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Review

Statins therapy: a review on conventional and novel formulation approaches

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Abstract

Background and objective High levels of cholesterol lead to atherosclerosis, a factor predisposing to the development of coronary artery disease. Statin drugs, i.e. HMG-CoA reductase inhibitors, have been known since the end of the last century for their benefits against cardio- and cerebrovascular diseases and are widely used clinically. 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 forms of statins.

Key findings Statin drugs can reduce the endogenous synthesis of cholesterol and prevent the onset and development of atherosclerosis, and are therefore used as an effective treatment against primary hypercholesterolemia. At present, statin drugs are most often administered orally, on a daily basis. After administration, the bioavailability and the general circulation of statin drugs is fairly low due to the first-pass metabolism in the liver and clearance by the digestive system. Extensive pharmaceutical research in understanding the causes of low oral bioavailability has led to the development of novel technologies to address these challenges.

Summary These technologies vary from conventional dosage forms to nanoparticulate drug-delivery systems, and have the potential to cause improvements in bioavailability and consequently therapeutic efficacy.

Keywords conventional drug delivery systems; novel drug delivery systems; statins

Introduction

As a regulator of homeostasis, a precursor to the corticosteroids and sex hormones, and a critical factor in the maintenance of cell wall integrity, cholesterol is essential to life.[1] 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). 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.

High levels of this lipophilic substance (LDL) leads to atherosclerosis, a predisposing factor to the development of coronary artery disease (CAD). Atherosclerosis involves an accumulation of cholesterol esters and other blood lipids and lipoproteins in macrophage cells found in the intima of arteries. Lipid-engorged macrophage cells become foam cells, and foam cell infiltration progresses to fatty streaks in the arterial wall. Plaque formation, thrombosis and vessel occlusion can follow, leading to CAD,[2] which involves one or more specific cardiovascular pathologies, including myocardial infarction, cardiac ischemia and angina. Between 13 and 14 million people in the USA are believed to suffer from this complex and life-threatening condition and over 25 million people worldwide are expected to die from cardiovascular-related pathologies by the year 2020.[3]

In addition to free cholesterol and its esters, triglycerides (long-chain fatty acid esters of the polyalcohol glycerol) and lipoproteins (macromolecular substances that solubilize blood lipids) are found in the bloodstream. High levels of triglycerides and the lipid-rich lipoproteins, which promote the formation of atherosclerotic plaques (LDLs and very low density lipoproteins),[4] are also a significant health risk in developed nations where lifestyles are sedentary, stress is high and fat-laden meals are too often the norm. Patients with elevated

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levels of triglycerides and LDLs are at risk of myocardial infarction and/or cerebral vascular accident (stroke), although the role of cholesterol as a stroke risk factor is less clear.[5]

It is clear that elevated blood cholesterol level is a major risk factor for CHD,[6] and many studies have shown that the risk of CHD events can be reduced by lipid-lowering therapy.[7] Prior to 1987, the lipid-lowering armamentarium was limited essentially to consumption of a low saturated fat and cholesterol diet, the bile acid sequestrants cholestyramine and colestipol, nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. With the introduction in 1987 of lovastatin, the first inhibitor of HMG-CoA reductase to become available for prescription, physicians were able for the first time to obtain comparatively large reductions in plasma cholesterol with very few adverse effects.[8]

Statin drugs have been known since the end of the last century for their benefits for cardio- and cerebrovascular diseases. Statin drugs can reduce the endogenous synthesis of cholesterols[9] and prevent the onset and development of atherosclerosis, and are therefore used as an effective therapy against primary hypercholesterolemia. In addition to their cholesterol-lowering properties, statins exert a number of pleiotropic (non-lipid-lowering actions), vasculoprotective actions. The pleiotropic effects of statins are postulated to be primarily responsible for their anti-ischemic and anti-anginal properties.[10] These include improvement of endothelial function, enhancement of the ischemic vasodilatory response, protection from ischemia–reperfusion injury, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, immunomodulatory actions, regulation of progenitor cells and stabilization of atherosclerotic plaques.[5,11]

The statin drugs known as hypolipidemic drugs have recently been examined for their usefulness in the treatment of the conditions such as osteoporosis, Alzheimer's disease,[12] cardiac diseases, organ transplantation, stroke and diabetes.[13] The synergism of statins with other drugs can also be useful in reducing the incidence of cardiovascular events. For example, synergism of simvastatin with losartan (angiotensin II type 1 receptor antagonists) prevents angiotensin II-induced cardiomyocyte apoptosis (which has an important role in the transition from compensatory cardiac remodelling to heart failure) *in vitro*. The synergism may provide a new therapeutic approach for the prevention of cardiac remodelling.[14] With CPU 0213, an endothelin receptor antagonist, simvastatin relieves renal lesions by blunting hypercholesterolaemia caused by the upregulated endothelin pathway system, induced nitric oxide synthetase and matrix metalloproteinase 9 in the kidney.[15]

Since the advent of statins, the pharmacological agents put into therapeutic use include lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and cerivastatin. Lovastatin, simvastatin and pravastatin have been derived from fungi, while fluvastatin, atorvastatin and rosuvastatin are entirely synthetic. Cerivastatin sodium, a novel statin, is a synthetic, enantiomerically pure pyridine derivative that effectively reduces serum cholesterol levels at microgram doses.[16] A number of clinical studies have confirmed its high pharmacological efficacy, its excellent pharmacokinetic properties, with fast and nearly complete absorption after oral uptake, linear kinetics over a broad concentration range, and a favourable safety profile.[17] Adverse effects on muscle, such as myopathy and rhabdomyolysis, have been noted in some statins, but are rare at standard doses.

In the liver, increasing levels of transaminases are unusual at standard doses of statins. Myopathy muscle pain and weakness, occurring in fewer than one in 10 000 patients, have been documented on standard statin doses. However, this risk varies between statins, and increases with use of higher doses and interacting drugs. Rhabdomyolysis is a rarer and more severe form of myopathy, with myoglobin release into the circulation and a risk of renal failure. Asymptomatic increases in concentrations of liver transaminases are recorded with all statins, but are not clearly associated with an increased risk of liver disease.[18] Unfortunately, cerivastatin has recently been withdrawn from the market because of 52 deaths attributed to drug-related rhabdomyolysis, leading to kidney failure. The risk was found to be higher among patients who received the full dose (0.8 mg/day) and those who received gemfibrozil concommitantly. The risk of rhabdomyolysis is ten times more common with cerivastatin in comparison to other approved statins.[19,20]

Nitrogen-containing bisphosphonates (alendronate and risedronate), which are widely used to treat osteoporosis, act as inhibitors of farnesyl pyrophosphate synthase, one of the key enzymes of the mevalonate pathway, and thus may have the potential to enhance the effect of statins. There would therefore be a risk of synergistic action between bisphosphonates and statins in the development of rhabdomyolysis while treating osteoporosis with hyperlipidaemia.[21] For most people, statins are safe and well-tolerated, and their widespread use has the potential to have a major effect on the global burden of cardiovascular disease.

The therapeutic efficacies of different statin molecules are dependent on the pharmacokinetics of the molecules, which in turn are dependent on the physicochemical properties of the molecule(s) in question. For instance, the solubility of statins in water is widely different, as indicated by their partition coefficients, which range from −0.23 to 4.7. All the active compounds are acid and have pKa values of approximately 5.5. The pharmacokinetic profiles of the statins are vary widely, but different statins have the common property of large intra- and interindividual variability when taken by the oral route.

Chemically, HMG-CoA reductase inhibitors can be divided into two categories: those containing a lactose function (lovastatin, simvastatin) and those containing a hydroxyl acid (or salt). The latter category involves, among others, pravastatin sodium and fluvastatin sodium. All the HMG-CoA reductase inhibitors are relatively unstable because the lactose function is very easily hydrolysed and this reaction is catalysed by several factors, such as like oxygen, humidity, acidity, alkalinity and temperature.

Another way of classifying these compounds is based on their lipophilicity, which is considered to be of importance since the hepatoselectivity of statins is related to their lipophilicity. The more lipophilic statins (cerivastatin, simvastatin, atorvastatin and fluvastatin) tend to achieve a higher level of exposure in non-hepatic tissues, while the hydrophilic statins (rosuvastatin and pravastatin) tend to be more

hepatoselective. The difference in selectivity is because lipophilic statins are passively and non-selectively diffused into both hepatocytes and nonhepatocytes, while the hydrophilic statins are largely transported only into the hepatocytes, where they exert their therapeutic effect.[22,23]

The main challenge for formulating a pharmaceutical composition comprising statin derivatives is therefore to obtain a stable formulation with high bioavailability after oral administration.[24]

Conventional immediate-release dosage form of statins

At present, statin drugs are most often administered orally on a daily basis (Table 1). Oral ingestion is the most convenient and commonly employed route of drug delivery due to ease of administration, high patient compliance, cost-effectiveness, minimal sterility constraints and flexibility in the design of the dosage form. As a result, many generic drug companies produce bioequivalent oral drug products. The high costs and time involved in new drug development, expiry of patents for a significant number of drug molecules, ease of manufacturing and ready availability of technology for the production of oral drug products are also driving the generic pharmaceutical companies towards the development of bioequivalent oral dosage forms. However, there are problems associated with daily oral administration. For example, after oral administration, the bioavailability and the general circulation of statin drugs is fairly low, due to first-pass metabolism in the liver and clearance by the digestive system. The oral bioavailability depends on several factors, including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are poor solubility and low permeability. Extensive pharmaceutical research has focused on understanding the causes of low oral bioavailability and has led to the development of novel technologies to address these challenges.

As the tendency of the poorly water-soluble drugs to enter the development pipeline has increased, so the challenges of finding innovative methods for developing stable and bioavailable dosage forms has grown too. Drug delivery approaches aim to develop a carrier system that can hold the drug molecules effectively and can deliver them to the right destination and at the same time permit control of drug-release characteristics. For water-insoluble drugs with high permeability, drug absorption by the gastrointestinal tract (GIT) is limited by the drug dissolution rate. Solubility and dissolution are good pointers and major contributors to drug bioavailability and are the driving forces for the development of new drug delivery systems.

Figure 1 depicts the differences in statin biodistribution after administration by conventional immediate–release (IR) and by modified-release delivery systems. Apart from the kinetic variation shown in the plasma level plots, conventional IR pharmaceutical formulations of statins allow the penetration of polar metabolites into the systemic circulation. Subsequent conversion into active open acid forms results in the inhibition of ubiquinone biosynthesis in peripheral tissues. Depletion of ubiquinone levels in peripheral tissues is believed to be the main cause of the sometimes fatal adverse events of HMG-CoA reductase inhibitor activity. Modified-release formulations of statins are designed to minimize the penetration of polar metabolites into the systemic circulation. They are designed to increase the hepatic availability of statins by minimizing release of drug in the stomach, duodenum and/or jejunum, while optimizing uptake from the ileum and/or colon to the hepatic portal vein. This can enhance drug availability to the hepatocytes, and can improve the therapeutic efficacy of the formulations while minimizing peripheral exposure and the potential for unwanted side effects.

The advantage of modified-release preparations over conventional forms can be exemplified by studying the case of fluvastatin. At high doses, the pharmacokinetics of fluvastatin IR formulations are non-linear, possibly due to saturation of hepatic uptake. Fluvastatin delivery to the liver in a slower but sustained fashion would be expected to avoid hepatic saturation without elevating systemic drug levels. In a pooled analysis, a comparison was made of the efficacy and tolerability of extended-release (XL) 80-mg and IR 40-mg formulations of fluvastatin in lowering LDL cholesterol (LDL-C) and triglyceride (TG) levels and raising HDL cholesterol (HDL-C) levels in patients with hypercholesterolemia. It was concluded that once-daily administration of fluvastatin XL 80 mg provided enhanced efficacy, producing an additional 10.4% reduction in LDL-C levels above that produced by fluvastatin IR, and a greater increase in HDL-C levels, particularly in patients with elevated TG levels ($P < 0.05$). Fluvastatin XL 80 mg had a good tolerability profile and was effective as a starting treatment and maintenance lipid-lowering treatment in patients

Table 1 A compilation of marketed formulations of statins

Statins	Dosage form	Brand	Manufacturer
Lovastatin	Tablet	Elstatin®	Glenmark Pharmaceuticals, India
		Mevacor®	Merck, Germany
Simvastatin	Tablet	Simvotin®	Ranbaxy Laboratories, India
		Starstat®	Lupin Laboratories, India
Atorvastatin	Tablet	Atorlip®	Ranbaxy Laboratories, India
		Lipitor®	Pfizer, USA
Pravastatin	Tablet	Pravachol®	Bristol-Myers, USA
Fluvastatin	Capsule	Lescol	Novartis, USA
	Prolonged-release tablet	Lescol	Novartis, UK
Rosuvastatin	Tablet	Crestor	AstraZeneca, USA

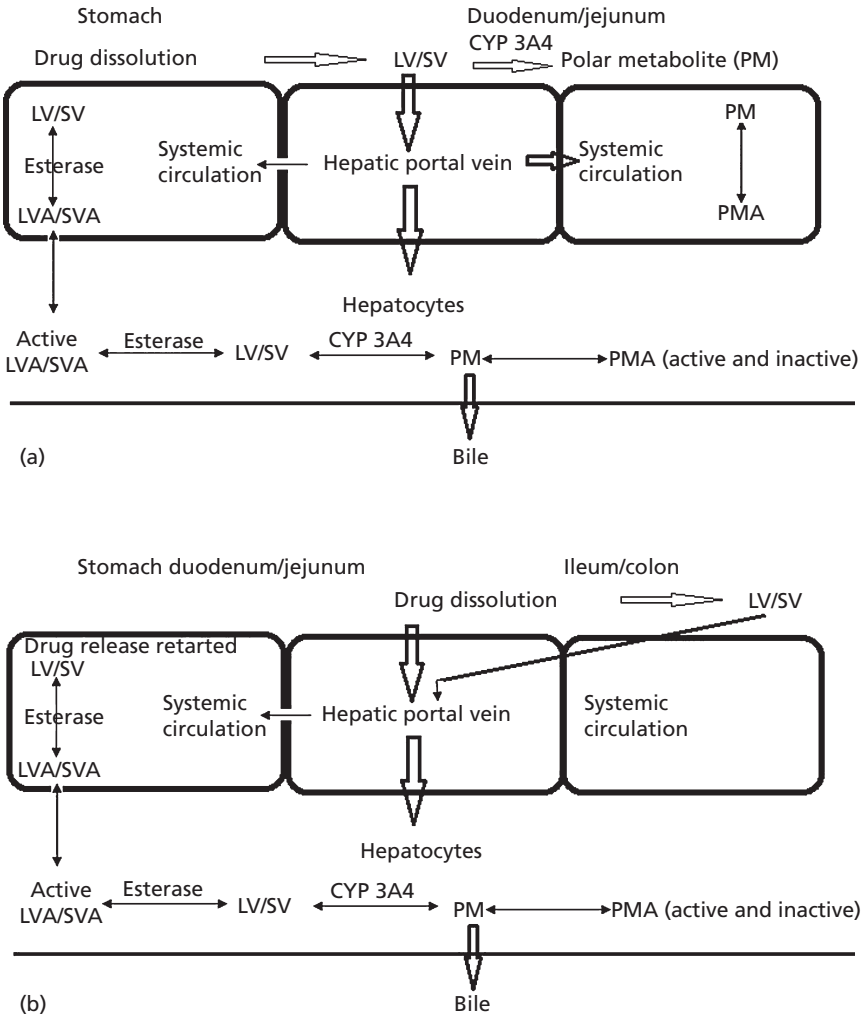

Figure 1 Comparison of (a) immediate release and (b) modified release of statins.

with type II hypercholesterolemia. Adverse events were mild, with similar frequency in all treatment groups.[25] Thus the role of formulation is evident and hence this review compiles research reports focused on product development aimed at improving the therapeutic efficacy of statins. Some key findings on statins have been compiled in Table 2.

Solubility enhancement approaches

Solid dispersion

Statins are poorly soluble drugs and solid dispersion is one of the most promising and efficient approaches for solubility enhancement and improvement of dissolution rate, which lead to higher bioavailability.[40] The term 'solid dispersion' refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drug. The mixture can be either crystalline or amorphous. There are many types of solid dispersion, including simple eutectic mixtures, solid solutions, glass solutions, amorphous precipitations in a crystalline carrier, etc. A variety of methods are available for preparation of solid dispersions, such as the melting method, the solvent method,[41] melt evaporation, melt extrusion lyophilization, the melt agglomeration process, use of surfactants, electrospinning and supercritical fluid technology[42] to name just some. Statins have also been investigated for their possible solubility enhancement by the solid dispersion technique.

Simvastatin (SIM) solid dispersions with polyethylene glycol (PEG 6000) or polyvinylpyrrolidone (PVP K15) were prepared and their stability and dissolution properties were investigated. Tablets containing a solid dispersion of SIM:PEG 6000 were prepared and their dissolution profiles revealed a gradual release of SIM, with a final dissolved quantity greater than 80% within 60 min. However, the solid dispersion of SIM:PVPK15 showed drug degradation. Hence it was concluded that the preparation of a solid dispersion of SIM with PEG 6000 would be a promising strategy to improve the bioavailability of the drug.[43] In another study,

Table 2 Key research reports on novel statin formulations

Drug-delivery approaches	Outcomes	Clinical significance
Solid dispersion	Enhancement in solubility	Promising strategy to improve the bioavailability of the statins[26]
Lipid nanoparticles	Improvements in bioavailability	Lipid nanoparticles may be a promising sustained-release and drug-targeting system for statin drug therapy[27–30]
Periodontal gels	Effects of simvastatin gels on murine calvarial bone	For the treatment of chronic periodontitis[31–33]
Biodegradable polymeric nanoparticle technology	Local delivery of statin via nanoparticles; useful in conditions where new blood vessel growth is desirable	To reduce the chances of adverse effects related to statins, such as rhabdomylosis and hepatic disorders[34]
Nanobeads	Locally delivered lovastatin nanoparticles enhance fracture healing in rats	Lovastatin administered in a nanobead preparation may be therapeutically useful in hastening repair of human fractures[35]
Hydrogel delivery system	Fluvastatin-releasing hydrogels may be useful in bone-tissue engineering applications	To harness the therapeutic effect of statins in orthopedic applications[36]
Bioerodible devices for intermittent release	Devices intermittently releasing simvastatin warrant for locally promoting osteogenesis	Used for mimicking the daily injection of simvastatin that has been reported to stimulate bone formation[37]
Statin-loaded microspheres in PolyRing device	Drug was encapsulated within the microspheres, which in turn were embedded in a polyethylene glycol block as a polymeric vascular wrap	Statin can be potent agent with antiproliferative properties for the inhibition of vascular intimal hyperplasia[38]
Plum-pudding gels	Manipulation of the relative hydrophobicities of both microgel and matrix components of plum-pudding gels results in tightly regulated release of fluvastatin over an extended time period	A potential therapeutic modal relevant to initiation and propagation for prevention of in-stent restenosis[39]

SIM solid dispersions were prepared with PEG 4000 by fusion cooling and solvent evaporation techniques, while a solid dispersion with PVP K30 was prepared by the solvent evaporation technique, in different drug-to-carrier ratios. Although the aqueous solubility of SIM was favoured by both polymers, the solid dispersion prepared with PVP K30 showed higher improvement in wettability and dissolution rate of SIM. When formulated as tablets, the solid dispersions prepared with PEG4000 and PVP K30 showed significant improvement in the release profile of SIM as compared to tablets containing SIM without PEG 4000 or PVP K30.[26]

Cyclodextrin inclusion system

The starch derivatives, cyclodextrins (CD) are the most widely investigated excipients for enhancing the solubility and dissolution rate of poorly soluble drugs and have been recognized as an important group of pharmaceutical excipients.[44] They are cyclic oligosaccharides consisting of (α-1,4)-α-D-glucopyranose units, and have a relatively hydrophobic central cavity and a hydrophilic outer surface. The hydrophilic exterior surface of CD molecules makes them water-soluble and the hydrophobic cavity provides a microenvironment for inclusion of appropriately sized non-polar molecules. CDs are capable of forming inclusion complexes with many drugs by including either the whole or partial drug molecules inside the cavity. In an aqueous solution, the complexes get readily dissociated, and the free drug molecules are in relatively rapid dynamic equilibrium with drug molecules bound within the CD cavity.[45–47] These non-covalent complexes show new physicochemical characteristics when compared with the guest molecules, including better stability, higher aqueous solubility, increased bioavailability and fewer undesirable side effects.[48] Therefore, if it is possible to form statin–CD inclusion complexes and control their solubility, it should be possible to control their drug-release properties. Since hydrophobic interactions between statin and CD would be the main mechanism for forming statin–CD inclusion complexes, it is important to control the hydrophobicity of the guest molecule. The hydrophobicity of statins is highly influenced by pH, as the characteristic dissociation of the carboxyl group depends on the pH of the surrounding medium. In addition, the crystallinity of the inclusion complexes will also influence the release character of the statin, which would concomitantly affect the solubility of statin–CD complex.

In general, the release character is influenced by two factors: the degree of substitution of the CD and the crystallinity of the inclusion complexes. Degree of substitution plays an important role in balancing CD water solubility and its ability to form complexes. Raising the degree of substitution induces binding of guests to CDs by increasing the surface area available for binding. In one study, the results showed that the lower the pH value of the SIM–CD solution, the higher was the degree of substitution. This was a consequence of the hydrophobic character of the guest molecule, SIM. SIM has a carboxylic acid group, which is almost completely dissociated at pH 6.8, and this carboxylic group gets gradually deionized with a decrease in pH. At a low pH values, therefore, SIM becomes stable and hydrophobic, resulting in enhanced hydrophobic interaction between SIM and CD. The crystallinity of the SIM–CD complexes influence the solubility of the coatings. These crystalline structures may have retarded the dissolution rate of the coatings, resulting in a delayed release of SIM.[49]

Solutions

As stated above, one of the main drawbacks associated with statins is poor aqueous solubility, resulting in a poor dissolution rate of the drug in the GIT and consequently limited bioavailability of drug. Poor aqueous solubility of statins is generally not related to their physical form, whether amorphous or crystalline. Many attempts have been made to improve solubility, including micronization and drug encapsulation techniques, but in these the active ingredient remains in a solid state so a poor dissolution rate persists. Conventional solid dosage forms of hydrophobic active ingredients, e.g. tablets or multiparticulates in capsules, have slow and incomplete dissolution and absorption, and they are therefore associated with chances of drug–food interaction.

One probable solution to these problems is liquid formulations of statins, but drug precipitation, the packaging challenges of non-solid formulations, chemical instability, capsule–shell incompatibility and potential leakage on storage are major drawbacks. In recent years, the application of solubilization phenomena to pharmaceutical systems has greatly increased. Solubilization is the spontaneous passage of poorly water-soluble solute molecules into an aqueous solution of soap or a detergent, in which a thermodynamically stable solution is formed.[50] In one innovation, an HMG-CoA reductase-inhibiting composition comprising atorvastatin, solubilizer (N-methyl pyrrolidone) and a mixture of carriers (PEG 400, PEG 1540, PEG 4000, etc.) has been claimed to improve bioavailability. The formulation can be given as a solution or suspension through conventional dispensing means, e.g. gelatin capsules, and it can also be formulated as either a tablet or a suppository. The developers formulated a solution of atorvastatin calcium, N-methyl pyrrolidone and PEG 400 that can be directly filled in a hard gelatin capsule. Alternatively it can be formulated as a solid dispersion and then filled in a hard gelatin capsule or a buccal tablet. A bioavailability study of the single-dose oral bioavailability of the developed atorvastatin buccal tablet showed a relative bioavailability of 49.77% in comparison with Lipitor®.[51]

Formulative approaches

Peroral administration

Omega-3 ester-based oil suspension

These suspensions are substantially free of any drug–food effects, 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 a portion thereof. Typical preparations are suspensions of amorphous and/or crystalline particles of one or more statins in omega-3 oil.[52]

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 eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) ratio of 1 : 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.[53]

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-emulsifying formulations, 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 and modification of their pharmacokinetic profiles.[54]

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 aqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium-chain triglyceride oils and non-ionic surfactants, the latter being less toxic. On peroral administration 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 solid dosage forms.

The process by which self-emulsification takes place is not yet understood completely. However, according to Reiss,[55] self-emulsification occurs when the entropy change that favours 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 direct function 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 interfacial area and subsequently the free energy of the systems. The emulsions resulting from aqueous dilution are therefore stabilized by conventional emulsifying agents, which form a 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 energy required to form the emulsion is either very low and positive, or negative (in which case the emulsification process occurs spontaneously). Emulsification requiring very little input energy 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 microemulsion preconcentrates, as the microemulsion is formed on dilution in aqueous media.

Incorporation of drug 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.[56]

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, can be 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.[57]

SMEDDS of SIM have also been prepared from labrasol, plural oleique, transcutol and maisine oil. These formulations were studied for bioavailability in albino rats and compared with SIM tablets. The mean plasma concentration profile for SMEDDS of SIM indicated better drug absorption than the oral tablet formulation. The pharmacokinetic parameters of SIM in the test (SMEDDS) and the reference treatments showed that peak concentrations of 24.83 ng/ml and 16.84 ng/ml were attained at 0.58 h and 0.92 h after administration, respectively. The self-emulsifying formulation was therefore found to be super-bioavailable as compared to the reference product, Zocor® 40 mg tablets.[58,59]

In another report, SIM SEDDS were formulated using a 1 : 1 (v/v) mixture of diesters of caprylic/capric acids and polyglycolysed glycerides, with varying concentrations of polyoxy castor oil and C8/C10 mono-/diglycerides. In-vivo performance of the optimized formulation was evaluated in rats using pharmacodynamic marker parameters such as plasma total cholesterol (CH), TG and HDL–CH for 21 days. SEDDS containing 9.1% (m/m) SIM and 23.0% (m/m) of each excipient showed a minimum mean droplet size of 124 nm and optimal drug diffusion. After oral administration for 21 days in rats, the test formulation produced a significant reduction in plasma CH and TG (around 5-fold and 4-fold, respectively) compared to the reference SIM suspension formulation, while the HDL-CH concentration was markedly higher (2-fold).[60] The study illustrates the potential of SIM SEDDS for oral administration and their good biopharmaceutical performance. Similarly, a study aiming to develop, optimize and evaluate a SMEDDS of the poorly water-soluble drug lovastatin demonstrated the potential of these systems to enhance drug absorption without interaction or incompatibility between the ingredients.[61]

One of the challenges in formulating microemulsions, SEDDS or SMEDDS is the limited availability of formulation components with ‘generally recognized as safe’ (GRAS) status. Liposomal formulations may therefore be preferred over colloidal drug-delivery systems for solubilization and enhanced oral bioavailability of the drugs,[62] because of the large number GRAS-status phospholipid constituents that can be used in liposomal formulations.

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.[63]

Polymeric emulsion beads

A polymeric emulsion bead is a pH-sensitive drug-delivery system consisting of a core and a capsule. The core is composed of oil and the dispersed drug. A novel semi-interpenetrating networks (semi-IPNs) system has been developed to provide a capsule network that shows pH-sensitive swelling behaviour. The first network consists of sodium alginate, which disintegrates in the intestinal fluid. The other is a polyacrylic acid, which provides pH-sensitive swelling capacity to the capsule network.[64] 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, enteric coating was performed with a polymeric emulsion bead. The drug-release pattern was controlled by the composition of the capsule materials and the environmental pH. A pH-sensitive drug-release pattern, due to both the diffusion of drug through

the capsule network and the escape of drug from the surface undergoing disintegration after swelling, was dependent on the chemical composition of the capsule network and the pH of the release medium.[65]

Lipid nanoparticles

Since the 1990s, solid–lipid nanoparticles (SLN) have been reported to be an advantageous alternative to emulsions, liposomes, microparticles and their polymeric counterparts, for various application routes. SLNs are a novel colloidal carrier system, with potential in the range 100–150 nm, where they are an alternative to polymers, being identical to oil-in-water emulsions for parenteral nutrition, but with the liquid lipid of the emulsion replaced by a solid lipid.[66] SLNs have many advantages, such as good biocompatibility, low toxicity and sufficient physical stability. Lipophilic drugs are also better delivered by SLNs.[67] Altering the surface characteristics of SLNs by coating them with hydrophilic molecules improves plasma stability, biodistribution and the subsequent bioavailability of the drugs entrapped. Hence SLNs are a promising sustained-release and drug-targeting system for statins.

One of the main disadvantages of statin therapy is the short half-life of statins and their low bioavailability. Researchers have therefore focused, as the first important step, on the development of methods to reduce the uptake of the nanoparticles by the cells of the reticuloendothelial system (RES). In one of the methods examined, coating of nanoparticles and nanocapsules with hydrophilic substances, such as polyoxypropylene block copolymers (poloxamers), chitosan, polyvinyl alcohol and PEGs, has been shown to have clear benefits, reducing phagocytic uptake but with minimal non-specific interaction with other proteins.

SLNs are produced by several methods, extensively described in the literature. These include high-pressure homogenization (cold and hot homogenization),[68] breaking of o/w microemulsions,[69] solvent emulsification–evaporation[70] or solvent emulsification–diffusion,[71] solvent injection,[72] preparation via water-in-oil-in-water double emulsion (w/o/w), high-shear homogenization[73] and/or ultrasonic dispersion,[74] and preparation membrane contactor.[75]

Today, the high-pressure homogenization technique has been shown to be the most effective approach. Its advantages include a narrow particle-size distribution of the product with a low content of microparticles (>5 μm is requested for intravenous injections), higher particle content in the dispersions, avoidance of organic solvents, acceptability of the homogenization equipment by regulatory authorities (even for parenteral products), scale-up feasibility and the availability of homogenization lines in industry. Depending on the size of production-scale homogenizers, a wide production range is possible.[76] Factors affecting the loading capacity of a drug in lipid are the solubility of drug in the lipid melt, the miscibility of the drug and lipid melts, the chemical and physical structures of the solid matrix lipid, and the polymorphic state of the lipid material.[77]

SLNs can be modified by incorporation of liquid lipid into the solid structure, giving nanostructured lipid carriers (NLC), which can overcome some of the limitations of older-generation SLNs. Muller *et al*. described NLCs with a special structure designed for better drug accommodation, which increased the payload and prevented drug expulsion during storage. In NLCs, the oil content of the particles dissolves the drug and combines controlled-release characteristics with high drug-loading capacity.[78]

Sustained-release lovastatin SLN, developed using triglycerides by hot homogenization followed by ultrasonication, was compared with a normal suspension. A stable lovastatin SLN was developed with a mean size range of 60–119 nm and a zeta potential range of −16 to −21 mV. More than 99% of the lovastatin was entrapped in the SLN. Lovastatin was dispersed in an amorphous state and triglycerides were in the $\beta 1$ form. In-vitro stability studies showed the slow release and stability of lovastatin SLNs. Bioavailability studies conducted in male Wistar rats after intraduodenal administration of lovastatin suspension and SLN demonstrated an increase in relative bioavailability of both lovastatin and lovastatin hydroxy acid (an active metabolite of lovastatin) of 173% and 324%, respectively, compared to the reference lovastatin suspension.[27]

In a series of investigations on SIM in our own laboratory, SLNs were prepared using glyceryl monostereate (GMS) and the optimized formulation was identified as the one that exhibited a particle size of 258.5 nm, Entrapment efficiency 75.81% and 82.67% cumulative drug release after 55 h. The release kinetics of the optimized formulation best fitted the Higuchi model and the recrystallization index of the optimized formulation was found to be 65.51%.[28] The high recrystallization index of SLNs indicated fewer chances of polymorphism and consequent drug expulsion on ageing. Pharmacokinetic studies in rats clearly indicated an increase in relative bioavailability (1.86 times) due to minimization of hepatic first-pass metabolism of SIM in the form of an SLN in comparison to a SIM suspension. This was confirmed by biodistribution studies, which demonstrated poor accumulation of the SLN in the liver within 2 h of administration.[29] In a further investigation, the lipid was varied and the SLNs of SIM were prepared using compritol 888ATO as the lipid component. The optimized formulation, with a particle size of 271.18 nm, entrapment efficiency 68.16% and 76.23% cumulative drug release, was evaluated in mice for its biodistribution and pharmacokinetics, using technetium-99 m (Tc-99m) radiolabelling. The relative bioavailability of the SIM of the optimized SLNs was found to be 220%, substantiating the protective action of SLNs against liver metabolism. However, although the drug initially bypassed the liver metabolism, SIM continuously entered the liver to exert its therapeutic action, as evidenced by the biodistribution study. On comparison, it was concluded that SLNs made with compitrol 888 ATO demonstrated higher bioavailability than SLNs made with GMS because of the more highly lipophilic nature of the former, which was responsible for a more sustained release of the drug.[29]

Another study on SIM SLNs, by Lai *et al*., used glyceryl monooleate (GMO) as the lipid in order to develop cubic nanoparticles as potential oral drug-delivery systems with enhanced bioavailability of the SIM.[30] The SIM-loaded cubic nanoparticles were prepared by fragmentation of GMO/poloxamer 407 bulk cubic-phase gel using high-pressure homogenization. The mean diameter of the cubic nanoparticles varied in the range of 100–150 nm. Almost complete entrapment, with efficiency over 98%, was achieved due to the

high affinity of the SIM for the hydrophobic regions of the cubic phase. Pharmacokinetic profiles in beagle dogs showed sustained plasma levels of SIM for cubic nanoparticles over 12 h. The relative oral bioavailability of SIM cubic nanoparticles calculated on the basis of the area under the curve was 241% of that achieved by SIM crystal powder. The enhancement of SIM bioavailability was possibly attributable to facilitated absorption by lipids in the formulation rather than improved release.

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 (monoacyl glycerol) and soyabean phosphatidyl choline.[79]

Orally disintegrable tablets

The main objective of orally disintegrable tablets is to administer drug 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.[80] 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.[81] 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.

In a development by Jansen,[82] orally disintegrating tablets of SIM were prepared by granulating butylated hydroxyanisol, sodium starch glycolate and povidone in a high-shear granulator. The granulate was sieved and dried, and mixed with the silicified microcrystalline cellulose, L-hydroxypropyl cellulose, aspartame, mint flavor and iron oxide yellow in a free-fall mixer. After addition of the sodium stearyl fumarate (the lubricant) the mixing was finalized and oval biconvex tablets were prepared. Subsequently, it was discovered that SIM-containing tablets based on above composition showed improved stability during storage, with disintegration time less than 30 s.

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 SIM and/or lovastatin and optionally one or more osmotic excipients was typically encased by a semipermeable membrane having at least one orifice. When the system was exposed 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.[83]

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, its pharmaceutically 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 burst-release 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.[84]

Buccal delivery

Among the various transmucosal sites available, the mucosa of the buccal cavity represent the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery in retentive dosage forms.[85] Buccal drug delivery has several advantages over peroral delivery. 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. 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 favourable aspects of the delivery systems. In one study, mucoadhesive bilayered buccal tablets of pravastatin sodium using carrageenan gum as the base matrix were prepared by the direct compression method and PVP K 30, Pluronic F 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 across the 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.[86]

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.[31,87] 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. ICR Swiss mice were treated with the following protocols: (1) injection of methylcellulose gel alone, subcutaneously over the calvarium (INJ-GEL); (2) injection of gel with SIM (INJ-SIM; 2.2 mg); (3) polylactide membrane (PLA) containing gel alone, implanted over calvarium (MEM-GEL); (4) implanted PLA membrane containing gel and SIM (MEM-SIM;); and (5) untreated mice. Animals were sacrificed after 22 or 44 days and the calvaria were decalcified and stained with hematoxylin and eosin. The images were digitized and measured for bone thickness and area. INJ-SIM stimulated a 53% increase at the thickest point of the calvarial bone, while MEM-SIM caused a highly significant increase in bone thickness (159–172%) and bone area (144–180%) compared to gel controls. SIM gels caused soft tissue inflammation, which appeared to be related to bone increases. If INJ-SIM animals showing leakage of gel and/or no inflammation were excluded from the analysis, INJ-SIM resulted in more bone (58–83%) than gel controls. An insignificant amount of SIM-stimulated bone was lost over the long term.[32]

In another study, an indigenously prepared biodegradable SIM controlled-release gel, as an adjunct to scaling and root planting, was developed for the treatment of chronic periodontitis. The results indicated greater decreases in gingival index and probing depth and more clinical attachment gain, with significant intrabony defect fill, at sites treated with scaling and root planting plus locally delivered SIM than the patients treated with scaling and root planting alone. Other periodontal applications of statins include granules and gels of SIM formulated using bioerodible/biocompatible polymers, namely hydroxypropylmethyl cellulose (H), sodium carboxymethyl cellulose (C) and chitosan (Ch), for the treatment of bony defects resulting from periodontitis or to induce osteogenesis around titanium implants. The results revealed variable extents of controlled drug release from the formulations depending on the polymer nature. About 50% cumulative SIM was released from both H granules and gel formulations within 24 h and approximately 66% and approximately 88% from C granules and gel, respectively. Ch formulations exhibited approximately 50% release from granules and approximately 30% from gel. Similarly, topical injection of SIM in methylcellulose gel stimulated bone growth and reduction of inflammation in mouse calvaria and in rat mandible models.[33]

Topical and local administration

Biodegradable polymeric nanoparticle technology

Recent studies have demonstrated the effectiveness of statins for the treatment of acne/or skin ageing. Statins can increase nitric-oxide-mediated vasodilation and blood vessel relaxation and can be helpful to prevent further myocardial infarctions thereafter.[88] Statins can also be used to promote angiogenesis in tissues, so they may be useful in conditions where new blood vessel growth is desirable.[89] 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 rhabdomylosis and hepatic disorders. One solution to this is local 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.

Nanoparticles are mainly prepared from biocompatible polymers, for example PLGA (polylactide–glycolide copolymers). The preferred polymers are those that are less irritating, less toxic, biocompatible and biodegradable, and release statins over a prolonged period. The surface of the polymer may be modified by PEG to increase the affinity of water-soluble statins, affording easier encapsulation. The statin-loaded nanoparticles have been prepared by the emulsion–solvent diffusion (ESD) method. In this method, two kind of solvents, a good solvent (dissolves polymer, encapsulates the drug and mixes with other solvent) and a poor solvent (which does not dissolve polymer) are used. The process details are depicted in Figure 2. Cationic polymer may be added to increase the loading rate of statin in the nanoparticles. It is believed that cationic polymer may be adsorbed to the surface of nanoparticles and prevent leakage of the statin in the poor solvent by interacting with the statin on the surface of the particles. The nanoparticles so obtained may be converted into redispersible aggregate powder (nanocomposite) by lyophilization.[34]

Transdermal delivery system for statin combination therapy

It is customary to compare the percutaneous route with oral delivery since the latter provides the most popular way of delivering drugs. Transdermal delivery of a drug may eliminate several variables associated with oral intake, since it bypasses gastrointestinal absorption. 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.[90] 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, rhabdomylosis 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

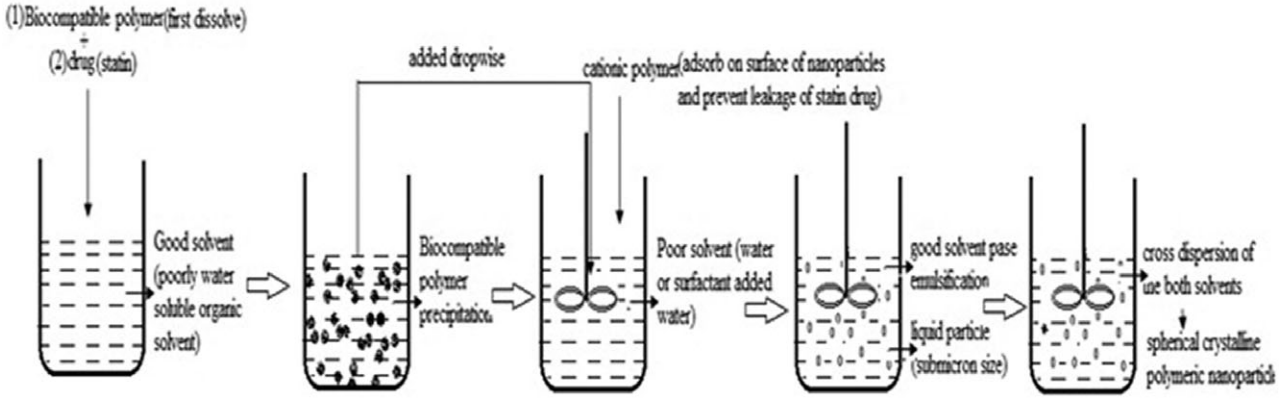

Figure 2 Emulsion-solvent diffusion method for production of polymeric nanoparticles.

also dose 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.[91,92]

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-Trans™, E-Trans™, Microflux™, Latitude™, Latitude Duo™, Climara Pro™ and other known technologies. Drugs that are advantageous in combination with or concomitantly with 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.[93]

Parenteral delivery

Systemic SIM is known to reduce cholesterol and stimulate modest bone formation, but local surgical placement in polylactic acid 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, short- and long-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). Long-term evaluation showed that 55% of the maximum new bone formed 24 days post-injection was retained for 90 days.[94]

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.[95] Statin liposomal formulations use a new and highly efficient liposomal encapsulation technique, termed micelle-liposome exchange. This liposomal encapsulation greatly increases the solubility of statins, in one example more than 1000-fold. This formulation was mainly developed for the treatment of rheumatoid arthritis. Preliminary studies in human plasma and synovial fluid have 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 study examined administration of lovastatin in biodegradable polymer nanobeads of poly(lactic-co-glycolide acid) and used a standard preclinical model of femoral fracture. It was reported 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 into the fracture site, and decreased cortical fracture gap at 4 weeks as assessed by microcomputed tomography. These preclinical results suggest that lovastatin administered in a nanobead preparation may be therapeutically useful in hastening the repair of human fractures.[35]

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. When copolymerized with a dimethacrylated poly(ethylene glycol) solution, this fluvastatin-containing molecule was covalently

incorporated into hydrogel networks, and hydrolysis of lactic acid ester bonds resulted in the release of the independent fluvastatin from the hydrogel into the surrounding solution. The rate of fluvastatin release was controlled by the length of lactic acid spacer (two to six repeats), and the dose was controlled by the initial comonomer composition (5–500 μg fluvastatin/gel). Released fluvastatin increased human mesenchymal stem cell (hMSC) gene expression of CBFA1, ALP and COL I 34-fold, 2.6-fold and 1.8-fold, respectively, after 14 days of in-vitro culture. In addition, treating hMSCs with the released fluvastatin resulted in an average of 2.0- and 1.5-fold greater BMP2 production, whereas mineralization increased an average of 3.0-fold and 2.5-fold, for 0.01 and 0.1 μM fluvastatin, respectively, over the 2-week culture period. Fluvastatin-releasing hydrogels may therefore be useful in bone-tissue engineering applications, not only for triggering osteogenic differentiation of hMSCs, but also by modulating their function.[36]

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 drug-loaded microspheres. Using a multilayered fabrication approach, pulsatile release profiles were obtained. Delivery was varied by changing the loading, the number of layers, the blend ratio and the incubation conditions. To determine the cellular effects of intermittent exposure to SIM acid, MC3T3-E1 cells were cultured with either alternating or sustained concentrations of SIM acid in the medium. DNA content, alkaline phosphatase activity and osteocalcin secretion were measured. For all three cell responses, cultures exposed to SIM acid showed higher activity than did control cultures. Furthermore, cell activity was greater for cells cultured with intermittent concentrations of SIM acid compared to cells that were constantly treated. These results imply that devices intermittently releasing SIM acid warrant further study for locally promoting osteogenesis.[37]

Intravenous statin formulation

Prinz *et al*. reported that rosuvastatin, when given as an intravenous formulation, as late as 4 h after ischemia and in doses as low as 0.2 mg/kg, provides protection from focal brain ischemia/reperfusion in the mouse.[96] The stroke-protective effects of intravenous rosuvastatin extended to 5 days after ischemia and were accompanied by functional improvements. Neuroprotection with intravenous rosuvastatin was achieved with peak plasma concentrations lower than 0.5 ng/ml (i.e. with the 0.2 mg/kg dose) and was associated with increased levels of phosphorylated Akt kinase and phosphorylated eNOS in the vasculature. An intravenous statin formulation can therefore be safely administered in healthy volunteers and it could be used in patients who can no longer be treated with statins, even via a nasogastric tube (e.g. those who are unable to swallow, intensive care patients or those about to undergo major surgery).

Surgical delivery

Statin-loaded microspheres in PolyRing device

PolyRing is a novel targeted drug-delivery system in which drug can be loaded in microspheres to attain controlled local release of the drug over a period of time. Initially, the PolyRing device was developed for the targeted delivery of the drug cyclosporine A for the treatment of vascular intimal hyperplasia (IH).[97] In this application, drug was encapsulated within the microspheres, which were in turn embedded in a PEG block as a polymeric vascular wrap, termed the 'PolyRing'. Statins can be other potent agents with antiproliferative properties, suggested for the inhibition of IH as statins have a more direct route for the inhibition of smooth muscle cell.

PolyRing is in the form of a ring structure, which is a polymeric device consisting of PLGA microspheres embedded in a PEG hydrogel block polymer as seen in Figure 3. PolyRing fabrication follows a step-by-step procedure in which first the PLGA microspheres are prepared by the oil-in-water (o/w) emulsion technique. The SIM is then encapsulated in the microspheres. After this the drug-loaded PLGA microspheres are embedded in the PEG hydrogel block polymer and drilled to get the desired PolyRing device. This process is followed by sterilization by hydrogen peroxide. After SIM is released from the device, it has to pass through the interstitial space into the adventitial tissue layer to the medium, then into the intima, after which it will be carried into the lumen and systemic circulation. The major drug transport parameters to be considered are diffusivity, partition coefficient and, to a lesser degree, the convective forces involved.[38]

PEG is considered excellent for biomaterial applications due to its biocompatible and non-toxic nature. In relation to controlled-release systems, the PEG-PLGA block polymer has the huge advantage of protein resistivity. Hydrophilic

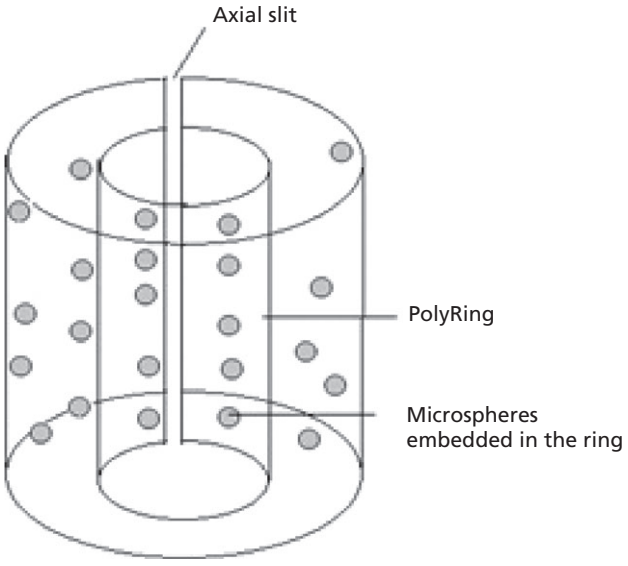

Figure 3 Structure of a polyring device.

PEG has been found to be most effective in repelling proteins within aqueous environments, thus preventing polymer-cell interactions *in vivo*. The PolyRing device has an axial slit, which helps the ring to slip around the arteries as well as around vascular grafts, where anastomatic intimal hyperplasia may develop. The drug, which is encapsulated within the PLGA microspheres, releases through the PolyRing device by diffusion and, over a period of time, degradation of the polymer. The drug is transported through the perivascular space into the artery wall by various physical forces, including diffusion, partitioning coefficient effect and convective forces. This happens over an extended period of time, thus inhibiting the proliferation of vascular smooth muscle cells in the medial/intimal layer. The PolyRing does not need additional retention devices, as it can be securely held to the wall because of the swelling of the PEG hydrogel. It is also capable of multiple drug encapsulations, which may be beneficial for combination therapy. Controlled-release drug-delivery devices provide local elevated concentrations in the targeted sites while diminishing systemic side effects.[98]

Novel plum-pudding gels

A novel gel structure called the plum-pudding gel is composed of randomly dispersed microgel particles (plums) in a conventional hydrogel network.[99] Depending on the preparation conditions, the microgels can be incorporated into the gel as expanded networks or dense collapsed globules. Where the microgel particles exist as collapsed globules, they have the potential to act as reservoirs for hydrophobic solutes (statins), from which the solutes are released very slowly.[100]

In one study, novel structural plum-pudding gels were evaluated as potential drug-eluting stent coatings. Controlled delivery of a HMG-CoA reductase inhibitor (statin) from the intravascular stent surface is a potential therapeutic modality for prevention of in-stent restenosis (ISR). Restenosis following ballon-based angioplasty is a most serious drawback and is especially prevalent in treatment of the coronary artery system. Intravascular stenting, however, noticeably reduces the restenosis rate following angioplasty procedures.[39] In this study, gels of fluvastatin-loaded thermoresponsive microgel particles containing the relatively hydrophilic N-isopropylacrylamide (NiPAAm), mixed with the more hydrophobic N-tert-butylacrylamide (NtBAAm) in different wt/wt ratios, were randomly dispersed in a 65/35 or 85/15 NiPAAm/NtBAAm copolymer matrix. Fluvastatin release from copolymer films (5 micron thick) was greatest from the most hydrophilic systems and least from hydrophobic systems. Release from hydrophobic matrices appeared to be via fickian diffusion, enabling use of the Stokes–Einstein equation to determine diffusion coefficients. Release from hydrophilic matrices was non-Fickian. The eluted drug retained its bioactivity, assessed as selective inhibition of human coronary artery smooth muscle cell proliferation. When stainless steel stent wires were coated (25 μm thickness) with fluvastatin-loaded 65/35 microgels in an 85/15 copolymer matrix, drug elution into static and perfused-flow environments followed similar elution profiles. In contrast to elution from copolymer films cast on flat surfaces, diffusion from stent wires coated with hydrophilic and hydrophobic systems both followed Fickian patterns, with slightly larger diffusion coefficients for elution from the flow system. It was concluded that manipulation of the relative hydrophobicities of both microgel and matrix components of plum-pudding gels resulted in tightly regulated release of fluvastatin over an extended time period relevant to initiation and propagation of ISR.[101]

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-better controls, improved efficacy and targeting, better drug loading and lowering of the drug dose to diminish side effects and toxicity. In this respect the use of lipid nanoparticles of ultra-low size 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. Statin-loaded microspheres in the PolyRing device and in intravenous formulations are desirable for clinical 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. New delivery 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. Success is only possible if the pharmaceutical industry also takes up development. To guarantee a broad application of a carrier system it is highly desirable that companies specialized in drug-delivery systems are involved.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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