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APPLICATIONS OF NANOPARTICLES FOR HYPERLIPIDEMIA- A REVIEW

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ABSTRACT

Hyperlipidemia is a leading risk factor causing atherosclerosis and leads to the development and progression of cardiovascular diseases. Many antihyperlipidemic drugs having several disadvantages of low water solubility, poor bioavailability thus, there is a considerable need for the development of efficient delivery methods and carriers. The present review focuses on the importance and role of various nanoparticulate systems as carrier for antihyperlipidemic drugs for the treatment of hyperlipidemia.

KEYWORDS

Nanoparticles, Bioavailability, Drug delivery and Hyperlipidemia.

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INTRODUCTION

Hyperlipidemia is a medical condition generalized by raised levels of total Cholesterol and triglycerides. It is commonly characterized by an increased flow of free fatty acids (FFA), increased triglycerides, cholesterol esters and phospholipids and plasma lipoproteins including very low-density lipoprotein and reduced high-density lipoprotein levels.

Hyperlipidemia classification

Primary hyperlipidemia is genetic defects, it may be monogenic: single gene defect or polygenic: multiple gene defect.

Secondary: It is acquired because it is caused by other disorders such as diabetes, nephritis syndrome, chronic alcoholism, hypothyroidism and

the use of drugs such as corticosteroids, beta blockers and oral contraceptives. Secondary hyperlipidemia along with significant hypertriglyceridemia may cause pancreatitis[1].

Classification of formulations for hyperlipidemia and their mechanism of action

The following drugs are used for the treatment of hyperlipidemia: HMG CoA reductase inhibitors, fibrates, cholesterol absorption inhibitors, nicotinic acid group, bile acid sequestrants.

Mechanism of action of various antihyperlipidemic agents

HMG CoA reductase inhibitors (Statins)

They are widely used in the treatment of hyperlipidemia and have resulted in substantial reductions in cardiovascular diseases and all-cause fatality in the prevention of atherosclerotic cardiovascular disease both primary and secondary. The statins function in the endogenous synthesis of cholesterol by inhibiting the rate-limiting enzyme HMG CoA reductase.3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) converts to mevalonate for further synthesis of cholesterol in the presence of HMG CoA and mevalonate, hence, statins function by inhibiting HMG CoA which further leads to a reduction in cholesterol levels and prevention of dyslipidemia[2].

Fibrates

These works by stimulating the peroxisome proliferator activated receptor alfa (PRAP) which regulates the expression of gene products that mediate the effect of High density lipoprotein (HDL) and Triglycerides (TG) as a result, synthesis of folic acid, triglycerides and very low density lipoproteins is reduced which helps to reduce cholesterol levels[3].

Cholesterol absorption inhibitors

Ezetamide is only a synthesized drug that works by inhibiting Niemann-C1-like 1 (NPC1L 1) protein that helps prevent the absorption of dietary cholesterol without altering the absorption of triglycerides, fat-vitamins, and bile acids. In general, cholesterol absorption inhibitors prevent the uptake of cholesterol from the intestine into the blood circulation contributes to compensatory up regulation of low density lipoprotein (LDL) receptors on the cell surface and increased uptake of LDL cholesterol into cells that eventually decreases the blood cholesterol content of LDL[4].

Nicotinic acid group

Its mechanism of action is to reduce hepatic production and release of very low density lipo protein (VLDL). Its lipid-reducing effect results in a reduction of triglycerides and LDL with increased high density lipoprotein (HDL). In pharmacological doses (in grams) niacin reduces peripheral FA release (by inhibiting lipolysis in adipose tissue) into the bloodstream that the liver uses for TG synthesis. This TG is essential in liver for VLDL synthesis, and LDL is also derived in plasma from VLDL. Hence a decline in VLDL production leads to a reduction in LDL levels. The result is a decline in Total cholesterol (TC) and TG while HDL is increased[5].

Bile acid sequestrants

These are anion exchange resins that bind to bile acids and bile salts that are negatively charged. This complex is excreted in feces and thus prevents the reabsorption of bile acids into the liver by enterohepatic circulation as a result, the liver improves denovo production of bile acids from hepatic cholesterol. The resulting decrease in hepatic cholesterol helps to regulate the activity of the LDL receptor and to reduce LDL in the same way as statins[6].

Nanoparticle Carrier System

Nanoparticles in the range of 10-1000nm are known as particulate dispersions or solid particles. The drug is dissolved, trapped in, encapsulated or bound to a layer of nanoparticles. Nanoparticles, nanospheres, or nanocapsules can be collected, depending on the preparation process[7].

Nanoparticles have been used as a functional tool to modify and improve the pharmacokinetic and pharmacodynamic properties of different types of drug molecules. They can be prepared from different polymer, which improves the therapeutic effect and decreases the side effect[8].

The results of using nanoparticles as a drug delivery system have included

1. Particle size and surface characteristics of nanoparticles can be easily manipulated after parenteral administration to achieve both passive and active drug targeting.
2. They are best suited for the various administrative routes.
3. Nanoparticles carry high efficiency.
4. Shelf-stability of drug increases
5. Ability to maintain and control drug release behaviors.
6. Suitable for combination therapy where two or more drug may be co-delivered.
7. Both hydrophobic and hydrophilic drug can be incorporated.
8. The system improves the bioavailability of drugs.
9. Imaging studies can be carried out using them.
10. The development of safer new medicines.

Drawbacks of nanoparticles:

1. The small size and large surface area can lead to the aggregation of particles.
2. Large surface area and small particles easily lead to limited drug loading and burst release.
3. The cost of manufacturing nanoparticles is high, resulting in the overall cost of the product.
4. Solvents are of a toxic nature used in the preparation process.
5. Can give an immune response and allergic reactions to the body.
6. Nanoparticles are difficult to deal with in physical form.

Importance of nanoparticles in treatment of hyperlipidemia

Enhancement of safety and efficacy of drug

Lipid lowering agent, Atorvastatin calcium (AC) is a second-generation 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor for clinical use associated with poor oral bioavailability and serious adverse effects like rhabdomyolysis on chronic administration. To ensure the safety and efficacy of Atorvastatin calcium, biodegradable nanoparticulate approach was introduced with the help of two stabilizers i.e. Vitamin E tocopheryl polyethylene glycol 1000 succinate (Vit E-TPGS) and didodecyl dimethyl ammonium bromide (DMAB). Poly lactide-co-glycolic acid (PLGA) nanoparticles were prepared using a cosolvent approach by emulsion-diffusion-evaporation method.

The safety and efficacy parameters of the prepared nanoparticles against the marketed formulation of high fat diets fed (hyperlipidemic) to rats were evaluated. Atorvastatin calcium nanoparticles were equally effective in comparison to Lipicure, at a 66%-reduced dose in treating hyperlipidemia defined by alterations in plasma Total Cholesterol, Low Density Lipoprotein -Cholesterol, Very Low-Density Lipoprotein -Cholesterol, High Density Lipoprotein –Cholesterol, Plasma Triglyceride in the high fat diet fed rats. In comparison to the marketed formulation nanoparticulate formulation showed no/negligible myotoxicity characterized by lower Blood Urea Nitrogen, Creatinine Kinase, Lactate dehydrogenase and Aspartate amino transferase levels[9].

Prospective use of drugs with decreased toxicity

To inspect the hypolipidemic effects of chitosan nanoparticles (CTS-NP) prepared with rotary evaporation, ionotropic gelation, and spray-drying technique. Male SD (Sprague-Dawley) rats were separated into five groups, a normal control diet group, a high fat emulsions group, CTS control group and CTS-NP groups treated with two different doses of CTS-NP. In rat fed on CTS-NP, CTS-NP was effective in reducing body weight gain and serum lipid levels. Acute toxicity has shown the non-toxicity of chitosan nanoparticles. All of these consequences indicate greater approach on the use of CTS-NP in humans[10].

Improve the efficacy of drugs

Chitosan, a deacetylated derivative of chitin, in animals and humans has been shown to lower cholesterol. Water-soluble chitosan reactivity is higher than chitosan. The study was recommended to explain the effects of water-soluble chitosan nanoparticles on hypercholesteromia caused by

high-fat diet in male spargue dawley rats. Results showed that WSC-NP significantly reduced blood lipids and plasma viscosity and increased the activity of serum superoxide dismutase (SOD). This study suggesting that the WSC-NP may be used to treat hypercholesterolemia. Several studies have shown that chitosan has qualities that lower cholesterol in both animals and humans[11].

Varieties of nanoparticulate carriers with their role in hyperlipidemia treatment

Polymers Nanoparticles

The solvent evaporation process can be used to prepare chitosan nanoparticles loaded with Atorvastatin for sustained release. The significant high first-pass effect results in low oral bioavailability of Atorvastatin calcium (14%) and makes it a major target for sustained oral drug delivery.

Atorvastatin loaded chitosan nanoparticles can be prepared by solvent evaporation method in four different ratios1:1, 1:2, 1:3 and 1:4. 1:4 ratios showed better yield compared to other 3 ratios, according to entrapment and yield efficiency[12].

Supercritical antisolvent (SAS) method used successfully to prepare methanol-based amorphous atorvastatin calcium nanoparticles with a mean particle size of about 152 to 863 nm. Following oral administration of amorphous atorvastatin calcium nanoparticles to rats, the absorption of atorvastatin calcium was significantly increased due to increased dissolution and super saturation properties. Hence, the preliminary results of the study indicated that the preparation of amorphous atorvastatin calcium nanoparticles using Supercritical antisolvent process might be a promising approach to improve the dissolution, super saturation and absorption characteristics of atorvastatin[13].

Nanoparticles containing simvastatin (SV) may be prepared with poly (D, Lactide-co-glycolide) using a nano-precipitation-solvent displacement approach to achieve a better release profile for oral administration with increased efficacy. The efficacy of encapsulation and the ability of drug loading have been improved as the concentration of drugs in polymers increases[14].

Lipidic Nanoparticles

Lipid nanoparticles are being used as one of the systems of choice to improve oral bioavailability of drugs with high first-pass metabolism that are poorly water-soluble[12].

Nano-assisted drug delivery system improves some of the characteristics of the poorly water-soluble product lovastatin, i.e. drug loading performance, stability, effective first-pass penetration of hepatic cells, lower toxicity, faster excretion, maximum plasma concentration and bioavailability. The nano-assisted drug delivery system is therefore an appropriate option for poorly soluble lipophilic drugs[15].

Fenofibrate, a poor water-soluble drug characterized by incomplete oral bioavailability, bitter taste and a tendency to destabilize in aqueous media, may be formulated as lipid nanoparticles. As regards the good solubility of fenofibrate in lipid materials, lipid nanoparticles seemed to be an excellent way to overcome these problems. Lipid nanoparticles have been a reliable way to improve the properties of fenofibrate dissolution and stability[16].

Solid-Lipid Nanoparticles

Solid Lipid Nanoparticles (SLN) is another carrier system used to load the drug for targeting, to improve bioavailability by enhancing its permeability, solubility, and to protect the drug from presystemic metabolism.

Hot homogenization is a great method for the successful incorporation of rosuvastatin calcium loaded solid lipid nanoparticle. Studies showed that increased lipid concentration increases particle size, entrapment efficiency and sustained drug release. In contrast, it may be assumed that the bioavailability could be increased if nanometer range particles were obtained. We can therefore infer that solid lipid nanoparticles improve the bioavailability as a drug delivery function of poor water-soluble and low lipophilic drugs like rosuvastatin calcium[17].

Ultrasonic homogenization is desirable for generating SLN ranging 50-125nm in size. Triglycerides, non-toxic surfactants such as Poloxamer 188 and phosphatidylcholine can be successfully combined with lipophilic drugs such as

atorvastatin. The effectiveness of the trapping and the drug release profile relies on the concentration of the lipid and surfactant mixture used. For SLN, the rate of drug release decreases with a higher lipid concentration, which is explained by the lipid particle physical morphology. The controlled release properties of the SLN formulations decreases as the surfactant concentration decreases from 1.5 percent to 0.75 percent. Stability studies have shown that mean diameters of SLNs remain virtually the same after 40 days of storage at different temperatures, which illustrates the physical stability of these lipid particles. Collectively, these data support SLNs as the effective delivery systems for poorly water-soluble drugs, such as atorvastatin[18].

Table No.1: Work done on various hyperlipidemic nanoparticle[19,12,13,20,16,21]

S.No	Drug	Formulation	Polymer/lipids	Method of preparation	Inference
1	Fenofibrate	Lipid nanoparticles of fenofibrate	Gelucire®50/13	Spray drying process	Efficient way to enhance dissolution and stability properties of fenofibrate. Talented approach to improve surface area and reduced particle size.
2	Atorvastatin calcium	Chitosan nanoparticles	Chitosan	Solvent evaporation method	Effective carrier to design controlled delivery of drugs.
3	Atorvastatin calcium	Amorphous atorvastatin calcium nanoparticles	Chitosan	Supercritical antisolvent process	Talented approach for improving the properties of atorvastatin dissolution, supersaturation and absorption.
4	Simvastatin	Solid- lipid nanoparticles of simvastatin	Compritol ATO888, Precirol ATO5, Geleol, Gelucire 50/13	hot melt emulsification process	Efficient method due to high entrapment efficiency, drug loading, satisfactory particle size distribution and favorable crystalline behavior.
5	Lovastatin	Lovastatin nanoparticle	Precirol and squalene	Hot homogenization Followed by ultrasonication	Nano-aided drug delivery system is an appropriate choice for low-soluble lipophilic drugs.
6	Rosuvastatin Calcium	Solid-lipid nanoparticles of rosuvastatin calcium	Glyceryl behenate (compritol ATO 888), Glyceryl monostearate and Glyceryl monooleate	Hot homogenization followed by ultrasonication	Nano-particle formulations of the least mean particle size showed better permeability than the pure drug solution.

CONCLUSION

Technology-based nanoparticles certainly enhanced the properties of less water-soluble drugs i.e., drug loading efficiency, improved drug solubility and absorption, reduced toxicity, maximum plasma concentration and also improved bioavailability. Some of the characteristics of lipophilic drug like Diffusion via membranes, release properties (sustained, controlled), target specificity must be improved via quantified selection of the lipidic material. Most of the extensive carriers used in the drug delivery system are solid lipid nanoparticles and nanolipid carriers. Among these nanolipid carriers are presently used carrier system and have a lot of benefits over other carriers, like excellent drug loading ability, improved release characteristics and multiple drug incorporation, so it can be assured that nano-assisted drug delivery system is a suitable option for poorly water-soluble lipophilic drugs. Each nanoformulation has its own promises and advantages but has its drawbacks to conquer in the meantime. These include aggregation of particles, complicated physical handling in the case of liquid and dry form, minimal drug loading, can form toxic metabolites. Efforts are underway to address each of these problems, and the focus will remain on the future studies. Diagnosis and target therapy are the fundamental uses of nanoparticles in medicine, but their broader use will still be in the future.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Sharma K, Kumar K, Mishra N. Nanoparticulate carrier system: A novel treatment approach for hyperlipidemia, *Drug Deliv,* 23(3), 2016, 684-699.
2. Kwiterovich P O. State-of-the-art update and review: Clinical trials of lipid-lowering agents, *Am J Cardio,* 82(12), 1998, 3U-17U.
3. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart J C. Mechanism of action of fibrates on lipid and lipoprotein metabolism, *Circulation,* 98(19), 1998, 2088-2093.
4. Rozman D, Monostory K. Perspectives of the non-statin hypolipidemic agents, *Pharmaco and Therap,* 127(1), 2010, 19-40.
5. Colletti R B, Roff N K, Neufeld E J, Baker A L, Newburger J W, McAuliffe T L. Niacin treatment of hypercholesterolemia in children, *Pediatrics,* 92(1), 1993, 78-82.
6. Shepherd J. Mechanism of action of bile acid sequestrants and other lipid-lowering drugs, *Cardiology,* 76(1), 1989, 65-74.
7. Mohanraj V J, Chen Y. Nanoparticles-a review, *Tro J Phar Re,* 5(1), 2006, 561-573.
8. Abhishek G, Sharad V, Pramod K S, Nitin K. Formulation, characterization and application on nanoparticle: A review, *Der Pharmacia Sinica,* 2(2), 2011, 17-26.
9. Meena A K, Ratnam D V, Chandraiah G, Ankola D D, Rao P R, Kumar M R. Oral nanoparticulate atorvastatin calcium is more efficient and safe in comparison to Lipicure® in treating hyperlipidemia, *Lipids,* 43(3), 2008, 231-241.
10. Zhang H L, Tao Y, Guo J, Hu Y M, Su Z Q. Hypolipidemic effects of chitosan nanoparticles in hyperlipidemia rats induced by high fat diet, *Int Immunopharmacol,* 11(4), 2011, 457-461.
11. Tao Y, Zhang H, Gao B, Guo J, Hu Y, Su Z. Water-Soluble chitosan nanoparticles inhibit hypercholesterolemia induced by feeding a high-fat diet in male Sprague-Dawley rats, *J Nanoma,* 2011, Article ID 814606, 2011, 5.

12. Bathool A, Vishakante G D, Khan M S, Shivakumar H G. Development and characterization of atorvastatin calcium loaded chitosan nanoparticles for sustain drug delivery, *Adv Mat Lett,* 3(6), 2012, 466-470.
13. Kim M S, Jin S J, Kim J S, Park H J, Song H S, Neubert R H, Hwang S J. Preparation, characterization and *in vivo* evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process, *Eur J Pharm Biopharm,* 69(2), 2008, 454-465.
14. Shinde A J, Harinath N. Formulation, development and characterization of Simvastatin nanoparticles by solvent displacement method, *Der Pharmacia Lettre,* 6(2), 2014, 145-155.
15. Hu L, Tang X, Cui F. Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs, *J Pharm Pharmacol,* 56(12), 2004, 1527-1535.
16. Seenivasan A, Panda T, Theodore T. Lovastatin nanoparticle synthesis and characterization for better drug delivery, *The Open Biotechnology Journal,* 5(1), 2011, 28-32.
17. Yousaf A M, Kim D W, Oh Y K, Yong C S, Kim J O, Choi H G. Enhanced oral bioavailability of fenofibrate using polymeric nanoparticulated systems: Physicochemical characterization and *in vivo* investigation, *Int J Nanomed,* 10, 2015, 1819-1830.
18. Dudhipala N, Veerabrahma K. Improved anti-hyperlipidemic activity of Rosuvastatin Calcium via lipid nanoparticles: Pharmacokinetic and pharmacodynamic evaluation, *Euro Jour of Pharma and Biopharm,* 110, 2017, 47-57.
19. Shinde S S, Hosmani A H. Preparation and evaluation lipid nanoparticles of Fenofibrate obtained by spray drying technique, *Pharmacophore,* 5(1), 2014, 85-93.
20. Padhye S G, Nagarsenker M S. Simvastatin solid lipid nanoparticles for oral delivery: Formulation development and *in vivo* evaluation, *Ind J of Pharm Sci,* 75(5), 2013, 591-598.
21. Sathali H, Abdul A, Nisha N. Development of solid lipid nanoparticles of rosuvastatin calcium, *J Pharm Res,* 1(5), 2013, 536-548.
22. Kumar P P, Gayatri P, Sunil R, Jaganmohan S, Rao Y M. Atorvastatin loaded solid lipid nanoparticles: Formulation, optimization, and *in vitro* characterization, *IOSR J Pharm,* 2(5), 2012, 23-32.

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