

STATIN THERAPY AND THEIR FORMULATION APPROCHES: A REVIEW

S. PUNITHA*, KL.SENTHIL KUMAR¹*Faculty of Pharmacy, PRIST University, Thanjavur 614904, ¹Padmavathi College of Pharmacy, Dharmapuri, TN.
Email: punithasundaresan@gmail.com

Received: 18 July 2011, Revised and Accepted: 5 Sep 2011

ABSTRACT

Hypercholesterolemia is a common disorder and is of major interest since it is one of the risk factor for ischaemic heart disease. For the management of hypercholesterolemia and dyslipidamias, statins are preferred drugs of choice which are proved as the most potent therapies for treating elevated Low Density Lipoprotein-Cholesterol (LDL-C) and congestive heart disease. The widely prescribed statins possess low bioavailability which limits their application in clinical use. To this concern, this review summarizes the clinical effects of statins, its properties and an overview of novel methods to improve its bioavailability.

Keywords: Hyperlipidemias, Solubility enhancement, Nanotechnology

INTRODUCTION

The year since 1967, the cause for major mortality are reported to be due to cardiovascular diseases. The preventive measures are needed to be taken at mean time when the early lesions of coronary atherosclerosis are observed, which are associated with obesity and diabetes. Hyperlipidemia is the common disorder will promotes the regression of the disease.

Therefore hypolipidemic drugs, also called as lipid-lowering agents are preferred for the treatment of the same. The selection of lipid lowering drugs depends on the type of hyperlipoproteinaemia. There are several classes of hypolipidemic drugs which differ in both their impact on cholesterol profile and adverse effects. The therapeutic indication of statins depend on patients cholesterol profile, the level of LDL (Low Density Lipoprotien) or HDL (High Density Lipoprotien), cardiovascular risk, and the liver and kidney functions.

This review aims to provide an update of the importance of statin therapy for multiple conditions and the research undergoing based on formulation aspects for improving the bioavailability of lipophilic drugs belonging to the same class.

Effect of Statins

Based on the clinical trial evidence, the most commonly prescribed lipid-modifying therapies are HMG-CoA reductase inhibitors (hydroxymethyl glutaryl-coenzyme A), commonly called as statins. HMG-CoA reductase are competitively involved in conversion of HMG-CoA to mevalonate, thus the cholesterol synthesis are limited in hepatocyte (fig 1). There by the LDL receptor expression is induced on the cell surface to extract the excess of LDL concentrations from the blood stream and reduces its concentration.¹

Statins also increase the HDL-C level, decrease triglyceride concentration,³ inhibit the synthesis of hepatic apolipoproteins B100 and also reduces the secretion of triglyceride-rich lipoproteins.^{4,5} Statins produce other actions, termed as pleiotropic effects which are beneficial to cardiovascular system and its effects are independent to their lipid modifying properties.⁶ From the large-scale clinical trials it has been demonstrated that the statins can substantially reduce cardiovascular related morbidity and mortality in patients with and without existing congestive heart disease.⁷⁻¹⁴ It also slows down the progression of coronary atherosclerosis, whose effect are comparable with the untreated hypercholesterolaemic patients.^{15, 16, 17}

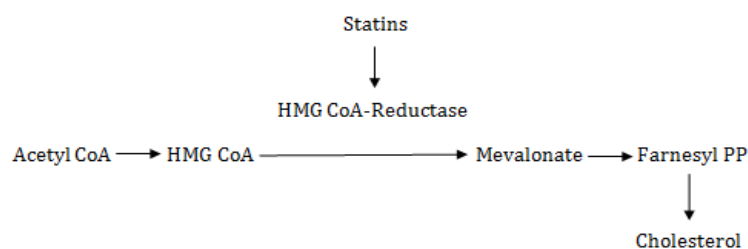


Fig. 1: Schematic representation of effect of Statin²

Statins are particularly well-suited for lowering LDL, which is having more potential to increase cardiovascular diseases. When statin is taken in standard doses the LDL concentrations are reduced by 18 to 55%, depending on the specific statins being used.

Source and Properties of Statins

Since from the statins introduction in clinical practice extensively, there is a large debate regarding the price and benefits of lipid-lowering treatment and in prevention of atherosclerosis. Clinically approved statins are given in table 1.

Statins are regarded as the safe and well tolerated class of drugs; exceptionally Cerivastatin withdrawn from the market in 2001.¹⁸ All the statins act competitively towards the enzyme with respect to the

binding of substrate at the active site. When the substrate-binding pocket of the enzyme undergoes a rearrangement process statins get accommodated.

Among all the approved statins (Table: 1) Atorvastatin, Fluvastatin, Lovastatin and Simvastatin are relatively lipophilic in nature^{19, 20} and metabolized by cytochrome P450 system.²¹ Simvastatin and Lovastatin are fungal-derived inhibitors of HMG-CoA reductase, which after administration is converted to their active form i.e. hydroxyacid²² while atorvastatin and Fluvastatin are fully synthetic compounds.²³ All the statins are hepatoselective in nature where the endogenous cholesterol production taking place in liver. The hepatoselective effect is based on the solubility profile of the statins.

Table 1: Clinically approved Statins – Comparative Properties²⁴

S. No.	Name of the drug	Bio-availability (%)	Protein binding (%)	Elimination Half-life (h)	Solubility	Source	Serum LDL-C reduction (%)
1	Atorvastatin	12	98	14	Lipophilic	Synthetic	50
2	Cerivastatin	60	>99	2.5	Lipophilic	Synthetic	28
3	Fluvastatin	24	>98	1.2	Lipophilic	Synthetic	24
4	Lovastatin	5	>95	3	Lipophilic	Fungal derived	34
5	Pravastatin	18	~50	1.8	Hydrophilic	Fungal derived	34
6	Simvastatin	5	95-98	2	Lipophilic	Fungal derived	41
7	Rosuvastatin	20	90	19	Hydrophilic	Synthetic	63
8	Pitavastatin	~80	96	11	Lipophilic	Synthetic	48

There is differences in extent of LDL-C lowering effect at the therapeutic doses between each agents (Table: 1). It also shows increase in HDL-C level at varying degrees.²⁵ The currently available statin generally possess a low systemic bioavailability indicating extensive first pass extraction.²⁶⁻²⁹ Next to Rosuvastatin, the most efficacious statins for lowering LDL-C are Atorvastatin, Simvastatin and Pravastatin. The recent clinical trials evidenced the minor effect of muscle problems with statin therapy with existing proteinuria.^{30,31} The elimination half-life of Atorvastatin is approximately 14 hrs³² which exhibit greater efficacy for lowering LDL-C as compared with the other statins³³ which have short elimination half life of 3 hrs or less.^{26, 27, 33}

Management of Hyperlipidaemia

The objective of the treatment of hyperlipidaemia is to normalize the lipid profile, so as to safeguard against the cardiovascular events. To achieve beneficial effects it is essential to do regular monitoring and following diet and drug regimes continuously.

- The cholesterol content in diet should be kept below 300 mg per day.
- Low saturated fat content of diet has antithrombotic effects, lowers BP and overall, contributes to reduced coronary death rates.
- Abstinence from smoking.
- Regular exercise and a balanced life style also contribute to normalizing the serum lipid levels.

Application of Statin Therapy

Statins are proven as lifesaving medications in US by reducing the coronary heart disease.³⁴ As secondary preventive landmark, statin trials have reported a reduction in the cause of mortality: 30% reduction in the Scandinavian Simvastatin Survival Study (4S);⁷ 22% reduction in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID);¹¹ and 13% reduction in the Heart Protection Study (HPS).¹² It is directed to treat hypercholesterolemia, hypertriglyceridemia and coronary heart disease which has major role as adjunctive therapy with diet for decreasing the total cholesterol level, LDL, triglycerides and Apo-B. Statins are also indicated for mixed dyslipidemia or primary hypercholesterolemia, Fredrickson Type IV and V hyperlipidemia. These diseases are directly or indirectly associated with elevated, uncontrolled cholesterol metabolism such as Restenosis and Alzheimer's disease. In this regard, statins are quite potent drug of choice. The potency is found to be better for the nanoparticulate formulation of drugs such as Lovastatin or Simvastatin and novel statin combinations whose average particle size are less than 2000nm.³⁵ This novel formulation might produce a comparable effect to conventional formulations in respect to size of the dosage form, pharmacological effect, bioavailability, dissolution rate and bioadhesive properties.

Formulation Approaches

Dissolution process is the rate-controlling step for hydrophobic drugs which shows erratic and incomplete absorption from the GI tract. Thus, one of the major challenges to drug development today is poor solubility, as estimated 40% of all newly developed drugs are

poorly soluble or insoluble in water.³⁶ In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their lipophilicity.³⁷ As a result, enormous research has been conducted in the methods of improving drug solubility and dissolution rates to increase the oral bioavailability of the hydrophobic drugs. The most common approaches are 'bottom-up' and 'top-down' techniques by reducing the particle size through milling / mechanical micronization process. An alternative to milling is growing the particle from a solution to the desired size range under controlled conditions, e.g. by spray drying, solvent diffusion³⁸ and super critical fluid technology.³⁹ The above methods help to design required formulations with beneficial characteristics like enhanced dissolution rate by inclusion of surfactant or increasing the stability of amorphous materials by incorporation of sugars.

Other formulation principles are also available which employ some of the novel methods for improving the solubility and bioavailability of the lipophilic drugs.

1. Pearl milling

Aqueous suspension of the drug is filled in a pearl mill containing glass/zirconium oxide pearls as milling media. The nanoparticles are formed due to movement of milling pearls. The effect is depending on drug properties, medium and stabilizer.

Eq. Rapamune, an immunosuppressant agent is developed using nanocrystal technology and approved by FDA.

2. High Pressure Homogenization

An aqueous surfactant solution containing the drug (dispersed) is passed through a high pressure homogenizer. The nanoparticles are formed due to cavitations force. This process depends on the hardness of drug, the processing pressure and the number of cycles applied. This technique offers several advantages like increased saturation solubility, dissolution rate, amorphous fractions, bioavailability, surface modification of the particles and possibility of large scale production.⁴⁰

3. Solution Enhanced Dispersion (SEDs)

This is achieved by Supercritical fluid process (SCF).⁴¹ The organic solution of drug is mixed with the compressed fluid CO₂ in the mixing chamber with help of a coaxial nozzle which flows into a vessel through a restricted orifice where the particles are formed. The solution is disintegrating into droplets due to high frictional surface forces.

4. RESAS processes (Rapid Expansion from Supercritical to Aqueous Solution)

This process induces nucleation of the SCF dissolved drugs and surfactants with a desirable particle size in a very short time. Surfactants can stabilize the particle and suppress particle agglomeration.⁴²

5. Spray freezing into liquid (SFL)

The solution/emulsion/suspension containing drug in aqueous/organic/combination of both phase is atomized into a compressed gas or cryogenic liquids. Then the particles are frozen and lyophilized to obtain free flowing micronized powder.⁴³ This technology is patented at Austin in 2003.

6. Evaporative precipitation into aqueous solution (EPAS)

The low boiling point organic solvent containing lipophilic drug is pumped, after the temperature is raised above the boiling point of the solvent. It is sprayed through a fine atomizing nozzle into a heated aqueous solution. The presence of surfactants in both phases will stabilize the particle formation.

7. Complexation

To increase the water solubility, dissolution rate and bioavailability of certain lipophilic drugs cyclodextrins are used as complexing agents. The driving forces for efficient complexation are attributed to the exclusion of high energy water from the cavity, the release of ring strain, Vander Waals interaction and hydrogen/hydrophobic bindings.⁴⁴

8. Solid dispersions/solutions

One or more active ingredients are dispersed in a carrier matrix in the solid state by various techniques such as solvent evaporation, fusion or melting solvent method.^{45, 46} Physical, chemical instability and scale up process are some of the problems arising in this technique.⁴⁷

9. Water soluble Carriers

The excipients like PEGs are used to solubilize the drug by improving the wettability.

10. Hot Homogenization with Ultrasonication

The result found from the solid lipid nanoparticle of Clozapine indicates that this method is suitable for the improvement of bioavailability of lipophilic drugs.⁴⁸

11. Surfactants containing microparticles

In the microparticle, hydrophilic surfactant will improve the particle wetting and hence dissolution rate can be increased.

CONCLUSION

Bioavailability problems will lead to therapeutic failure of certain drugs. From the economic point of view, when the drug is highly expensive a large portion of an oral dose is wasted due to poor bioavailability and leads to increased cost for drug therapy. Hence, our research is focused towards the development of some stable formulations which might be providing better solution.

ACKNOWLEDGEMENT

The authors are thankful to the management of PRIST University, Thanjavur, for encouraging and providing the necessary facilities.

REFERENCES

- Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolaemia. *Hum Mutat* 1992; 1: 445-466.
- Siobhra, O'Sullivan. Statin: A review of benefits and risks. *Rev Pharmacol* 2007; 8:52-56.
- Maron DJ, Fazio S, Linton MF. Current perspective on statins. *Circulation* 2000; 101:207-213.
- Ginsberg HN, Le NA, Short MP, Ramakrishnan R, Desnick RJ. Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin: implications for the regulation of apolipoprotein B synthesis. *J Clin Invest* 1987; 80:1692-1697.
- Volume with supplement: Grundy SM. Consensus statement: role of therapy with "statins" in patients with hypertriglyceridemia. *Am J Cardiol* 1998; 81 Suppl 4A: IB-6B.
- Liao JK. Beyond Lipid lowering: the role of statins in vascular protection. *Int J Cardiol* 2002; 86:5-18.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383-1389.
- Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia for the West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; 333: 1301-1307.
- Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L. et al, The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335: 1001-1009.
- Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al, Primary prevention of acute coronary events in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279: 1615-1622.
- The Long-term intervention with pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349-1357.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised Placebo-controlled trial. *Lancet* 2002; 360: 7-22.
- Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al, Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet* 2002; 360: 1623-1630.
- Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multicentre randomized controlled trial. *Lancet* 2003; 361: 1149-1158.
- Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? *Pharmacol Ther* 1998; 80: 1-34.
- Vaughan CJ, Gotto AM, Jr, Basson CT. The evolving role of statins in the management of atherosclerosis. *J Am Coll Cardiol* 1999; 35: 1-10.
- Smilde TJ, Van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomized, double-blind trial. *Lancet* 2001; 357: 577-581.
- Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med* 2001; 2: 205-207.
- McTavish D, Sorkin EM. Pravastatin. A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. *Drugs* 1991; 42: 65-89.
- McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, et al, Preclinical and clinical Pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 2001; 87 Suppl B: 28-32.
- Bottorff M, Hansten P. Longterm safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors: the role of metabolism - monograph for physicians. *Arch Intern Med* 2000; 160: 2273-2280.
- Corsini A, Maggi FM, Captapano AL. Pharmacology of competitive inhibitors of HMG-CoA reductase. *Pharmacol Res* 1995; 31: 9-27.
- Davidson MH. Rosuvastatin: A highly efficacious statin for the treatment of dyslipidaemia. *Expert Opin. Invest Drugs* 2002; 11: 125-141.
- Schachter M. Chemical, Pharmacokinetic and Pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* 2005; 19(1):117-25.
- Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E. et al, for the STELLAR Study Group. Comparison of efficacy and safety of rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; 92: 152-160.
- Tse FL, Jaffe JM, Troendle A. Pharmacokinetics of fluvastatin after single and multiple doses in normal volunteers. *J Clin Pharmacol* 1992; 32: 630-638.

27. Pan HY, DeVault A, Wang-Iverson D, Ivashkiv E, Swanson BN, Sugerman AA. Comparative pharmacokinetics and Pharmacodynamics of pravastatin and lovastatin. *J Clin Pharmacol* 1990; 30: 1128-1135.
28. Lennernas H. Clinical Pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; 42: 1141-1160.
29. Martin PD, Warwick MJ, Dane AL, Brindley C, Short T. Absolute oral bioavailability of rosuvastatin in healthy white adult male volunteers. *Clin Ther* 2003; 25: 2553-2563.
30. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003; 289: 1681-1689.
31. Sidaway J, Davidson R, Mc Taggart F, Orton T, Scott R, Graham J. et al, Effect of statin on protein uptake and cholesterol biosynthesis in kidney proximal tubule cells (abstract). *Toxicol Lett* 2003; 144 Suppl 1: S96.
32. Cilla DD, Jr, Gibson DM, Whitefield LR, Sedman AJ. Pharmacodynamic effects and Pharmacokinetic of atorvastatin after administration to normocholesterolemic subjects in the morning and evening. *J Clin Pharmacol* 1996; 36: 604-609.
33. Naoumova RP, Dunn S, Rallidis L, Abu-Muhana O, Neuwirth C, Rendell NB, et al, Prolonged inhibition of cholesterol synthesis explains the efficacy of atorvastatin. *J Lipid Res* 1997; 38: 1496-1500.
34. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T et al, Heart disease and Stroke Statistics-2006 Update. A Report from the American Heart Association statistics Committee and Stroke statistics Subcommittee. *Circulation* 2006; 113: e85-e151.
35. Eugene R, Cooper, Douglas Hovey, Greta Cary, Marie Linder, Elaine Liversidge, Gary G. Liversidge, Tuula Ryde. USPTO Application # 20080213378.
36. Naseem A, Olliff CJ, Martini LG, Lloyd AW. Effects of plasma irradiation on the wettability and dissolution of compacts of griseofulvin. *Int J Pharm* 2004; 269: 443-450.
37. Gursoy RN, Benita S. Self-emulsifying drug delivery system (SEDDS) for improved oral delivery of lipophilic drug. *Biomed Pharmacother* 2004; 58: 173-182.
38. Quintanar-Guerrero D, Allemann E, Fessi H, Doelker E. Preparation techniques and mechanism of formation of biodegradable nanoparticles from preformed polymers. *Drug Dev Ind Pharm* 1998; 24: 1113-1128.
39. Hu J, Johnston KP, Williams III RO. Spray freezing into liquid (SFL) particle engineering technology to enhance dissolution of poorly soluble drugs: Organic solvent versus organic /aqueous co-solvent systems. *Eur J Pharm Sci* 2003; 20: 295-303.
40. Muller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations of in therapy rationale for development and what we can expect for the future. *Adv drug Deliv Rev* 2001; 54: 131-155.
41. Hanna MH, York P. Method and apparatus for the formulation of particles. U.S. Patent 5,851,453; 1998.
42. Pace GW, Vachon MG, Mishra AK, Henrikson IB, Krukons V. Processes to generate submicron particles of water -insoluble compounds. U.S. Patent 6,177,103; 2001.
43. Rogers TL, Johnston KP, Williams RO III. A comprehensive review: Solution based particle formation of pharmaceutical powders by supercritical or compressed fluid carbon dioxide and cryogenic spray-freezing technologies. *Drug Dev Ind Pharm* 2001; 27 (10):1003-1016.
44. Ross PD, Rekharsky MV. Thermodynamics of hydrogen bond and hydrophobic interactions in cyclodextrin complexes. *Biophys J* 1996; 71: 2144-2154.
45. Punitha S, Karthikeyan D, Devi P, Vedha Hari BN. Enhancement of solubility and dissolution of celecoxib by solid dispersion technique. *J Pharm Sci Tech* 2009; 1 (2): 63-68.
46. Punitha S, Vedha Hari BN, Karthikeyan D. Enhancement of Celecoxib Solubility by Solid Dispersion Using Mannitol. *Int J Pharm Pharm Sci* 2010; 2(4):109-111
47. Craig DQM. The mechanism of drug release from solid dispersion in water soluble polymers. *Int J Pharm* 2002; 203:131-144.
48. Manjunath K, Venkateshvarlu V. Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nanoparticles after intravenous and intraduodenal administration. *J Control Release* 2005; 107 (2): 215-228.