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Review Article

STATIN THERAPY AND THEIR FORMULATION APPROCHES: A REVIEW

S. PUNITHA*, KL.SENTHIL KUMAR[1]

*Faculty of Pharmacy, PRIST University, Thanjavur 614904, [1]Padmavathi College of Pharmacy, Dharmapuri, TN.
Email: punithasundaresan@gmail.com

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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 prefered 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 apolipoprotiens 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]

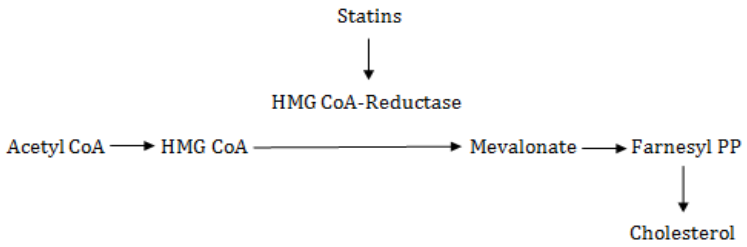

Fig. 1: Schematic representation of effect of Statin[2]

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 coverted to their active form i.e, hydroxyacid[22] 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 Properties [24]

S. No.	Name of the drug	Bio-availability (%)	Protien 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 posses a low systemic bioavailbility 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 hrs[32] which exhibit greater efficacy for lowering LDL-C as compared with the other statins[33] 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 antithrombogenic 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 Scandanavian 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 diffusion[38] and super critical fluid technology.[39] The above methods helps 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 employs 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.

Eg. Rapamune, an immunosuppresent 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 CO_2 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.

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