IJIRR

International Journal of Information Research and Review
Vol. 04, Issue, 08, pp.4373-4382, August, 2017

S

REVIEW ARTICLE

COMPARATIVE STUDY OF STATINS AND DIFFERENT FORMULATION OF STATINS- A REVIEW

Dr. Pathak, D.P. and *Akanksha

Delhi institute of Pharmaceutical Science & research, India

ARTICLE INFO

Article History:

Received 02nd May, 2017
Received in revised form
21st June, 2017
Accepted 13th July, 2017
Published online 30th August, 2017

Keywords:

Statin, new approaches of Statin,
conventional approach,
New approach of statins.

ABSTRACT

Statins are very commonly used antihyperlipidaemic in all over theworld. Statins are the main API occurred in all antihyperlipidaemic drugs. This classes of compounds are the most efficacious and the best tolerated hypolipidaemic drugs. Statins reduced the raised LDL-CH associated mortality and morbidity is now established. Up to certain therapeutic dose is useful but anoverdose of Statins start side effects like a headache, Nausea, vomiting and bowel upset, rashes on the body. This review aims at compiling the research inputs being made for developing therapeutically efficacious dosage forms that have the potential to surmount the limitations of conventional dosage of statins.

INTRODUCTION

The cholesterol-lowering medicines known as statins lower the chances of a heart attack and death in people who have an elevated risk of developing heart disease or who already have heart disease. According to the American Heart Association (AHA), total cholesterol levels should be less than 200 mg/dl and high-density lipoprotein (HDL) cholesterol level more than 60 mg/dl is desirable, in order to put people at a lower risk of coronary heart disease (CHD)[1]. A person with a total cholesterol level of 240 mg/dl and above and less than 40 mg/dl (for men) or 50 mg/dl (for women) of HDL cholesterol has more than twice the risk of CHD of someone whose cholesterol is below 200 mg/dl. If a person has CHD or diabetes, the low-density lipoprotein (LDL) goal is less than 100 mg/dl.There are seven statins, but they're not all the same. Some deliver a greater reduction in cholesterol than others. In addition, some statins are backed by stronger evidence that they reduce the risk of a heart attack or death from heart disease or a stroke. Statins, also known as HMG-CoA reductase inhibitors. A number of statins are on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. The statins are divided into two groups: fermentation-derived and synthetic.

***Corresponding author:* Akanksha,**
Delhi institute of Pharmaceutical Science & research, India.

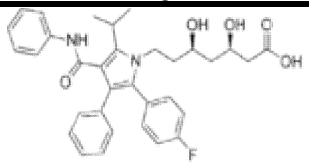
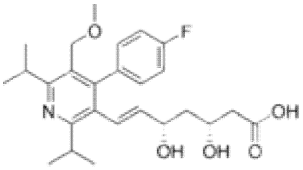
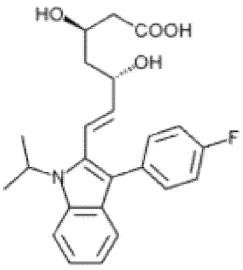
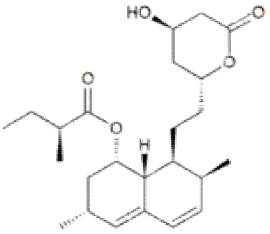
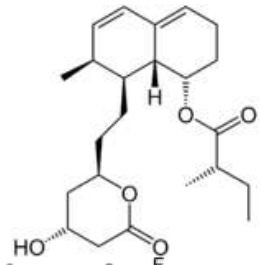
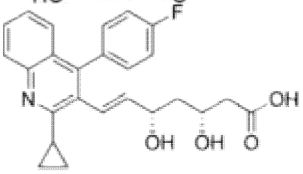
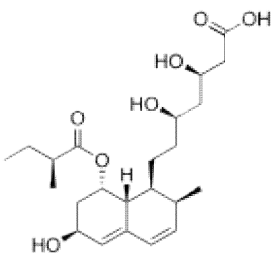
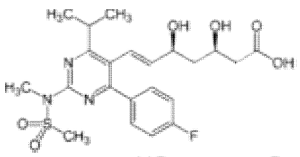
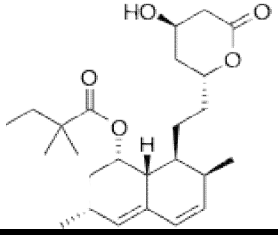
They include, along with brand names, which may vary between countries:

LDL-lowering potency varies between agents. Cerivastatin is the most potent, (withdrawn from the market in August 2001 due to therisk of serious rhabdomyolysis) followed by (in order of decreasing potency), rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin. The relative potency of pitavastatin has not yet been fully established.Firststatinare lovastatin naturally occurring fermentation derived product. Classified according to half life:

STATINS	HALF LIFE
Simvastatin	More than 5 hours
Atorvastatin	14 hours
Cerivastatin	2-3 hours
Fluvastatin	1 to 3 hours
Lovastatin	2 to 5 hours
Rosuvastatin	19 hours
Pravastatin	1-3 hours
Pitavastatin	1.5 to 3 hours
Mevastatin	2 to 5 hours

Use of statins

Statins are the first choice of drug for primary hyperlipidaemias with raised LDL and total CH levels, with or without raised TG levels Type IIa,IIb,V, as well as for secondary (diabetes,nephroticsyndrome) hypercholesterolemia.

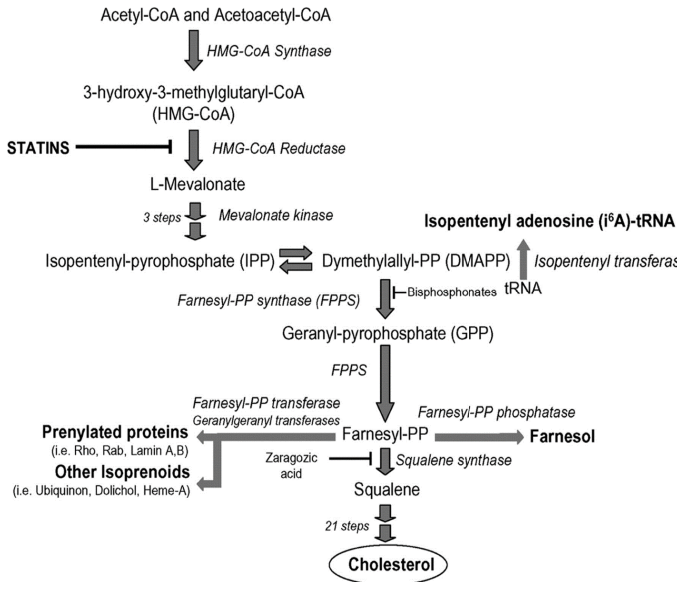
Statin	Image	Brand name	Derivation	Metabolism
Atorvastatin		Lipitor, Ator	Synthetic	CYP3A4
Cerivastatin		Lipobay, Baycol. (Withdrawn from the market in August 2001 due to risk of serious rhabdomyolysis)	Synthetic	various CYP3Aisoforms
Fluvastatin		Lescol, Lescol XL	Synthetic	CYP2C9
Lovastatin		Mevacor, Altocor, Altoprev	This is a naturally occurring, fermentation-derived compound. It is found in oyster mushrooms and red yeast rice.	CYP3A4
Mevastatin		Compactin	This is a naturally occurring compound found in red yeast rice.	CYP3A4
Pitavastatin		Livalo, Pitava	Synthetic	
Pravastatin		Pravachol, Selektine, Lipostat	Fermentation-derived. (A fermentation product of bacterium *Nocardiaautotrophica*).	Non CYP[116]
Rosuvastatin		Crestor	Synthetic	CYP2C9 andCYP2C19
Simvastatin		Zocor, Lipex	Fermentation-derived. (Simvastatin is a synthetic derivate of a fermentation product of*Aspergillusterreus*.)	CYP3A4

Efficacy of Statin in reducing raised LDL-CH associated mortality and morbidity is now well established. Comparison of different statin which shows the maximum reduction of CH level.

Statins	Total ch level reduction	LDL-ch reduction	Raised HDL-ch
Simvastatin	25%	40-55%	8%
Atorvastatin	25-60%	40-55%	7%
Cerivastatin	25-30%	21-23%	2%
Fluvastatin	21-24%	22-24%	5%
Lovastatin	10-30%	30-35%	5-15%
Rosuvastatin	28-32%	40-55%	15-20%
Paravastatin	30-35%	35-40%	15%
Pitavastatin	20-22%	20-25%	11%
Mevastatin	23%	20-25%	15%

Physiological effects of statins

The use of Statins in hyperlipidaemic is well established in pharmaceutical formulations. Statins in combination with Fibrates and niacin to enhance the maximum reduction of cholesterol level and raised the HDL-CH levels. Acute consumption of low dose Statins over- the counter (OTC) given. The action of Statins Competitively inhibits theconversion of 3- hydroxy-3-methyl glutaryl coenzyme A (HMG-COA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-COA reductase. Therapeutic dose reduces CH synthesis by 20-50%. This results in acompensatory increase in LDL receptor expressions on liver cells →increase receptor mediate uptake and catabolism of IDL and LDL.Overlong term feedback induction of HMG-COA reductase tend to increase CH synthesis, but a steady- state is finally attained with dose -dependent lowering of LDL-CH levels. The mevalonate Pathway Different Statins differ in their potency and maximal efficacy in reducing LDL-CH.



The daily dose for lowering LDL-CH by 30-35% is lovastatin 40 mg, pravastatin 40 mg,simvastatin20mg, atorvastatin 10 mg, and rosuvastatin can reduce LDL-CH reduction upto45-55% while ceiling effect of lovastatin and pravastatin is 35-40% LDl-CH reduction. All Statins produce Peak LDL-CH lowering after 1-2 weeks therapy. Hepatitis synthesis of VLDL is concurrently reduced and its removal from plasma is enhanced.

Pharmacokinetic Properties of Statins

The pharmacokinetic properties of the statins are affected by several factors, including their active or lactone form, their lipophilic/hydrophilic rate, and their absorption and metabolism. Statins are administrated orally as active hydroxy acids, except for lovastatin and simvastatin, which are administrated as lactone pro-drugs and then hydrolyzed to hydroxy acid form.Thestatin pharmacological properties referred to as doses administered as open acid and lactone forms.The percentage of absorption is between 30 and 98% and the time to reach peak plasma concentration (T_{max}) is within 4 h after administration.The daily absorption may vary according to the time of administration and food intake ,for instance, changes in lipid and apolipoprotein values were similar after morning and evening administration of atorvastatin. Rate and extent of equivalent absorption of atorvastatin were lower during theevening than morning administration. When consumed with food, lovastatin is more efficiently absorbed with respect to fluvastatin,atorvastatin, and pravastatin, which have a reduced absorption, whereas rosuvastatin, simvastatin, and cerivastatinabsorption is not affected by food consumption. Because the liver is the target organ of statins, an efficient first-pass uptake may be more important than high bioavailability to achieve the statin effect. An extensive first-pass extraction implies a low systemic bioavailability; indeed, the bioavailability of cerivastatin is approximately 60% and that of pitavastatin is 80%, whereas fluvastatin bioavailability ranges from 19 to 29%. Furthermore, increased doses of fluvastatin enhance the drug circulating levels without time-related changes of its pharmacokinetic profile, thus suggesting a saturable first-pass effect of fluvastatin.

Pravastatin is the only statin not bound to plasma proteins; thus, as result of a systemic exposure to unbound drug, the pharmacologically active drug is relatively low, and its circulating level is high compared with other statins. The solubility profile is a fundamental characteristic that governs the hepatoselectivity of the statins and their inhibitory effect on HMG-CoA reductase. Lipophilic statins enter the hepatocytes by passive diffusion, whereas hydrophilic statin uptake is carrier-mediated. Lipophilic statins show an efficient activity at both hepatic and extrahepatic sites, whereas hydrophilic statins are more hepatoselective. The human transporters involved in the hepatic uptake of statins are located either at the basolateral or apical membrane in polarized cells and may be classified as influx (uptake into cells) and efflux (out of cells) transporters. The sequential crossing of the basolateral and apical membranes may require interplay of influx and efflux transporters together with phase I and II metabolism. Indeed, in the liver, organic anion transporting polypeptides (OATP) may transport drug substrates from the portal blood into hepatocytes. In particular, pravastatin, cerivastatin, pitavastatin, rosuvastatin, and atorvastatin are substrates of human OATP1B1, a member of the OATP family. In the hepatocytes, other drug transporters, such as multidrug resistance protein, breast cancer resistance protein, and bile salt export pump, may be involved in the metabolite efflux. These mechanisms of transport may represent a crucial step for the statin metabolism and elimination

Factors That May Affect Statin Metabolism

Other factors or their concomitant occurrence may influence the statin metabolism. These factors including race or ethnicity, food intake, age and sex, and concomitant diseases may affect the pharmacokinetic and pharmacodynamic profile of the statins.

Race or ethnicity

There is no evidence of clinically relevant interethnic differences in cerivastatin pharmacokinetics in white, black, and Japanese patients after oral therapeutic doses.

Food intake

Concomitant administration of statins with food may alter their pharmacokinetic and pharmacodynamic profile. It has been reported that consumption of pectin or oat bran soluble fiber together with lovastatin reduces its absorption, whereas alcohol intake does not affect the efficacy and safety of fluvastatintreatment. On the other hand, fluvastatin treatment in rats on high-fat and high-sucrose diet was lethal, suggesting that both altered statin metabolism and elimination increase plasma levels of aspartate aminotransferase and creatine kinase, resulting in skeletal muscle toxicity. Moreover, olive oil, consumed in a Mediterranean-style diet, can increase the cholesterol-lowering effect of simvastatin compared with sunflower oil. In contrast, the consumption of polyunsaturated rich oils, through the cytochrome P450 activation, could decrease the half-life of some statins and therefore their cholesterol-lowering effects.

Age and sex

The influence of differences in age and sex on pharmacokinetic properties of statins has also been reported. The administration of separate dosage regimens of lovastatin and simvastatin in patients with hypercholesterolemia increases the plasma concentrations of active and total statins only in elderly persons (aged 70–78 years) and in women. However, this age- and sex-related differences do not require modification of dosage regimens, because statin plasma concentrations are not necessarily related to their efficacy and the therapeutic window of lovastatin and simvastatin is quite wide. Likewise, age- and sex-related differences have been reported in the equivalent maximum concentration (C_{max}), in the AUC_{∞}, and in the half-life after the administration of a single dose of atorvastatin. In contrast, the pharmacokinetic profiles of pravastatin are not affected by age and sex. Indeed, although the mean AUC of pravastatin is higher in the elderly women, C_{max} and $\beta\ t_{1/2}$ values are similar in young and elderly volunteers. Finally, several studies demonstrated that pharmacogenetic variants in HMG-CoA reductase influence the degree of lipid reduction during statin therapies. In particular, patients carrying HMG-CoA reductase single-nucleotide polymorphisms experienced reduced statin sensitivity and smaller reductions in cholesterol, apolipoprotein B, and triglyceride.

Concomitant diseases

Statin treatment is required in patients affected by renal and hepatic diseases. However, in pathological conditions of severe renal dysfunction, the elimination kinetic of statins seems to be altered: indeed, plasma levels of total and active lovastatin are increased in affected compared with healthy subjects. In contrast, in patients with hyperlipidemia and chronic renal failure subjected to hemodialysis, there was no evidence of increased accumulation of atorvastatin or its major active metabolite upon multiple dosing, compared with healthy volunteers. Similar evidence has been also reported for fluvastatinadministration. In patients receiving long-term dialysis, plasma concentrations of cerivastatin and its metabolites are higher (up to 50%) than in healthy subjects. The half-lives of both parent drug and metabolites remain unaffected without accumulation under repeated dosage. In addition, cerivastatin clearance is not increased by concurrent dialysis as would be predicted from the high plasma protein-binding without significant difference in cerivastatin exposure between the dialysis and the dialysis-free profile days. Moreover, in patients with end-stage kidney disease undergoing continuous ambulatory peritoneal dialysis, the pharmacokinetic profile of rosuvastatin is very similar to that observed in healthy volunteers; therefore, a lower dose of rosuvastatin may be administered. With regard to hepatic diseases, the steady-state pharmacokinetics of rosuvastatin and its lactone, after the administration of a single dose, are very similar in male patients with liver cirrhosis and male volunteers without liver disease. In contrast, these patients showed increased pitavastatin plasma concentration after administration. It is noteworthy that, according to available data, genetic variations in the P450 family of enzymes alter the in vivo availability of many commonly used statins. For instance, gain or loss of catalytic function in the *CYP2C8* gene causes an alteration of cerivastatin metabolic clearance of up to six-fold compared with the wild-type enzyme, altering cerivastatin pharmacokinetics and influencing, at least in part, the susceptibility to the development of myotoxicity. Conversely, a recently discovered polymorphism of CYP3A5 gene seems not to be an important factor in the modification of atorvastatin disposition and pharmacodynamics in humans.

Dosage of Statin

STATINS	Dosage of Statin
Simvastatin	5,10,20 mg
Atorvastatin	10,20 mg
Cerivastatin	0.2mg,0.3mg,0.8mg
Fluvastatin	20mg,40mg,80mg
Lovastatin	10mg,20mg,40mg
Rosuvastatin	5,10,20 mg
Pravastatin	10,20 ,40 mg
Pitavastatin	1mg,2mg,4mg
Mevastatin	1mg,5mg

Pravastatin new approach to makingmucoadhesive and microbeads to overcome the problem like low bioavailability, half life of drugs.

Formulative approaches
Peroral administration

Omega-3 ester-based oil suspension

These suspensions are substantially free of any drug–foodeffects, are effective in small volumes and are readily bioavailable. It has been claimed that novel pharmaceutical compositions of one or more statins based on omega-3 oil have unexpected therapeutic properties. Notably, because the

pharmaceutical compositions of the products contain omega-3 oil as a major ingredient, they will not only provide an antihypercholesterolemic effect due to the active statin ingredient, but can also provide the recommended daily dose of omega-3 oil (1 g of omega-3 oil per day, as per AHA guidelines), or aportion thereof. Typical preparations are suspensions of amorphousand/or crystalline particles of one or more statins in omega-3 oil.

Microcapsule suspension

Microcapsule suspensions consist of an oil with a high concentration of alkyl esters of polyunsaturated fatty acids (PUFA) and microcapsules comprising at least one polymer and a statin. The statins are isolated from contact with the alkyl ester of PUFA by means of a polymeric membrane that can easily disintegrate in the gastrointestinal medium. This coating provides stabilization, eliminating degradation products of the statin during the preparation of the microcapsule suspension and during incorporation of the microcapsule suspension in the delivery system (soft gelatin capsules, hard gelatin capsules, granules, tablets, etc.), even though these processes are carried out at temperatures exceeding 40°C. Microcapsules of SIM prepared with gelatin and carboxymethyl cellulose by means of complex coacervation processes resulted in a microcapsule powder that was directly dispersed in oil containing 88% ethyl ester of PUFA with an eicosapentaenoicacid (EPA)/docosahexaenoic acid (DHA) ratio of1 : 2. Thus a new formulation of SIM microcapsules in oil with a high content of alkyl esters of PUFA was developed, which avoided the problems of degradation of statins in the GIT.

Self-emulsifying drug-delivery system

One of the ongoing efforts to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, self-emulsifyingformulations, emulsions, and liposomes, with each formulation approach having its unique advantages and limitations. These self-organizing systems often lead to an improvement in the therapeutic index of the lipophilic drugs through increased solubilization andmodification of theirpharmacokinetic profiles.Self-emulsifying drug-delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into theaqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium-chain triglyceride oils and non-ionic surfactants, the latter being less toxic. On peroraladministration and with mild agitation provided by gastric motility, these systems form fine emulsions (or microemulsions)in the GIT.

The potential advantages of these systems include enhanced oral bioavailability, enabling reduction in dose, more consistent temporal profiles of drug absorption,selective targeting of drug(s) to specific absorption windows in the GIT, protection of drug(s) from the hostile environment in the gut, control of delivery profiles, reduced variability, including food effects, protection of sensitive drug substances, high drug payloads and a choice of liquid or soliddosage forms. The process by which self-emulsification takes place is not yet understood completely. However, according to Reiss,self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of conventional emulsion formation is a directfunction of the energy required to create a new surface between the two phases. With time, the two phases of the emulsion will tend to separate in order to reduce the interfacialarea and subsequently the free energy of the systems. The emulsions resulting from aqueous dilution are therefore stabilized by conventional emulsifying agents, which form monolayer around the emulsion droplets and hence reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energyrequired to form the emulsion is either very low andpositiveor negative (in which case the emulsification process occurs spontaneously). Emulsification requiring very little inputenergy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. Self-microemulsifying drug delivery systems (SMEDDS) are distinguished from SEDDS by the much smaller emulsion droplets produced on dilution, resulting in a transparent or translucent solution. SMEDDS generally contain relatively high concentrations of surfactant (typically 40–60% w/w) and regularly contain hydrophilic co-solvents (propylene glycol, polyethylene glycols). These are often described as microemulsionpre-concentrates, as the microemulsion is formed on dilution in aqueous media.Incorporation of thedrug in SMEDDS/SEDDS increases its solubility because it circumvents the rate-limiting dissolution step in the case of BCS class II drugs (low solubility and high permeability). Formulation of statins in BCS class II as SMEDDS/SEDDS can increase their bioavailability. A 1.5- fold increase in bioavailability of SIM and atorvastatin when compared to Lipitor® tablets has been reported for SEDDS formulations of statins.The ability of a SEDDS to reduce degradation as well as improve absorption may be especially useful for drugs for which both low solubility and degradation in the GIT contribute to low oral bioavailability. Many drugs are degraded in physiological systems, which may be because of the acidic pH in the stomach, enzymatic degradation or hydrolytic degradation. Such drugs, when presented in the form of a SEDDS, canbe protected against these degradation processes, as a liquid crystalline phase in the SEDDS might act as a barrier between the drug and the degrading environment. SIM shows low solubility and degrades in the stomach due to the acidic environment, hence a SEDDS has been explored as a useful drug-delivery system.

Self-nanoemulsifying granules

Self-nanoemulsifying granules of ezetimibe and SIM have been formulated with the objective of improving bioavailability.The composition of the self-nanoemulsifying system (SNS) was optimized using various modified oils, and surfactant and co-surfactant mixtures. SNSs were mixed with water and the resultant emulsions were characterized for mean globule size and stability. SNSs were adsorbed on hydrophilic colloidal silicon dioxide to give free-flowing self nanoemulsifying granules. Self-nanoemulsifying granules effected a substantial increase in dissolution of the drugs as compared to the pure powder of the drugs. In-vivo evaluation

in rats showed a significant decrease in total cholesterol and triglyceride levels, as compared with the positive control, confirming the potential of self-nanoemulsifying granules as a drug-delivery system for poorly water-soluble drugs.

Polymeric emulsion beads

A polymeric emulsion bead is a pH-sensitive drug-deliverysystem consisting of a core and a capsule. The core is composed of oil and the dispersed drug. In one study, the lipid nanoparticles of lovastatin were encapsulated into the polymeric emulsion bead with high drug-loading efficiency. For application as an oral drug-delivery system, entericcoating was performed with a polymeric emulsion bead.

Lipid nanoparticle

SLNs are a novel colloidal carrier system, with potential in the range 100–150 nm, where theyare an alternative to polymers, being identical to oil-in-wateremulsions for parenteral nutrition, but with the liquid lipid ofthe emulsion replaced by a solid lipid. SLNs have manyadvantages, such as good biocompatibility, low toxicity andsufficient physical stability. Lipophilic drugs are also betterdelivered by SLNs. Altering the surface characteristics ofSLNs by coating them with hydrophilic molecules improvesplasma stability, biodistribution and the subsequent bioavailability of the drugs entrapped. Hence SLNs are a promisingsustained-release and drug-targeting system for statins.One of the main disadvantages of statin therapy is the shorthalf-life of statins and their low bioavailability NLCs made from mixtures of Precirol (Glyceryl palmitostearate) and squalene were prepared to investigate whether the bioavailability of lovastatin could be improved by oral delivery. It was observed that the oral bioavailability of lovastatin was enhanced from 4 to 24 and 13%, respectively when the drug was administered from NLCS containing Myverol (monoacylglycerol) and soybeanphosphatidyl choline.

Orally disintegrable tablets

The main objective of orally disintegrable tablets is to administer thedrug to a patient without the need for water. Such dosage forms have proved to be ideal for geriatric and pediatric populations, people suffering from dysphagia, situations where water is not available and for drugs undergoing high first-pass metabolism. The orally disintegrating tablet should disintegrate and optionally dissolve directly in the oral cavity, with the aid of saliva or in some cases a small amount of water. The resulting liquid is then easily swallowed and causes simple and immediate entry of the dissolved or dispersed drug into the GIT. In some cases, it may be absorbed by the oral mucosa or the esophageal lining as it passes down to the stomach. It should disintegrate in the oral cavity in a time not exceeding 1 min or so.

Osmotic-type dosage forms

Osmotic delivery is highly suited for controlled release of the drug, independent of environmental physiological factors, and has been utilized for developing drug-delivery systems of statins. In an osmotic pump dosage form, a core containing the simvastatin and/or lovastatin and optionally one or more osmotic excipients was typically encased by a semipermeable membranehaving at least one orifice. When the system wasexposed to body fluids, water penetrated through the semipermeable membrane into the core, which contained the drug and optional osmotic excipients that increased the osmotic pressure within the system. Consequently, the drug was released in a controlled manner through the orifice(s), in an attempt to equalize the osmotic pressure across the semipermeable membrane. In more complex pumps, the dosage form contains at least two internal compartments in the core. A first compartment contains the drug (statins) and the second compartment a polymer, which swells on contact with aqueous fluid. After ingestion, this polymer swells into the drug-containing compartment, diminishing the volume occupied by the drug, thereby delivering the drug from the device at a controlled rate over an extended period of time. Such dosage forms are often used when a zero-order release profile is desired.

Colon-targeted drug delivery system

Colon targeting of statins aims to provide localized absorption of the drug. The deficiencies of known formulations of statins have been overcome by providing a localized controlled absorption formulation, preferably for once-a-day administration, in which rapid release of the active ingredient preferentially occurs in the lower GIT, including the colon. This formulation provided significant plasma levels of a statin, itspharmaceutically acceptable salts,and esters, or its metabolites, and maintained them for an extended period after administration – at least 12 h and more up to 24 h after the burstrelease occurred. Local intestinal production of a greater amount of the active metabolite, probably through the activity of colonic natural flora or via other metabolic routes, is assumed to further enhance the desired clinical effect and allow achievement of intestinal drug levels of these metabolites that are unattainable by systemic or conventional oral delivery.

Buccal delivery

Among the various transmucosal sites available, the mucosa of the buccal cavity represents the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery in retentive dosage forms.Buccal drug delivery has several advantages over peroraldelivery. Administration of compounds via the mucosa of the oral cavity avoids pre-systemic metabolism in the GIT and hepatic first-pass elimination. In addition, the buccal mucosa is a well-vascularized tissue and is easily accessible for both application and removal of a delivery device. The inclusion of a permeation enhancer/enzyme inhibitor or a pH-modifier in the formulation, and versatility in design as a multidirectional or unidirectional release system and for local or systemic action, are other favorable aspects of the delivery systems. In one study, mucoadhesivebilayered buccal tablets of pravastatin sodium using carrageenan gum as the base matrix were prepared by the direct compression method and PVP K 30, PluronicF 127 and magnesium oxide were used to improve the tablet properties. The tablet was coated with an impermeable backing layer of ethyl cellulose to ensure unidirectional drug release. Different penetration enhancers were tested to improve the permeation of pravastatin sodium through the buccal mucosa. A formulation containing 1% sodium lauryl sulfate showed good permeation of pravastatin sodium acrossthe

mucosa. Histopathological studies revealed no mucosal damage. It was thus concluded that the buccal route is a possible alternative for the administration of pravastatin sodium.

Periodontal delivery

Periodontitis is an inflammatory disease that results in bone resorption, creating bony defects, which may cause tooth loss. Various drugs, including statins, have been studied for improvement of periodontal health and to achieve periodontal regeneration, using local delivery methods. The cholesterol-lowering drug SIM has been shown to stimulate murine calvarial bone growth after multiple injections. Thus a study was conducted to test if bone stimulation similar to periodontal therapy could be induced by two single-dose drug delivery systems.

Topical and local administration Biodegradable polymeric nanoparticletechnology

Recent studies have demonstrated the effectiveness of statins for the treatment of acne/or skin aging. Statins can increase nitric-oxide-mediated vasodilation and blood vessel relaxation and can be helpful to prevent further myocardial infarctions thereafter. Statins can also be used to promote angiogenesis in tissues, so they may be useful in conditions where new blood vessel growth is desirable. These beneficial effects have been obtained as a result of systemic administration of statins and the dose required is higher than the dose used in clinical settings. However, systemic administration of higher doses increases the risk of statin-related adverse effects, such as rhabdomyolysis and hepatic disorders. One solution to this is thelocal delivery of statins via nanoparticles made with biodegradable polymers. Here, the term 'local' means not only the topical but also oral, administration to cause the drug to be delivered selectively to, for example, ischemic or other tissues.

Transdermal delivery system for statin combination therapy

In transdermal delivery, the drug enters the systemic circulation without first passing into the hepatic portal system and traversing the liver. This route, therefore, avoids the first-pass phenomenon by which the liver can significantly reduce the amount of intact drug. Additionally, the drug avoids the enzymes present in the gut wall. The transdermal systems have been designed to produce a reduction or elimination of the side effects that commonly occur with statin drugs, and permit treatment of patients who cannot begin or continue statin therapy due to concomitant drug therapies, potential side effects, etc. Patient compliance for statin drugs is known to be low, especially over the long term, due to various factors. Side effects can include liver transaminase elevations, hepatitis, and liver failure (rare), myopathy, rhabdomyolysis and resulting renal failure (rare), proteinuria not related to myopathy and general malaise. The lipid-lowering effects of statin drugs are dose related, and the associated side effects are alsodose-related. For this reason, the more the lipid-lowering effect (at higher doses) the higher the likelihood and potential severity of side effects. Combination drug therapy can also be used to lower serum cholesterol because some drug combinations result in a synergistic effect, which allows lower doses of each drug in the combination. Lower doses can, therefore, cause a reduction in side effects, although some side effects may persist. Transdermal delivery of combinations of drugs in the same dosage form can be made with a single reservoir, matrix or adhesive or, if a biostability problem exists, it can be constructed with two separate reservoirs, adhesives or matrices – one for each compound. Some suitable transdermal technologies that are compatible with statin drugs include those used in D-TransTM, E-TransTM, MicrofluxTM, LatitudeTM, Latitude DuoTM, ClimaraProTM and other known technologies. Drugs that are advantageous in combination with or concomitantlywith a transdermally administered statin drug include a second statin drug, antihyperglycemic drugs (such as metformin and glyburide), antihypertensive drugs (such as lisinopril, propranolol, and nifedipine), fibrate drugs, cardiovascular drugs, coenzyme Q10 and others.

Parenteral delivery

Systemic SIM is known to reduce cholesterol and stimulate modest bone formation, but local surgical placement in polylacticacid domes causes robust bone formation and local swelling. A less invasive and more flexible injection protocol has been studied to evaluate the bone-inducing effects compared to surgical implantation. Bone formation rate, shortandlong-term bone augmentation histology, and mechanical properties were evaluated to characterize the new bone in a rat bilateral mandible model. Results demonstrated that multiple injections of 0.5 mg SIM effectively reduced soft-tissue swelling while preserving bone growth (60% increase of bone width at 24 days) compared to SIM dome placement (43%increase at 24 days). The long-term evaluation showed that 55% of the maximum new bone formed 24 days post-injection was retained for 90 days.

Liposomes

Liposomes have been shown to be promising carriers for enhancing the bioavailability of poorly soluble drugs such as ibuprofen, amphotericin B, cyclosporine, griseofulvin and statins. Statin liposomal formulations use a new and highly efficient liposomal encapsulation technique, termed micelleliposome exchange. This liposomal encapsulation greatly increases the solubility of statins, in one example more than 1000-fold. This formulation was mainly developed for thetreatment of rheumatoid arthritis. Preliminary studies in human plasma and synovial fluid has shown excellent stability.

Nanobeads

Statins stimulate bone formation *in vitro* and *in vivo* and, when given in large doses or by prolonged infusions, stimulate biomechanical strengthening of murine long bones with healing fractures. However, administration of statins in large oral doses or prolonged infusion to a fracture site is not a feasible therapeutic approach to hasten healing of human fractures. Research has been conducted to determine if lovastatin delivered in low doses in nanoparticles of a therapeutically acceptable scaffold could increase rates of healing. The studyexamined theadministration of lovastatin in biodegradable polymer nanobeads of poly(lactic-co-glycolide acid) and used a standard preclinical model of femoral fracture. It wasreported that these nanobeads stimulated bone formation

in vitro at 5 ng/ml, produced increased rates of healing in femoral fractures when administered as a single injection intothe fracture site, and decreased cortical fracture gap at 4 weeks as assessed by microcomputed tomography. These preclinical results suggest that lovastatin administered in a nanobeadpreparation may be therapeutically useful in hastening the repair of human fractures.

Hydrogel delivery system

Increases in bone formation have been demonstrated in mice and rats treated with statins, a group of molecules that increase the production of bone morphogenetic proteins-2 (BMP2) by stimulating their promoter. However, clinical use of statins (e.g. fluvastatin) is limited by the lack of a suitable delivery system to localize and sustain release. To harness the therapeutic effect of statins in orthopedic applications, a fluvastatin-releasing macromer was synthesized.

Bioerodible devices for intermittent release

The association polymer system of cellulose acetate phthalate (CAP) and Pluronic F-127 (PF-127) was used to create intermittent-release devices for mimicking the daily injection of SIM that has been reported to stimulate bone formation. To enhance solubility in water, prodrug SIM was modified by lactone ring opening, which converts the molecule to its hydroxyacid form. CAP/PF-127 microspheres incorporating SIM acid were prepared by a water–acetone–oil–water (W/A/O/W) triple emulsion process. Devices were then fabricated by pressure-sintering ultraviolet-treated blank and drugloadedmicrospheres. Using a multilayered fabrication approach, pulsatile release profiles were obtained.

Conclusion

The therapeutic advantage of statin treatment using novel drug-delivery methods has been well recognized by the scientific community. Many steps have been taken in this direction,but research must continue to provide ever-bettercontrols, improved efficacy, and targeting, better drug loading and lowering of the drug dose to diminish side effects andtoxicity. In this respect, the use of lipid nanoparticles of ultralowsize that have long circulating properties, and the added advantage of targetability by attachment of surface ligands,holds great promise for the future of statin delivery. Statinloaded microspheres in the PolyRing device and in intravenous formulations are desirable for clinical[4] use because they can be used in patients who are unable to swallow, in intensive care patients, and in patients about to undergo major surgery. Bioerodiable intermittent-release devices would also be beneficial to replace daily injections of statins. An innovative reformulation of a drug could extend its patent life. Newdelivery systems for old molecules, whether natural or out of patent, could lead to reduced side effects, achieving more effective therapy. There will be no breakthrough for a delivery system if only academic research groups are involved in its development.

REFERENCES

Bennett PN, Brown MJ. *Clinical Pharmacology.* London: Churchill Livingstone, 2003.

Benoit, D.S. *et al*. 2006. Synthesis and characterization of a fluvastatin-releasing hydrogel delivery system to modulate hMSC differ-entiation and function for bone regeneration. Biomaterials., 36: 6102–6110.

Benson HAE. 2005. Transdermal drug delivery: penetration enhance-ment techniques. *Curr Drug Deliv*, 2: 23–33.

Bhatnagar, D. *et al*. 2008. Hypercholesterolemia and management. *BMJ.,* 337: 993.

Bhatti, S. *et al*. Preparation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by compression method. *Ind J Pharm Sci*., 69: 80–84.

Butler, J. *et al*. Inventors; Pharmaceutical formulations and methods for modified release of statin drugs. United States patent US 20040132802. 2004 Jul 8.

Carminati, P, Duena, A.P. 2009. Inventors; Pharmaceutical composition comprising microcapsules of statins suspended in alkyl esters of poly unsaturated fatty acids (PUFA). United States patent US 20090196920. Aug 6.

Cavalli R *et al*. 1997. Sterilization and freeze-drying of drug-free and drug-loaded solid lipid nanoparticles. *Int J Pharm*., 148: 47–54.

Cavalli R *et al*. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. *Int J Pharm*., 238: 241–245.

Charcosset, C. *et al*. Preparation of solid lipid nanoparticles using a membrane contactor. *J Control Release.,* 108: 112–120.

Chen, C.C. *et al*. Effects of lipophilic emulsifiers on the oral administration of lovastatin from nanostructured lipid carriers: physicochemical characterization and pharmacokinetics. *Eur J Pharm Biopharm*., 74: 474–482.

Demierre M-F *et al*. Statins and cancer prevention. *Nat Rev Cancer*., 5: 930–942.

Dixit, R.P., Nagarsenker, M.S. 2008. Formulation and in vivo evaluation of self-nanoemulsifying granules for oral delivery of a combi-nation of ezetimibe and simvastatin. *Drug Dev Ind Pharm.,* 34: 1285–1296.

Egashira, K. 2010. Inventor; Pharmaceutical composition contain-ing statin encapsulated nanoparticle. United States patent US 20100086602. Apr 8.

Endres M. Statins and stroke. *J Cerebral Blood Flow Metabo,* 2005; 25: 1093–1110.

Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert Opin Drug Deliv 2007; 4: 403–416.

Fresta M *et al*. 1993. 5-Fluorouracil – various kinds of loaded liposomes- encapsulation efficiency, storage stability and fuso-genic properties. *Int J Pharm*., 99: 145–156.

Gao, P. 2004. Enhanced oral bioavailability of a poorly water soluble drug PNU- 91325 by supersaturable formulations. *Drug Dev Ind Pharm.,* 30: 221–229.

Garrett, I.R. *et al*. 2007. Locally delivered lovastatin nanoparticles enhance fracture healing in rats. *J Orthop Res* 25: 1351– 1357.

Gujman, H. *et al*. 2006. Inventors; Novel statin pharmaceutical com-positions and related methods of treatment. United States patent US 20060034815., Feb 16.

Ismail FA. Design and in vitro evaluation of polymeric formu-lae of simvastatin for local bone induction. Drug Dev Ind Pharm 2006; 32: 1199–1106.

Jang, G.D. 2000. Inventor; Intravascular stent. United States patent US 6152957. Nov 28.

Jansen, K.A. Inventor; Orallydisintegratable simvastatin tablets, United States patent US 20070087050. 2007 Apr 19.

Jenning V *et al*. 2000. Vitamin A-loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Eur J Pharm Biopharm.,* 49: 211–218.

Jeon, J.H. *et al*. 2007. Bioerodible devices for intermittent release of simvastatin acid. *Int J Pharm*., 340: 6–12.

Kang, B.K. *et al*. 2004. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int J Pharm* 274: 65–73.

Kanjickal D *et al*. 2004. Polymeric sustained local drug delivery system for the prevention of vascular intimal hyperplasia. *J Biomed Mater Res*., 68A: 489–495.

Krzic M *et al*. Improved skin oxygenation after benzyl nicotinate application in different carriers as measured by EPR oximetry in vivo. *J Control Release*., 70: 203– 211.

Kureishi Y *et al*. 2006. The HMG-CoA reductase inhibitor simvasta-tin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000; 6: 1004– 1010.

Lachman, L. *et al*. 1991. The Theory and Practice of Industrial Phar-macy. Bombay: Varghese Publishing House.

Lane EM. 2005. Inventor; Fairfield Clinical Trials LLC., assignee. Transdemal delivery system for statin combination therapy. United States patent US 20050281868. Dec 22.

Laufs U *et al*. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97: 1129– 1135.

Lazer HL. The role of statin therapy in the coronary bypass patient. Ann ThoracSurg 2009; 78: 730–740.

Lee Y *et al*. 2008. The effect of local simvastatin delivery strategies on mandibular bone formation in vivo. *Biomaterials*., 29: 1940–1949.

Lee, K.E. *et al*. 2003. Microencapsulation of lipid nanoparticles containing lipophilic drug. *J Microencapsul.,* 20: 489– 496.

Leuner, C., Dressman, J. 2000. Improving drug solubility for oral deliv-ery using solid dispersions. *Eur J Pharm Biopharm*., 50: 47–60.

Loftsson T, Duchene D. Cyclodextrins and their pharmaceuti-cal applications. Int J Pharm 2007; 329: 1–11.

Lovich, M.A. *et al*. 1998. Arterial heparin deposition: role of diffusion, convection and extravascular space. *Am J Physiol Heart CircPhysiol* 1998; 275: 2236–2242.

Manca, M.L. *et al*. 2005. Diclofenac-b-cyclodextrin binary systems: physicochemical characterization and in vitro dissolution and diffusion studies. *AAPS PharmSciTech.,* 6: 464–472.

Morris, S. *et al*. 2009. Injectable simvastatin in periodontal defects and alveolar ridges: pilot studies. *J Periodontol* 79: 1465– 1473.

Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles. *J Biotechnol*., 113: 151–170.

Muller, R.H. *et al*. 2000. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. *Eur J Pharm Biopharm.,* 50: 161–177.

Muller, R.H. *et al*. 2002. Nanostructured lipid matrices for improved microencapsulation of drugs. *Int J Pharm*., 242: 121–128.

Nelson, D.L., Cox, M.M. 2008. Lehninger Principles of Biochemistry. New York: Macmillan.

Patel, P.A. *et al*. 2008. Self emulsifying drug delivery system: a review. *Res J Pharm Technol.,* 1: 313–323

Pathak, D. *et al*. 2008. Solid dispersion of meloxicam: factorially designed dosage form for geriatric population. *Acta Pharm.,* 58: 99–110.

Patil, P. *et al*. 2007. Formulation of a self-emulsifying system for oral delivery of simvastatin: in vitro and in vivo evaluation. *Acta Pharm.,* 57: 111–122.

Pradeep, A.R., Thorat, M.S. 2010. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. *J Periodontol* 2010; 81: 214–222.

Prinz VP *et al*. 2008. Intravenous rosuvastatin for acute stroke treat-ment. Stroke., 39: 433–438.

Punitha, S., Girish, Y. 2010. Polymers in mucoadhesive buccal drug delivery system – a review. *Int J Res Pharm Sci.,* 1: 170–186.

Quintanar-Guerrero D *et al*. 2005. Adaptation and optimization of the emulsification-diffusion technique to prepare lipidicnano-spheres. *Eur J Pharm Sci.,* 26: 211–218.

Ranade VV, Holinger MA. Drug Delivery. 2004. New York, FL: CRC Press.

Roche VF. Antihyperlipidemic statins: a self-contained, clinic-eally relevant medicinal chemistry lesson. *Am J Pharm Edu.,* 2005; 69: 546–560.

Sami, F. *et al*. 2010. Effects of auxiliary substances on complexation efficiency and intrinsic dissolution rate of gemfibrozil-beta-CD complexes. *AAPS PharmSciTech.,* 11: 27–35.

Schubert MA, Muller-Goyman CC. 2003. Solvent injection as a new approach for manufacturing lipid nanoparticles-evaluation of the method and process parameters. *Eur J Pharm Biopharm*., 55: 125–131.

Shahgaldian P *et al*. 2003. Para-acyl-calix-arene based solid lipid nanoparticles (SLNs): a detailed study of preparation and stability parameters. *Int J Pharm*., 253: 23–38.

Sharma, V. *et al*. Modified polysaccharides as fast disintegrating excipients for orodispersible tablets of roxithromycin. AAPS PharmSciTech 2008; 9: 87–94.

Shen, H., Zhong, M. 2006. Preparation and evaluation of selfmicro-emulsifying drug delivery systems (SMEDDS) containing atorvastatin. *J Pharm Pharmacol*., 58: 1183–1191.

Shidhaye, S.S. *et al.* 2010. Buccal drug delivery of pravastatin sodium. *AAPS PharmSciTech.,* 11: 416–424.

Silva, T.D. *et al*. 2010. Preparation and characterization of solid disper-sion of simvastatin. *Drug Dev Ind Pharm.,* 36: 1348–1355.

Singh, S.K. *et al*. 2009. Development and characterization of a lovastatin-loaded self-microemulsifying drug delivery system. *Pharm Dev Technol.,* 14: S1097–S9867.

Singla, N. *et al*. 2009. Oral bioavailability of simvastatin novel formulation in albino rats. *J Pharm SciTechol*., 1: 84– 87.

Song C, Liu S. 2002. A new healthy sunscreen system for human: solid lipid nanoparticles as carrier for 3, 4, 5-trimethoxybenzoylchitin and the improvement by adding Vitamin E. *Int J BiolMacromol.,* 36: 116–119.

Stalenhoef, A.F.H. 2005. Management of mixed hyperlipidemia. *Eur Heart J*., 2

Stella, V.J. *et al*. 1999. Mechanisms of drug release from cyclodextrin complexes. *Adv Drug Deliv Rev*., 36: 3–16.

Thylin, M.R. *et al*. 2002. Effects of simvastatin gels on murine calvarial bone. *J Periodontol.,* 73: 1141–1148.

Tsompanidi, E.M *et al*. 2010. HDL biogenesis and functions: role of HDL quality and quantity in atherosclerosis. Atherosclerosis, 208: 3–9.

Uekama, K. 2004. Design and evaluation of cyclodextrin based drug formulation. *Chem Pharm Bull.,* 52: 900–915.

Uner, M. *et al*. 2005. Solid lipid nanoparticles (SLN) and nanostruc-tured lipid carriers (NLC) for application of ascorbyl palmitate. *Pharmazie.,* 60: 577–582.

Vasconcelos T. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007; 12: 1068–1075.

Venkataram S *et al*. 2003. Inventors; HMG CoA reductase inhibiting composition, method for competitively inhibiting HMG CoA reductase using such composition. United States patent US 20030162827. Aug 28.

Vishwanathan A. 2008. A thesis on in vitro characterization of simv-astatin loaded microspheres in the PolyRing device. 1–79.

Yie, H. *et al*. 2009. Inventors; Pficker Pharmaceuticals Ltd., assignee. Sustained-release preparation of statin drug. United States patent US 20090196910. Aug 6.

Yoshinari, M. *et al*. 2007. Controlled release of simvastatin acid using cyclodextrin inclusion system. *Dent Mater J*., 26: 451–456.

Yuk, S.H. *et al*. 1995. pH-sensitive drug delivery system using o/w emulsion. *J Control Release.,* 37: 69–74.

****