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CURRENT TRENDS IN SIMVASTATIN THERAPY FOR ENHANCED EFFICIENCY

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ABSTRACT

Statins are mainly used as the inhibitors of enzyme 3-hydroxy-3 methyl glutaryl coenzyme A (HMG COA) reductase which is responsible for the synthesis of cholesterol. Apart from the cholesterol reducing activity they also facilitate as anti-inflammatory and cardio-protective agents. Solubility is one of the main parameter for any drug to achieve the expected therapeutic effects. Since Simvastatin is poorly soluble drug with less half life of about 2 hours, various types of formulations are being currently prepared to enhance its solubility which in turn may improve the bioavailability of the drug. Studies reveal that different methodologies were carried out to overcome the bioavailability issue which is the key limiting factor. The present study focuses on the different types of novel formulation approaches of Simvastatin, currently available for enhancing the bioavailability and efficacy of the drug in the biological system.

KEYWORDS: Simvastatin, Hypercholesterolemia, Anti-inflammatory, Cardio-protective, Bioavailability

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INTRODUCTION

Simvastatin belonging to a member of statin class is a hypolipidemic drug. It is derived from Aspergillus terreus and is marketed generically in the trade name Zocor® which is used along with exercise and diet for weight-loss, for the treatment of hypercholesterolemia which reduces levels of low-density lipoprotein, while increases the levels of high-density lipoprotein in people suffering with diabetes, ischemic heart disease. Simvastatin is a prodrug type, which is hydrolyzed into its active form as β-hydroxyacid also called Simvastatin acid. It is an inhibitor of HMG-CoA reductase enzyme which is responsible for transforming HMG-CoA into mevalonate which is the key limiting step in the process of cholesterol biosynthesis.

The normal range of dosage is 10 or 20 mg once daily in the evening and for patients with high risk of diabetes, cerebrovascular disease the recommended dosing is 40 mg/day since higher doses (160 mg) are found to be toxic. The drug undergoes hydrolysis mainly in liver, which usually takes place very slow in human plasma. It is absorbed completely in man. The site of action of the active form of drug is in the liver. The bioavailability of the active form of Simvastatin in the oral administration was less than 5% of the given dose since it undergoes rapid hepatic first-pass extraction. Maximum plasma concentration reached in 1-2 hours roughly after oral dosing. The pharmacokinetics reported no accumulation of drug even after multiple dosing since the half life of the drug is less. The active metabolite and the protein binding of Simvastatin are found to be greater than 95%. In man, β-hydroxyacid and four additional active metabolites are the main metabolites of Simvastatin. Studies showed an oral administration of radioactive Simvastatin in man led to excretion of 13% of the radioactivity in urine and around 60% in faeces representing the well absorbed and unabsorbed drug that was eliminated in bile.

Novel formulation approaches
Sustained/controlled release of various drugs is achieved through the novel methods of formulating a drug incorporated carrier system. This review sketches the outline of various novel formulation approaches of Simvastatin being carried out in different studies which is further discussed here (Fig: 1).

**Figure 1**

Novel formulation approaches of Simvastatin

**Hydrogel**

Hydrogels are crosslinked polymeric network which easily swells out since it has the ability of imbibing more quantity of biological fluids due to its porous nature. Simvastatin facilitates in treatment of bone disorders. In 2010, a biodegradable hydrogel was formulated for Simvastatin which was solubilized by gelatin that was grafted with oligomer of L-lactic acid, chemical cross linking method. The release was found to depend on biodegradation of hydrogel. The
hydrogel facilitated the Simvastatin-induced bone regeneration with great potential. A year later Photo-cured hyaluronic acid (HA) hydrogels incorporated with drug Simvastatin were prepared by Min Soo Bae et al. (2011), which had a sustained release of Simvastatin. The biocompatibility of HA hydrogels was shown by MTT assays which has been utilized in the form of scaffolds in bone tissue regeneration. The in-vitro and in-vivo studies showed a better influence on osteogenesis. Yet another attempt was made in formulating a Gelatin-Poly (ethylene glycol)-tyramine (GPT) hydrogel based on gelatin by horse radish peroxidase reactions and H$_2$O$_2$ induced cross-linking by Yoon Shin Park et al. (2013) for curing various degenerative disorders. The in-vitro Simvastatin release profiles exhibited a biphasic pattern of release with rapid burst release in the formulated GPT-hydrogel. This study highlighted the prolonged treatment of chronic degenerative diseases through the formulated GPT-hydrogel by controlled release of Simvastatin.

**Emulsion**

Emulsion is a combination of more than one immiscible liquid which enhances the permeability of lipophilic drugs when incorporated into emulsion. Bok Ki Kanga et al. formulated a Self-micro emulsifying drug delivery system (SMEDDS) in the year 2004 and reported the advantage of the use of SMEDDS to deliver the Simvastatin orally. The rate of release of Simvastatin from the formulation was comparatively high which showed 1.5 fold increase in the bioavailability than the available marketed tablet when observed by administering the capsule filled with the formulation to fasted dogs. A similar form of nano based Super-SNEDDS containing Simvastatin were formulated by Nicky Thomas et al. (2013) to improve the drug bioavailability. The study showed that the super-SNEDDS were stable and it could be used to improve the bioavailability of poorly aqueous soluble drug Simvastatin by reducing the burden of pill by means of increased drug loading that was done in the formulation of SNEDDS. In the same year parenteral lipid nanoemulsions were formulated for cancer treatment by the technique of homogenization with high pressure was planned for subsequent use in the form of combination chemotherapy of Tocotrienol Rich Fraction (TRF) and Simvastatin which was checked for its stability over a period of 6 months of storage and also the anti-proliferating effect of the was retained throughout the study. The study revealed that the prepared injectable lipid formulation of nano emulsions were viable systems used in drug delivery for treatment of cancer chemotherapy.

**Micelle**

Surfactant molecules dispersed in a liquid aggregates to form micelle which acts as a carrier for delivery of the incorporated drug. An attempt was made by Xiangning Liu et al. (2013) for preparing polymeric micelles by a drug polymer conjugation method for treatment of bone degeneration. The proliferation of cell analysis and calcification of cell was done to find the effect of Simvastatin-loaded micelles on osteoblast-like MG-63 cells. The results showed that Simvastatin-loaded poly(ethylene glycol)-poly(-caprolactone) micelles suppresses the early proliferation inhibition of the osteoblast and stimulated the differentiation of osteoblast. Thus it was concluded that the Simvastatin-loaded micelles has a great potential application in the regeneration of bones.

**Nanoparticles**

A nanoparticle loaded with drug is targeted to the site of action which in turn enhances the drug availability and efficiency in the biological system. In 2009 Katy Margulis et al. formulated nanoparticles for Simvastatin by a new evaporation method in which the volatile solvents were evaporated from oil-in-water microemulsion that was spontaneously formed. Enhancement of solubility was found by incorporation of Simvastatin nanoparticles in tablets. X-ray diffraction showed that the formulation which was amorphous at initial stage after storing at room temperature slowly turned into crystalline form. In the same year lipid nanoparticles were developed by Hazem Ali et al. in the form of Simvastatin–tocotrienol lipid nanoparticles which was formulated by the inclusion of tocotrienol rich fraction (TRF) into the nanoparticles entrapped the drug within the nano compartments. The drug release profile of the
formulation showed a 20% in 10 h and then a plateau. It was observed that the particle size was unchanged even after storing it for about six months. The IC50 value of the α-tocopherol reference nanoparticles was found to be 17.7 µM and that of Simvastatin-TRF nanoparticles were 0.52 µM. This study confirmed the potency of the formulation to be used in combination treatment. Another attempt on preparation of lipid nanoparticles (SLNs) was done by Zhiwen Zhanga et al (2010) which had a high efficiency of encapsulation (>95%). The concentration of Simvastatin and Simvastatin acid (SVA) in blood plasma was determined by Liquid chromatography–mass spectrometry method. Absorption of SLNs was site specific where enterocytes uptake SLNs via lathrin and endocytosis pathway which was mediated by caveolae. The bioavailability of the drug improved when incorporated into the lipid nanoparticles. It was 3.37-fold for SLNs I and 2.55-fold for SLSs II. Results suggested that formulated lipid nanoparticles could be used as a significant drug delivery system to facilitate better oral bioavailability. Monireh Kouhi et al (2013) formulated Simvastatin nanocomposite nanofibers with Poly (ε-caprolactone) incorporated bioactive glass nanoparticles by electrospinning method for treatment of degenerative disorders. This nanofiber showed a controlled release of the drug which led to the formation of a glassy tissue interface on the surface of the nanofiber in the biological fluid, which showed the potential effect of nanofiber in the treatment of bone regeneration.

**Implants**

Implants are surgical devices which support the damaged part of the biological system and acts as a carrier for drug delivery. Studies proved that Simvastatin treatment (120 mg/kg of body weight) by particle implantation was done in mouse by Fabian von Knocha et al (2005) which promoted formation of bone and net growth rate of bone was induced in a murine calvarial model. It showed that Simvastatin had a better osteoanabolic effects after surgical repair of joints which involved use of local stimulation implants in osteoblastic bone formation. Later, a novel device which release drug in modified fashion was designed for replacing the daily injection of Simvastatin which were made by pressure assisted sintering blank and microspheres loaded with the drug for treatment of bone disorder. Osteoblast precursor cell lines were cultured in the medium to check the effect of cells on exposure to Simvastatin acid. Thus results showed that the cell activity was greater for cells grown with random concentrations of Simvastatin acid when compared to constant concentration of Simvastatin acid treated cells. The study concluded that the device releasing Simvastatin acid intermittently should be further studied to progress osteogenesis locally.

Attempts have been made by Z. Wu et al (2008) to design a Simvastatin–PLGA scaffold as a carrier containing Simvastatin which was implanted into the sockets of mandibular incisors of the Wister rats bone replacement. The bone mineral density was found to be high in the control whereas in the experimental group there was a formation of enostosis. The finding reveals that local Simvastatin application could preserve the alveolar bone effectively by supporting the formation of bone in the socket. Similarly Fan Yang et al (2011) designed a porous implant of Simvastatin by the cells cultured on titanium disks were used as the control and Simvastatin loaded discs were the experimental groups. Experimental group had elevated alkaline phosphatase (ALP) which was about 4 fold within 4 days than that of the control. Thus the study concluded that the surface of the porous implant loaded with Simvastatin helped in osteogenic differentiation of alkaline phosphatase-positive cells that had the potential to enhance the formation of the tissues between the implant and bone without any intervention. Two years later similar work on Local statins implant was designed by dissolving 200 mg polylactic acid Mw 20,000 Dalton, with or without 50 mg simvastatin in 2 mL acetone and injected into a round glass mold (15 mm diameter, 2 mm depth) for healing the bone defect. The mechanism involved in the higher expression of HIF-1a and BMP-2, thus raising the autogenous osteogenic and angiogenetic stem cells to the defective bone area which was implanted with Simvastatin.
**Topical Formulation**

The main advantage of topical medication upon skin is the prevention of first pass metabolism and immediate action of drug for ailment treatment. Marina Adami et al (2012) tested the efficacy of the Simvastatin ointment for its activity in both acute and chronic models of mice for treating oedema. Inflammation of the skin was induced in mice ears by applying 12-O-tetradecanoylphorbol acetate (TPA) which created ear oedema that was indicated by raise in thickness of the ear in the acute model. In the chronic model the application of TPA was done for several times for every 9 days. From the ointments prepared with Simvastatin, 1% and 3% was optimized from acute model and 1% was optimized for chronic model in reducing the ear swelling. The findings showed that the anti-inflammatory activity of drug Simvastatin upon skin application was very effective in curing ear oedema in both the cases of acute and chronic model. In 2011, another follow-up study on the topical formulation of Simvastatin for anti-inflammatory properties was tested against a mice model and it was found that the application of formulation reduced inflammation in acute contact dermatitis which was induced by croton oil in the mice model under study. Further studies were done to confirm the safety and efficacy of the topical formulations in other animal models. Also the effect of the anti-inflammation was investigated. Similar attempt was made by Hitesh Kulharia et al in the same year on polyamidoamine (PAMAM) dendrimer based Simvastatin formulations which was prepared by conjugation method for controlled delivery of drug. The pure drug released within 5 h whereas the PEGylated complexes took 5 days to release and the non-PEGylated formulations had the complete drug release in 24 h. Again, a topical application of Simvastatin was formulated in the form of ointment by Jun Asai et al (2012) and applied on the wounded skin of the mice possessing diabetics for improvement in wound recovery. Simvastatin exerted an antiapoptotic effect on lymphatic endothelial cells in-vitro. The results concluded that Simvastatin help in the formation of lymphatic vessels which may be due to both the direct influence on lymphatics or indirectly through the macrophages and when applied topically Simvastatin had a significant efficacy and better wound healing especially in patients with irregular microcirculation.

**Microspheres**

Microspheres are small spherical micron size particles which has the ability of encapsulation of different types of drugs for various treatments. Subrata Deb Natha et al (2013) formulated microparticles of Simvastatin by electrospraying method. The entrapment efficiency and drug release profiles of the formulation showed more than 90% efficacy, also the release of the drug was sustained and it lasted up to 3 weeks which facilitated as a better drug delivery system and had suitable application in field of bone tissue engineering. Another study was performed on Simvastatin-loaded polymeric microspheres was formulated using O/W emulsion-solvent evaporation method. The formulated microspheres successfully presented a slow release due to its biodegradable characteristics and the duration of the release was found to last for more than a month that significantly enhanced the formation of bone which was revealed by an in vivo experiment.

**Sustained-release pellets**

Poorly soluble drugs are formulated into sustained release pellets for improving the bioavailability. Based on this aspect, Lili Zhang et al (2010) formulated to sustain release pellets loaded with nicotinic acid (NA) and Simvastatin by coating with double layer of polymers which was stable and both the drugs showed a uniform drug release profile even after a storage period of 6 months at 40°C/75% RH. The results reported that Simvastatin was released immediately without having any influence on NA release and suggested that possibilities of preparation and the advantage of combination of high dose of NA coupled with mere dose of immediate release Simvastatin with a thin film coating of EC polymer had a potential therapeutic effect.

**Tablet**

Tablets are solid dosage forms possessing the medicament to cure various diseases for
which Darrel P. Francis *et al* used a single statin tablet to evaluate the time course of risk reduction. The study deals with quantification of the events occurring in the cardiovascular tissues and the prevention of tissue damage from a single tablet of statin, with the help of the data available from trials of periodic administration. The reduction in the risk levels was mainly due to the ongoing delivery of the statin tablet. Studies confirmed that from 90,056 patient’s trial data, a single tablet of statin prevents 0.137% annual mortality in a year. In case of an average 60yr man the mortality rate of reduction was 143 million of a percent. This was a great evidence to show the prevention of cardiovascular events and lowering the risk effects by taking a statin tablet even though the reduction of mortality rate was less $^{36,37}$.

**Liposome**

Liposomes are small vesicles composed of bilayer lipid film which is used mainly to enhance the stability and time of circulation of the drug in the biological system $^{38}$. Eyal Afergan *et al* worked on suppression of neointimal formation for which IV injection of Liposomal Simvastatin was administered to carotid artery of rats possessing balloon-injury (n=30). Liposomal Simvastatin was found to be 2 times more efficient than the free drug and the IV injection of liposomal simvastatin resulted in a reduction of monocytes and the neointima to media (N/M) ratios were determined for 14 days which was found to be $1.56\pm0.16$ and $0.90\pm0.12$ for the control and liposomal Simvastatin respectively. Thus, single charging of liposomal Simvastatin suppressed the neointimal formation in the rat model used in the study $^{39}$. Beretta *et al* (2011) performed a similar work as intravascular continuous infusion of lipophilic Simvastatin lactone and hydrophilic Simvastatin acid for ischemia in guinea pig brain. Results showed that the brains which were Simvastatin lactone treated had slow onset of ischemic depressions and increased brain anti oxidant capacity comparative to the other infusion. Thus the findings revealed that Simvastatin delivered via intravascular route exerts a lipophilicity-dependent effect in the initial stages of cerebral ischemia $^{40}$. Various researches are being carried out in improving the limiting factor of solubility by means of modifying the already existing formulation into a novel form which improves the bioavailability (Fig: 2). The current trend in the enhancement of efficiency of simvastatin therapy through novel formulation approaches is shown in table: 1.

Table 1  
**Novel formulation approaches and its application**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation</th>
<th>Materials used</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrogel</td>
<td>Gelatin, Hyaluronic acid, Gelatin polyethylene glycol triamine</td>
<td>Bone regeneration $^6$, Osteogenesis $^7$, Controlled release $^8$</td>
</tr>
<tr>
<td>2</td>
<td>Emulsion</td>
<td>Carpyral 90, Cremophor EL, Carbitol</td>
<td>Improve bioavailability $^{11}$</td>
</tr>
<tr>
<td>3</td>
<td>Micelle</td>
<td>Poly(ethylene glycol)-poly(-caprolactone)</td>
<td>Regeneration of bones $^{14}$</td>
</tr>
<tr>
<td>4</td>
<td>Nanoparticles</td>
<td>Tocotrienol</td>
<td>Combination therapy $^{17}$</td>
</tr>
<tr>
<td>5</td>
<td>Implants</td>
<td>Titanium discs, Poly(lactic acid)</td>
<td>Formation of bone $^{23,24,25}$</td>
</tr>
<tr>
<td>6</td>
<td>Topical formulation</td>
<td>Polycaprolactone, Pluronic 123, cetyl tri methyl ammonium bromide</td>
<td>Sustained release $^{27}$, Immediate release $^{29}$</td>
</tr>
<tr>
<td>7</td>
<td>Microspheres</td>
<td>Ethylcellulose</td>
<td>Bone tissue engineering $^{21}$</td>
</tr>
<tr>
<td>8</td>
<td>Sustained release pellets</td>
<td>Nicotinic acid, Ethylcellulose</td>
<td>Combination therapy and immediate release $^{35}$</td>
</tr>
<tr>
<td>9</td>
<td>Tablet</td>
<td>Starch, Lactose</td>
<td>Prevention of cardiovascular events $^{37}$</td>
</tr>
<tr>
<td>10</td>
<td>Liposome</td>
<td>Egg phosphatidyl choline, Cholesterol</td>
<td>Suppression of neointimal formation $^{39,40}$</td>
</tr>
</tbody>
</table>
CONCLUSION

The present review outlines about various formulation approaches of Simvastatin for treatment of various diseases such as hypercholesterolemia, asthma allergy and facilitates in cardio-protection, ischemia reperfusion, regeneration of bones and other anti-inflammatory effects. Despite its poor solubility the drug has shown an improvement in its bioavailability while being formulated into different other forms for the novel drug delivery approaches. Apart from the enhanced bioavailability, the stability of the drug could be increased when being made into a modified novel formulation which could lead to the better residence time of the drug having a site specific action in the biological system. The literature survey of the various researches carried out in each formulation approaches was analyzed from which the percentage of studies being carried out recently were found. This provides an idea about the various fields of researches, their present studies and the future works to be done along with their scopes.

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