxygen supply to the heart, often linked to elevated lipid profiles.[8]

4.3 Myocardial Infarction (MI)

Myocardial infraction occurs when cardiac arteries are cut off, causing heart damage or death. Heart attacks are common, and 25% of myocardial infarction survivors have high blood cholesterol. [9]

4.4 Angina Pectoris

Angina is chest pain, discomfort, or constriction indicating a hidden cardiac problem, often caused by coronary artery blockage, rather than a disease itself.

4.5 Ischemic stroke or Cerebrovascular Accident (CVA)

Astroke occurs when blood flow to the brain is disrupted, leading to brain cell death and dysfunction. A 15% reduction in total and LDL cholesterol can significantly lower the risk of a first stroke. [10]

5 TREATMENT THERAPY FOR DYSLIPIDEMIA

5.1 Non – Pharmacological Therapy

The objectives of dietary therapy are to decrease the intake of total fat, saturated fatty acids, and cholesterol progressively and to achieve a desirable body weight.

1. Reduced saturated and total fat intake to 7% and 23 to 35% of daily calories, respectively.
2. Optimized dietary cholesterol to less than 20 mg per day.
3. Eating 20 to 30 grams a day of soluble fiber, which is found in oats, beans, and certain fruits.
4. Increase intake of plant sterols, substances found in nuts, vegetable oil, corn, and rice, to 2 to 3 g daily. [11]

5.2 Pharmacological Therapy

Classification of Hypolipidemic drugs –

1. HMG-CoA reductase inhibitors (statins): Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, and Pitavastatin.
2. Bile acid sequestrants: cholestyramine, colestipol, and colesevelem

3. Lipolysis and triglyceride synthesis inhibitor: Nicotinic acid
4. Lipoprotein lipase activators (PPAR alpha activator: fibrates): Gemfibrozil, Bezafibrate, and Fenofibrate
5. Sterol absorption inhibitor: Ezetimibe.[12]

6 DRAWBACKS OF AVAILABLE TREATMENT

❖ The most common side effects that can occur with the use of Simvastatin include:

- Pain in the stomach area, Nausea, heartburn, constipation, headache, weakness or lack of energy, muscle pain, memory loss or forgetfulness, confusion, Inability to fall asleep

❖ Serious side effects: serious side effects and their symptoms can include the following:

- Muscle problem symptoms can include
  - Muscle pain, muscle tenderness, and muscle weakness
- Liver problem symptoms can include
  - Dark-colored urine, Yellowing of your skin or white tissue of your eyes
- Stomach problem symptoms can include –
  - pain in the upper right part of the stomach area, nausea, loss of appetite
- Central nervous system problem symptoms can include
  - lake of energy, weakness, and extreme tiredness.[13]

7 DIFFERENT NANO CARRIERS USED IN DRUG DELIVARY SYSTEM

Different nanocarrier preparations have been developed to decrease harmful side effects and increase therapeutic efficacy. Nanocarriers offer enhanced drug localization and cellular uptake, along with continuous, direct, and controlled drug release to cancerous cells. Automated nanoparticles can distinguish between cancerous and healthy cells and transfer drugs with precision while avoiding contact with healthy cells. Additionally, the development of nanocarrier-based drug delivery systems has allowed for the overcome of a number of disadvantages, such as chemo resistance, low oral bioavailability, decreased solubility, narrow therapeutic indices, and systemic toxicity. [14-16]

With the development of nanotechnology, a wide range of nanocarriers with significant physical and chemical properties as well as nano-sized effects, including solid lipid nanoparticles, micelles, dendrimers, polymeric nanoparticles, quantum dots, and magnetic nanoparticles, are now possible **shown in fig 1.** The results of numerous studies on cancer have generally confirmed that, when compared to free drugs, nanoparticle-based drug delivery systems with increased bioavailability and minimal side effects embrace favorable anticancer effects.[17-19]

7.1 Nanocarriers Developed from Polymer

In order to prepare nanocarriers, a variety of polymers are used. The active therapeutic agents are either covalently bound to the polymeric matrix or physically entangled with it. The synthesized polymeric systems may resemble a complex, branched macromolecule, capsule, or amphiphilic system. The creation of nanocarriers involves the use of both synthetic and natural polymers.

7.2 Micelles-based Delivery Systems

Micelles, made of amphiphilic block copolymers, are ideal for intravenous administration due to their hydrophobic cavity and outer hydrophilic shell. They can be enriched with drug molecules through physical encapsulation or chemical covalent attachment.

7.3 Lipid-based Drug Carriers

Liposomes, a lipid-based nanocarrier, have been widely used in nanomedicine since 1965. They are effective drug delivery vehicles due to their easy breakdown and ability to encapsulate both lipophilic and hydrophilic substances. Polyethylene glycol coating enhances their stability.

7.4 Nanoparticles Developed from Solid Lipids

Solid lipid-derived nanoparticles are spherical, colloidal carriers of synthetic or natural lipid-based drug delivery systems, known for their low toxicity and biocompatibility.

7.5 Quantum Dots

Semiconductor quantum dots are used in disease treatment due to their biocompatibility, water solubility, and ability to act as fluorescent probes. Surface modification enhances their absorption spectra and optical properties.

7.6 Dendrimers

Dendrimers are synthetic polymeric macromolecules used in nanoscale drug delivery systems. They have customizable surfaces, monolithic size, internal cavities, and multivalences.

Conjugated polyamidation dendrimers are commonly used as scaffolds, with a unique exterior property allowing conjugation with multiple molecules.

7.7 Carbon Nanotubes

Carbon nanotubes are used in biological fields for diagnostic purposes, such as detecting DNA, proteins and distinguishing protein types in serum samples, but pose health risks due to their insoluble delivery systems.

7.8 Magnetic Nanoparticles

Magnetic particles (MNPs) are nanostructures ranging from 1-10 nm, composed of pure metals like iron, cobalt, nickel, and manganese. They are categorized into paramagnetic, ferromagnetic, diamagnetic, anti-ferromagnetic, and super-paramagnetic materials.[20]

Figure 1: Different nano carriers used in drug delivery system

8 POLYMERIC NANOPARTICLES

The properties of polymeric nanoparticles (NPs), which stem from their small size, have garnered significant attention in recent years. The potential for controlled release, the capacity to shield drugs and other molecules with biological activity from the environment, the enhancement of bioavailability, and the therapeutic index are among the benefits of using polymeric NPs as drug carriers.

Particles with sizes ranging from 1 to 1000 nm are known as polymeric nanoparticles (NPs), and they can contain active substances that are either surface-adsorbed onto the polymeric core or trapped inside it.

Both nanospheres and nanocapsules, which have different morphologies, are included in the term "nanoparticle" **shown in fig 2.** The composition of nanocapsules consists of an oily core that dissolves the drug and a polymeric shell that regulates the drug's release profile from the core. The drug can be adsorbed onto the surface of nanospheres or retained inside them thanks to their continuous polymeric network structure. These two categories of polymer NPs are identified as a matrix system (nanospheres) and a reservoir system (nanocapsules).[21]

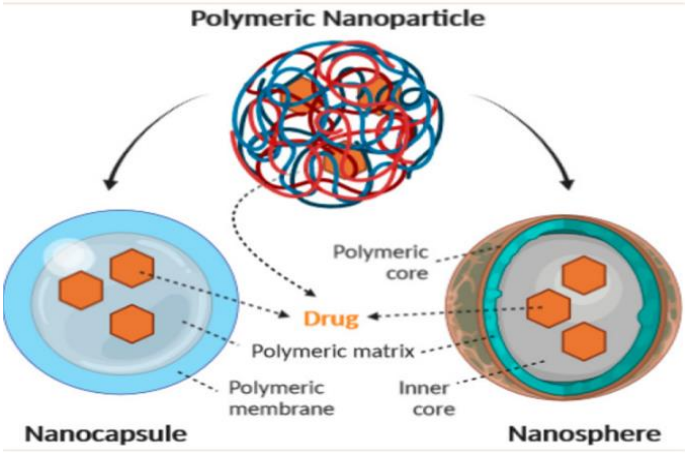

Figure 2: Schematic representation of the structure of nanocapsules and nanospheres.[21]

The NPs derived from chitosan are less toxic, simpler to make, stable, biocompatible, and biodegradable. The US FDA has classified chitosan, a polymeric substance that is found in nature and has high biocompatibility and biodegradability, as GRAS (Generally Recognized as Safe).[22] Chitosan nanoparticles (NPs) can be prepared without the use of hazardous organic solvents because of their solubility in acidic aqueous solutions. Furthermore, these nanoparticles can release the chemicals they have encapsulated in a controlled way.[23] Similar to cellulose in structure, chitosan is a polysaccharide derived from chitin that is made via chitin deacetylation.[24]

9 ADVANTAGES OF POLYMERIC NANOCARRIERS:

1. Drug release in a controlled and sustained manner
2. Incorporation of hydrophilic and hydrophobic drugs
3. Tunable chemical and physical properties
4. Use of a lot of biodegradable materials when desired

5. Existence of pH, enzymatic, hydrolytic, etc., sensitive properties when preferred proper polymers
6. Reproducible data when using synthetic polymers
7. Higher stability than lipid-based ones
8. There are many methods to prepare them. [25]

10 METHODS OF PREPARATION

In general, two primary methods are used **shown in fig 3.**

Table 2. Methods of preparation [21]

Polymeric Nanoparticles	Preparation Methods
Nanospheres	Solvent evaporation, Emulsification/solvent diffusion, Emulsification/reverse salting-out, Nanoprecipitation, Inotropic gelation method
Nanocapsules	Nanoprecipitation

10.1 Solvent Evaporation

Solvent evaporation is a method for preparing polymeric nanoparticles from a preformed polymer. It involves dissolving the polymer in a polar organic solvent and evaporating the solvent through magnetic stirring. The nanoparticles can be stored for long-term storage or used in biomedical applications.

10.2 Emulsification/Solvent Diffusion

This method creates an o/w emulsion between a partially water-miscible solvent containing polymers and drugs and an aqueous solution with a surfactant. Dilution causes solvent diffusion, producing colloidal particles. Commonly used for producing nanospheres and nanocapsules, it eliminates the need for high aqueous phase volumes.

10.3 Emulsification/Reverse Salting-Out

The emulsification/solvent diffusion method is a modification of the salting-out method, involving separating a hydro-miscible solvent from an aqueous solution to form nanospheres. The emulsion is prepared under intense stirring, diluted with deionized water or an aqueous solution, and cross-flow filtered. The nanospheres' dimensions range from 170 to 900 nm.

10.4 Nanoprecipitation

The solvent displacement method is a technique for preparing polymeric nanoparticles (NPs) with dimensions around 170 nm. It involves two miscible solvents, with the polymer dissolved in a miscible organic solvent and then dissolved in a water-miscible solvent. Surfactants are added for stability.As the solvent diffuses out of the nanodroplets, the polymer precipitates in the form of nanocapsules or nanospheres.[21]

10.5 Ionic Gelation Method

This is a general technique for creating microparticles, or NPs, that relies on the electrostatic interaction of opposite charge types containing a minimum of one polymer while being stirred mechanically.[26] NPs were synthesized using the following materials: polymers (CS, carboxymethyl cellulose, collagen, dextran, fibrin, gelatin, gellan gum, hyaluronic acid, sodium alginate, pectin), anions (Ba, Ca, Mg, Cu, Zn, and Co), sulfate salts (Na, Mg, or octyl-, lauryl-, hexadecyl-, cetostearyl-), polyphosphate salts (pyro-, tri-, tetra-, octa-, and hexameta-), ferrocyanide, and ferricyanide salts. The most widely used ones are TPP (anion) and CS (polymer-cation). Moreover, medications or bioactive compounds can be encapsulated within NPs to boost their effectiveness.[26-28]

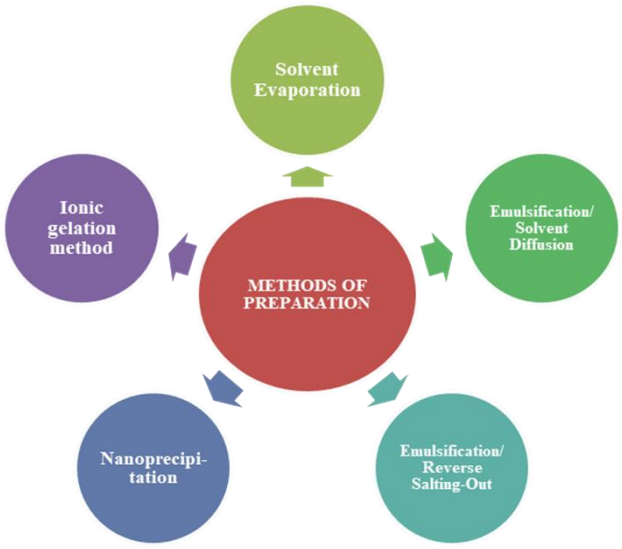

Figure 3: Different methods of preparation

11 EVALUATION

11.1 Morphology

Scanning and transmission electron microscopy (SEM and TEM) and atomic force microscopy (AFM) are commonly used to analyze the shape and size of polymeric nanoparticles, often combined with cryofracture techniques, to determine nanocapsule and nanosphere thickness.

11.2 Particle Size Distribution

Polymeric nanoparticles (NPs) have diameters between 100-300 nm, with polydispersity near zero. Size measurements can be done using techniques like TEM, SEM, and AFM. Factors influencing NP size include oil composition and drug dosage, leading to larger particles with a wider size distribution.

11.3 Zeta Potential

The zeta potential (ζ) measures particle surface charge, influenced by interface changes, functional group dissociation, ionic species adsorption, and the solvation effect. It's determined using Doppler techniques, is crucial for colloidal suspension stability and drug association, and can be customized with surfactants or coatings.[21]

11.4 Drug Loading

The drug molecules in hydrophilic drugs are embedded in a polymeric crosslinked matrix and are found in the aqueous phase. Drug payload, percent drug incorporation, and drug release may be determined and regulated by drug-polymer affinity and interaction.Certain suitable organic solvents are needed for the encapsulation of drugs in hydrophilic polymers, depending on the formulation and procedural aspects.

11.5 *In vitro* Release Profile of Lipophilic Drugs

The *in vitro* release behavior of lipophilic compounds is influenced by the polymeric colloidal system's internal structure. Drug partitioning from nanocapsules depends on solubility in the oily core and receptor medium. Lipophilic compounds *in vitro* release properties are primarily polymer erosion with a biphasic release pattern.

11.6 *In vitro* Release Profile of Hydrophilic Drugs

Hydrophilic molecules can be trapped in a polymer matrix or adsorbed onto nanospheres. Drug release from nanoparticles depends on drug binding, polymer degradation rate, and nanoparticle composition.[29]

12 APPLICATION

Table 3: Application of polymeric nanoparticles[30-41]

S.No.	Polymer /lipid	Drug	MOA	Uses	Ref.
1	Eudragit	Atorvastatin	HMG-CoA reductase	Hypo lipidemic agent	30
2	Chitosan/ alginate	Lovastatin	HMG-CoA reductase	Hypo lipidemic agent	31
3	Polylactic-co-glycolic acid (PLGA)	Simvastatin	HMG-CoA reductase	Hypo lipidemic agent	32
4	Polylactic-co-glycolic acid (PLGA)	Pravastatin sodium	HMG-CoA reductase	Hypo lipidemic agent	33
5	Gum Rosin, chitosan	Fluvastatin sodium	HMG-CoA reductase	Hypo lipidemic agent	34
6	Ethyl cellulose	Atorvastatin	HMG-CoA reductase	Hypo lipidemic agent	35
7	Alginate/ chitosan	Lovastatin	HMG-CoA reductase	Hypo lipidemic agent	36
8	Chitosan	Pravastatin	HMG-CoA reductase	Hypo lipidemic agent	37
9	Chitosan	Atorvastatin	HMG-CoA reductase	Hypo lipidemic agent	38
10	Gum rosin	Fluvastatin sodium	HMG-CoA reductase	Hypo lipidemic agent	39
11	Polylactic-co-glycolic acid (PLGA)	Atorvastatin	HMG-CoA reductase	Hypo lipidemic agent	40
12	Chitosan	Atorvastatin calcium	HMG-CoA reductase	Hypo lipidemic agent	41

13 CONCLUSION

Polymeric nanoparticles present a promising avenue for addressing dyslipidemia, a prevalent risk factor for cardiovascular diseases. Through their unique properties, including their small size, high surface area, and tunable surface chemistry, polymeric nanoparticles offer several advantages for the targeted delivery of lipid-lowering agents. These nanoparticles can encapsulate lipophilic drugs, protecting them from degradation and improving their bioavailability. Furthermore, their ability to selectively accumulate in target tissues enhances drug efficacy while minimizing systemic side effects. Additionally, polymeric nanoparticles can be used for sustained release kinetics, allowing for prolonged therapeutic effects and reduced dosing frequency. This not only improves patient compliance but also enhances the overall therapeutic outcome. Overall, polymeric nanoparticles hold

great promise as a tool for revolutionizing the treatment of dyslipidemia, offering targeted and efficacious therapy with the potential to mitigate the burden of cardiovascular diseases worldwide.

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