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Antihyperlipidemic drugs and their novel formulation approaches: A review

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Abstract
Hyperlipidemia is an elevated condition of lipid levels in the body and is known to speed up a process of atherosclerosis that may prove fatal in the development of various cardiovascular diseases. Increase in lipids like LDL i.e. low density lipoproteins, cholesterol and triglycerides are mainly responsible for hyperlipidemia. Present pharmacotherapy for hyperlipidemia includes statins, niacin, fibric acid derivatives and cholesterol absorption inhibitors. 90% of the pharmacotherapy of hyperlipidemia includes statins and these statins also suffer from limitations like, inadequate solubility, less absorption, less bioavailability and ineffectiveness in lowering of cholesterol levels only upto maximum 40% risk reduction. These drugs are to be given on daily basis which make it cumbersome for patients. Novel Drug Delivery System is an advanced drug delivery system with improved solubility, absorption, bioavailability, drug potency, control drug release to give a sustained therapeutic effect, and target oriented to a desired tissue as well as patient compliance is good. So it is the need of hour to formulate such kind of drug delivery systems which will combat the limitations of anti hyperlipidemic therapy. The present review emphasise on applications of novel drug delivery systems in pharmacotherapy of anti hyperlipidemic drugs.

Keywords: hyperlipidemia, pharmacotherapy, novel drug delivery system, bioavailability

Introduction
It is seen that most of the deaths are occurring due to diseases of cardiovascular system. There is a significant impact of lifestyle changes on the quality of health. Utilization of food highly rich with saturated fat and having low fiber content is one of the factors of disarray in energy balance. It is now evinced that hyperlipidemia is depicted as a major risk factor for the premature development of atherosclerosis and its cardiovascular complications. The prevalence of obesity has doubled in the past 25 years; today, two-thirds of adults are overweight in the United State [1].

Hyperlipidemia is an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters and phospholipids and or plasma lipoproteins including very low density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels [2, 3]. Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD) [4]. There is a strong relation between IHD and the high mortality rate. Furthermore elevated plasma cholesterol levels cause more than four million deaths in a year [5].

Atherosclerosis is a process of arteries hardening due to deposition of cholesterol in the arterial wall which causes narrowing of the arteries. Atherosclerosis and atherosclerosis associated disorders like coronary, cerebrovascular and peripheral vascular diseases are accelerated by the presence of hyperlipidemia [6]. Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins, which present a significant function in the initiation and progression of atherosclerosis and associated cardiovascular diseases [2].

Pathophysiology
Cholesterol is composed of three lipoproteins (LDL, HDL and VLDL). (Table 1) High level of LDL results in the deposition of lipid on the wall of arteries causing reduction in blood flow due to formation of plaque on inside wall of arteries which causes narrowing and stiffening of arteries. Pathophysiology of hyperlipidemia can be categorized into primary and secondary hyperlipidemia [7].

Table 1: Characteristics of major lipoprotein classes

Lipoprotein class	Density (g/ml)	Diameter (nm)
Chylomicrons	<<1.006	500-80
VLDL	<1.006	80-30
IDL	1.006-1.019	35-25
LDL	1.019-1.063	25-18
HDL	1.063-1.210	5-12
Lp(a)	1.055-1.085	30

Primary hyperlipidemia involves the idiopathic hyper chylomicronemia defect in the lipid metabolism caused by a defect in lipoprotein lipase activity or due to absence of surface apoprotein C II. Primary hyperlipidemia can occur either due to over production or impaired removal of lipoproteins, it has genetic effect. Primary hyperlipidemia is due to single gene defect. It is familial and called as monogenic or genetic or poly gene defect which is a multiple genetic defect. Primary hyperlipidemia can be further categorized in to different types, According to Fredrickson familial hyperlipidemia is classified into five types (table 2) on the basis of electrophoresis or ultracentrifugation pattern of lipoproteins [9].

i) Type I familial hyper chylomicronemia,
ii) Type IIA familial 2 hypercholesterolemia,
iii) Type IIB familial combined(mixed) hyperlipidemia,
iv) Type III familial dysbetalipoproteinemia,

v) Type IV familial hypertriglyceridemia,
vi) Type V familial mixed hypertriglyceridemia

Secondary hyperlipidemia is associated with other diseases like diabetes, myxoedema, chronic alcoholism, with use of drugs like corticosteroids, oral contraceptives and beta – blockers. Secondary hyperlipidemia is either due to the defect in lipoprotein or its receptor caused by other diseases like diabetes mellitus, hypothyroidism, chronic renal failure, obesity, alcohol, etc. these factors worsen the condition of the person having primary hyperlipidemia. There are four types of secondary hyperlipidemia (i) Hypercholesterolemia, (ii) Hypertriglyceridemia, (iii) Hypocholesterolemia and (iv) Low HDL [8].

Table 2: Fredrickson classification for hyperlipidemia

Hyper lipoproteinemia	Synonyms	Defect	Increased lipoprotein	Symptoms	Treatment
TYPE I	Familial hyperchylomicronemia Familial apoprotein CII deficiency	Decreased lipoprotein lipase (LPL) Altered ApoC2	Chylomicrons	Acute pancreatitis, lipemia retinalis, xanthomas, hepatosplenomegaly	Diet control
TYPE II A	Familial hypercholesterolemia	LPL inhibitor in blood LDL receptor deficiency	LDL	Xanthelasma, arcus senilis, tendon xanthomas	Bile acid sequestrants, statins,niacin Statins,niacin, fibrate
B	Familial combined hyperlipidemia	Decreased LDL receptor and increased Apo B	LDL and VLDL		
TYPE III	Familial dysbetalipoproteinemia	Defect in Apo E2 synthesis	IDL	Tuboruptive xanthomas and palmar xanthomas	Fibrate, statins
TYPE IV	Familial hypertriglyceridemia	production and decreased elimination	VLDL	Can cause pancreatitis at high triglyceride levels	Fibrate, niacin, statins
TYPE V		Increased VLDL production and decreased LPL	VLDL and chylomicrons		Niacin, fibrate

Enzymes involved in lipoprotein metabolism

Lipoprotein lipase (LPL), Hepatic lipase (HL), Lecithin cholesterol acyl transferase (LCAT), Cholesteryl ester transfer protein (CETP), Microsomal TG protein (MTP), Acyl Co-A transferase (ACAT) [10].

Mechanism of lipid transport

Lipids are insoluble in water. Hence, they are transported around the body as lipoproteins. Lipids originate from two sources: endogenous lipids, synthesized in the liver, and exogenous lipids, ingested and processed in the intestine. Approximately 7% of body's cholesterol circulates in plasma in the form of (LDL). The level of plasma cholesterol is influenced by its synthesis and catabolism in which liver plays a crucial role (figure. 1).

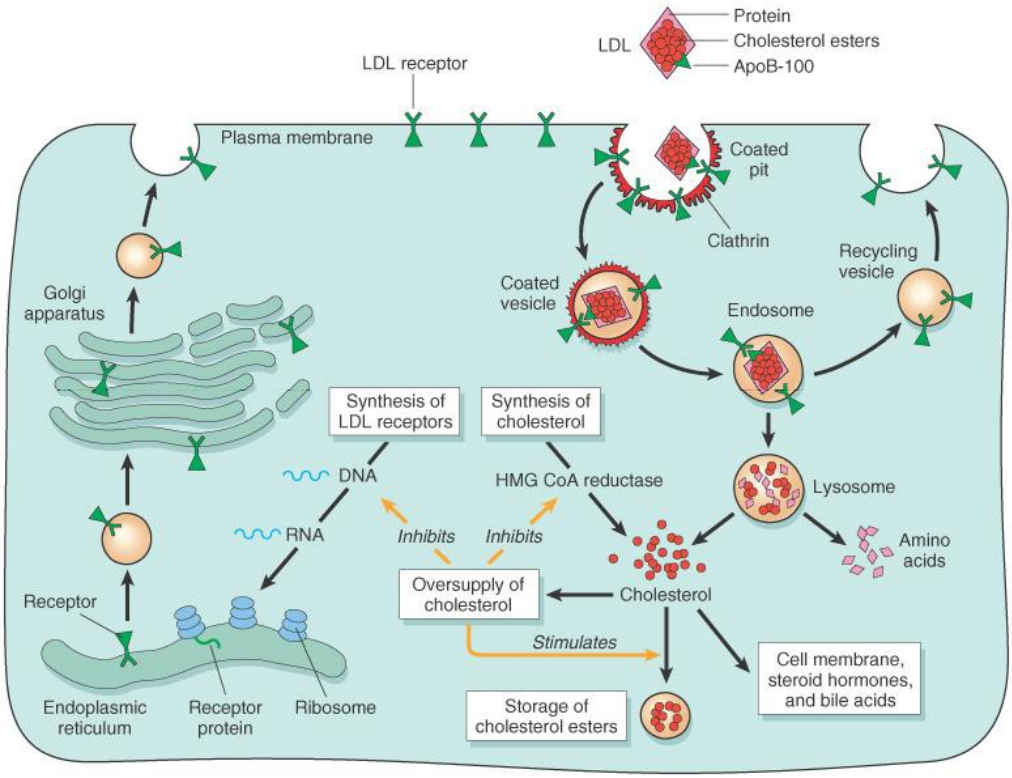

Fig 1: Mechanism of lipid transport

Symptoms of hyperlipidemia

Generally hyperlipidemia does not have any obvious symptoms but they are usually discovered during routine examination or until it reaches the danger stage of a stroke or heart attack. Patients with high blood cholesterol level or patients with the familial forms of the disorder can develop xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body [11].

Causes of hyperlipidemia

Lifestyle habits or treatable medical conditions. Lifestyle contributors include obesity, not exercising, and smoking, Diabetes (type 2), Kidney disease, Pregnancy, An under active thyroid gland, Environmental and genetic factors, Alcohol, Monoclonal Gammopathy, Nephrotic Syndrome, Obstructive Jaundice, Hypothyroidism, Cushing's Syndrome, Anorexia Nervosa, High dietary simple carbohydrates, Estrogen therapy [12].

Treatment therapy

In 1987 the National Institute of Health (NIH) established the National Cholesterol Education Program (NCEP) to be directed by the Adult Treatment Panel (ATP) for the purpose of issuing information for health professionals and the general public concerning testing, evaluating, monitoring and treating hyper-lipidemia. An important criterion of ATP guidelines is the development of treatment goals for hyperlipidemia based on patient's risk of CHD.

ATP recommends two methods of treatment: 1) Therapeutic lifestyle changes; 2) Drug therapy.

Therapeutic lifestyle changes

Diet modification, regular physical activity, smoking cessation, and weight reduction should be tried as initial treatment, especially in mild cases of hyperlipidemia and in persons without CHD or CHD risk equivalent and<2 risk factors. It should be kept in mind that when dieting, cholesterol intake is reduced. At the same time, production of cholesterol, especially by the liver, increases. It is recommended that the intake should be restricted to 25%-35% of energy intake and that saturated fatty acids make up less than 7% of energy intake and that cholesterol intake should be less than 200 mg daily. The intake of plant sterol esters and soluble fibre is advisable. A healthy diet can result in 10% to 15% reduction of cholesterol blood level.

Drug therapy

High LDL, the presence of risk factors, and documentation of CHD should qualify initiating drug therapy along with TLC. Monotherapy has been shown to be effective in treating hyperlipidemia, but combination therapy may be required for a comprehensive approach. Current lipid-lowering drugs include statins, ezetimibe, bile acid sequestrants or bile binding resins, niacin, fibric acid derivatives, and plant sterols. Medication specially designed to reduce blood cholesterol levels may be prescribed when dietary modifications prove inadequate. In rare patients with extremely high cholesterol levels, repeated removal of blood plasma may be recommended to lower blood cholesterol levels. Most people require lifelong treatment of hyperlipidemia with both lifestyle measures and medications [13].

Conventional drug delivery system used for hyperlipidemia

Non-invasive peroral route of administration, where the dosage form is consumed through the mouth, is the most conventional way for delivering the anti hyperlipidemic drugs [14]. This route has certain limitations such as drugs with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. It is difficult to obtain a steady state condition due to unavoidable fluctuations in the drug concentration. First pass metabolic effect on the drugs is another major limitation of this route which reduces the bioavailability of several important drugs [15], lack of water solubility, poor site specificity, low therapeutic response despite high doses and elevated side effects and toxicity. To overcome these limitations, development of novel drug delivery systems (NDDS) which include drug modification (chemically or physically), drug entrapment within lipidi corpolymeric small vesicles or particle size reduction of drugs, is necessary [16]. This advent of NDDS will not only reduce the shortcomings of drugs which are cited pharmacologically and bio pharmaceutically but will also aid to remove the drawbacks of conventional drug delivery system [17].

Novel formulation approaches

Sustained/controlled release of following drugs is achieved through the novel methods of formulating a drug incorporated carrier system. Table 3 outlines various novel formulation approaches of drug carried out in different studies.

Table 3: Clinically approved statins – comparative properties [30]

S.no	Name of the drug	Bioavailability (%)	Protein binding (%)	Elimination Half life	Solubility	Source	Serum LDL-C Reduction (%)
1	Atorvastatin	12	98	14	Lipophilic	synthetic	50
2	Cerivastatin	60	>99	2.5	Lipophilic	synthetic	28
3	Fluvastatin	24	>98	1.2	Lipophilic	synthetic	24
4	Lovastatin	5	>95	3	Lipophilic	fungal derived	34
5	Pravastatin	18	~50	1.8	hydrophilic	fungal derived	34
6	Simavastatin	5	95-98	2	Lipophilic	fungal derived	41
7	Rosuvastatin	20	90	19	hydrophilic	synthetic	63
8.	Pitavastatin	~80	96	11	lipophilic	synthetic	48

Various novel drug delivery systems which can help to overcome the limitations of various drugs and the conventional dosage forms pertaining to them. As a result, different novel drug delivery systems have been developed which are discussed in the subsequent sections. Novel Formulation Approaches for Lipophilic Drugs.

Mechanism of action of different antihyperlipidemic agents

HMG CoA reductase inhibitors (statins) The HMG CoA reductase inhibitors, or statins, are commonly used in the treatment of hyperlipidemia and have led to the significant reductions in cardiovascular and all-cause fatality in the setting of both primary and secondary prevention of atherosclerotic CDV. The statins work by inhibiting the ratelimiting enzyme, HMG CoA reductase, in the endogenous synthesis of cholesterol (Figure 2). HMG CoA converts to mevalonate in the presence of HMG CoA and mevalonate aids to further synthesis of cholesterol. Therefore, statins works by inhibiting HMG CoA which further leads to decrease in cholesterol level and prevention of dyslipidemia [18].

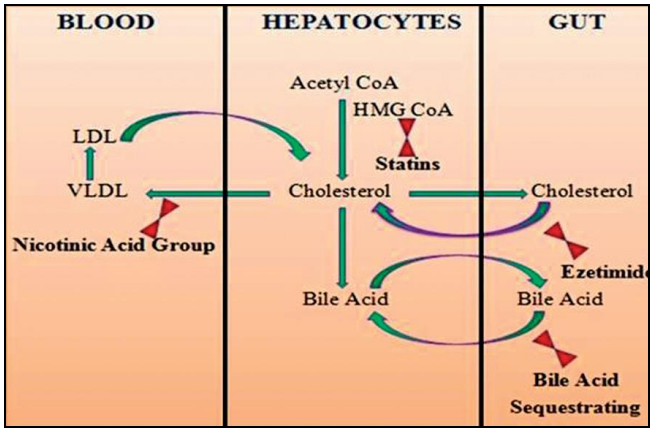

Fig 2: Mechanism of action of different antihyperlipidemic agents: HMG CoA reductase inhibitors (statins), cholesterol absorption inhibitors, nicotinic acid group and bile acid sequestrants

Different Novel Drug Delivery Systems:

- Oral Delivery Drug Delivery Systems.
- Parenteral and Implant Drug Delivery Systems.
- Pulmonary and Nasal Drug Delivery.
- Transmucosal Drug Delivery.
- Transdermal and Topical Drug.

Novel Drug Delivery Systems for Anti- Hyperlipidemic Drugs

Most of the anti-hyper lipidimic drugs have poor water solubility hence poor dissolution which lead to poor bioavailability. So when these drugs are given in conventional dosage forms they do not meet the therapeutic requirements hence are given in large doses which lead to various side effects. Therefore it is the required to formulate that kind of dosage form in which the drug shows greater bioavailability and less side effects. Researchers are going on in this field and various novel drug delivery systems are formulated and evaluated which have shown the increase in bioavailability of these drugs. Some of the novel drug delivery systems for anti-hyper lipimic drugs are:

Self-emulsifying drug delivery system

This work aims to examine the effect of different amount of oil or surfactant incorporated in self-micro emulsifying drug delivery systems on the intestinal lymphatic transport of sirolimus using the single-pass intestinal perfusion (SPIP) technique, and a chylomicron flow blocking approach leads to inhibition of cholesterol synthesis.[19]. Lovastatin is poorly soluble in gastric fluid when administered through conventional dosage forms like tablet, so SMEDDS are formulated to increase the solubility of drug in gastric fluid and hence improving the bioavailability by increasing gastrointestinal absorption through passive diffusion [20].

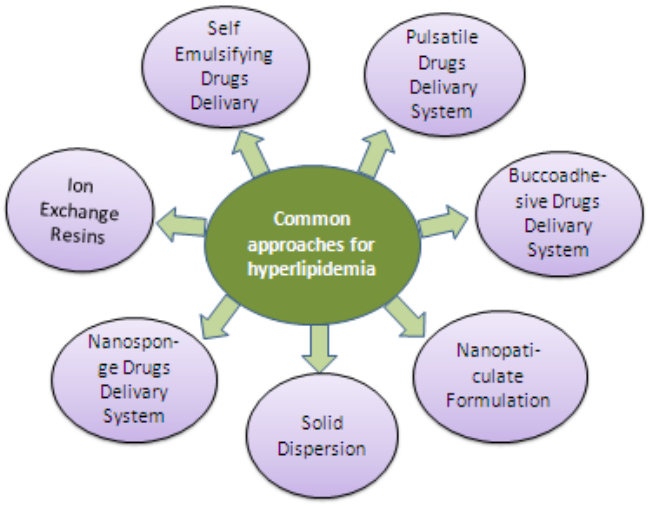

Fig 3: Common approaches for Hyperlipidemia

Pulsatile Drug Delivery System

Pulsatile Drug Delivery System is useful in the diseases in which the drug release is timed to match rhythms of the disease so as to optimize the therapeutic effect and minimize the side effects. Circadian rhythm occurs during hepatic cholesterol synthesis which is higher during the night than daylight and diurnal synthesis represent upto 30-40% of daily cholesterol synthesis [21]. However the maximal production occurs in the morning. So there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body [22].

Buccoadhesive Drug Delivery System

Bio adhesive systems are useful for the administration of drugs, which are susceptible to extensive gastrointestinal degradation and first pass metabolism, with short half-lives, requiring sustained and controlled delivery, with poor aqueous solubility. The buccal cavity provides a highly vascular mucous membrane site for the administration of drug. Buccal mucosa presents a relatively smooth and immobile surface for the placement of a bio adhesive dosage form [23]. The dosage forms developed for this purpose includes tablets, adhesive patches, adhesive gels, and adhesive ointment. Buccoadhesion is achieved by using various types of hydrophilic polymers. Lovastatin undergoes extensive first-pass metabolism in the liver and as a consequence of this the availability of Lovastatin in general circulation is very low and variable. The buccal formulation of Lovastatin in the form of buccoadhesive tablets was developed which increased the bioavailability of the drug [24].

Nanoparticle Formulation

Nanomaterials have unique physicochemical properties, such as ultra-small size, large surface area to mass ratio, and high reactivity, which are different from bulk materials of the same composition. The use of materials in nanoscale provides un parallel freedom to modify fundamental

properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics, and immunogenicity. As therapeutic delivery systems, nanoparticles allow targeted delivery and controlled release. Nanocrystalline fenofibrate Tricor is a clinically approved nanoparticle formulation [25].

Solid dispersion

Solid dispersions have been extensively used to improve the solubility, dissolution rate, absorption as well as bioavailability of poor water-soluble drugs. Fenofibrate compound are practically insoluble in water due to their high lipophilicity, and thus the dissolution rate of fenofibrate is omened to limit its absorption from the gastrointestinal tract. The solid dispersion of the fenofibrate were prepared by spray-drying technique using Poloxamer 188 as carrier and tocopheryl polyethylene glycol succinate (TPGS) as surfactant expressed maximum solubility enhancement of fenofibrate.Solid dispersion has been used to enhance the dissolution of Ezetimibe along with an adsorption technique that employed a water-soluble adsorbent for low-soluble drug, which leads to combined effect of hydrophilic carriers and increased surface area [26].

Nanosponge Drug Delivery

Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules (Subramanian, 2012) [27]. This technology offers entrapment of ingredients and is believed to reduce side effects by controlling the release, improve stability, increase elegance and enhance formulation flexibility [28]. These complexes can be also used to increase the dissolution rate and solubility, to mask unpleasant flavours and to convert liquid substances to solids. By controlling the ratio of polymer to the cross-linker the particle size and release rate can be modulated. Nanosponges enable the insoluble drugs and protect the active moieties from physicochemical degradation and controlled release. Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin can be formulated into nanosponges [27]. Nanosponges improve the solubility of the drugs effectively but the technology employed in this process is not cost effective as this technique utilizes some polymers which are costly in nature.

Ion Exchange Resins

Ion exchange resins are cross-linked, water insoluble, polymer-carrying, ionizable functional groups. They contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them. An ion exchange resin is exhibited like small bead with a diameter between 1-2 mm [29]. Drugs can be loaded onto the resins by an exchanging reaction, and hence, a drug-resin complex (drug resinate) is formed. Ion exchange can be defined as a reversible process in which ions of like sign are exchanged between liquid and solid, a highly insoluble body in contact with it. The drug is released from resinates by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. Ion-exchange systems are advantageous for drugs that are highly susceptible to degradation by enzymatic process. A major advantage of ion exchange system is low running cost. It requires little energy and the regenerated chemicals are cheap [29]. Cholestyramine resin USP, when used as an active ingredient, binds bile acids; this leads to replenishment of bile acids; through increased metabolism of serum cholesterol resulting in lowered serum cholesterol levels [30]. Ion exchange resins no doubt are very effective in enhancing the bioavailability of the drugs but due to the utilization of some polymers it also enhances the cost of the delivery system.

Mucoadhesive Microcapsules

Oral route serves as the most convenient route for drug delivery. An ideal dosage regimen in the drug therapy of every disease is the one which maintains the desired therapeutic concentration of drug in the plasma for entire duration of treatment. An ideal oral controlled drug delivery system is one which delivers the drug at a predetermined rate, locally or systematically for a specified period of time (Kumar, 2012) [31]. Simvastatin (SV) is a cholesterol lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus* and is widely used to treat hypercholesterolemia. Microcapsules of Simvastatin were prepared by complexation with HPBCD and thereby including this complex in the polymeric matrix by use of orifice gelation technique resulted in more improved drug delivery [32].

Conclusion

In spite of extensive research and development of numerous drugs, anti hyperlipidemic therapy is still deprived of the efficiency, safety, thorough knowledge of the exact mechanisms of the real causes of hyperlipidemia, and finally 'cost'. The various novel drug delivery systems are employed to improve the solubility, bioavailability and effectiveness of anti hyperlipidimic drugs and the above explained systems are useful for the same. Nanoparticles, nanosuspensions and nanosponges are used to enhance the solubility of the drug by minimizing the particles size. Bucoadhesive and mucoadhesive drug delivery systems are employed to enhance the bioavailability of drugs that are degraded in the stomach by aiding the delivery of drug in buccal cavity where the vascular circulation is high. While as pulsatile drug delivery system is the system which responds to the circadian rhythms of the body and therefore this system is very effective because cholesterol synthesis depends on circadian rhythms. SMEDDS can be used to enhance the solubility of the drugs by decreasing the particle size in the emulsion base which will effectively increase the bioavailability of the drug. Among all the systems above SMEDDS seems to be the most successful delivery system for antihyperlipidemic drugs because it is very easy to formulate and does not require any costly polymers which make it effective in therapy as well as in cost. Many other novel drug delivery systems can be used to enhance the effectiveness of these drugs.

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