Rosuvastatin Calcium Loaded Novel Nano Delivery Systems for Enhanced Oral Bioavailability
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Abstract: Rosuvastatin calcium is a hypolipidemic drug and has low oral bioavailability of about 20% due to poor aqueous solubility and hepatic first-pass metabolism. These are major boundaries inefficient delivery of RC by oral route. Several delivery approaches are known to moderate the difficulties of solubility and increase the oral bioavailability of RC. Among numerous approaches, nanotechnology-based delivery of RC has prospective to overcome the challenges associated with the oral administration. This review focuses on various nano-based delivery systems such as nanoparticles, lipid nanoparticles, SEDDS and SNEDDS and tried for improving the aqueous solubility, dissolution and subsequently bioavailability of RC upon oral administration. Of all, solid lipid nanoparticles appear to be promising delivery system, based on current reported results, for delivery of RC, as this system improved the oral bioavailability and possessed prolonged pharmacodynamic effect.

Keywords: Rosuvastatin calcium, oral bioavailability, nano carrier systems, pharmacokinetic, pharmacodynamics.

INTRODUCTION
Rosuvastatin calcium (RC) is a competitive inhibitor of HMG-CoA reductase [1]. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis [2].

Chemical RC is bis-[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methyl sulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The Log P (partition coefficient) of RC was 2.6 with melting range of 122-131°C.

RC acts primarily in the liver. Decreased hepatic cholesterol concentrations stimulate the up regulation of hepatic low density lipoprotein (LDL) receptors which increases hepatic uptake of LDL. Rosuvastatin also inhibits hepatic synthesis of very low density lipoprotein (VLDL). The overall effect is a decrease in plasma LDL and VLDL. The BA of RC is approximately 20% as it is metabolized by the liver via CYP 450 isoenzyme. Absolute bioavailability is approximately 20%. Peak plasma concentrations attained within 3-5 h after administration. Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters and is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations. RC is not extensively metabolized. Only ~10% is excreted as metabolite. CYP450 is primarily responsible for the formation of rosuvastatin's major metabolite, N-desmethyl rosuvastatin. N-desmethyl rosuvastatin has approximately 50% of the pharmacological activity of its parent compound in vitro [3].

RC is approved for the treatment of high LDL cholesterol (dyslipidemia), total cholesterol (hypercholesterolemia), and/or triglycerides (hypertriglyceridemia) [4]. In February 2010, rosuvastatin was approved by the FDA for the primary prevention of cardiovascular events (Astra Zeneca).

RC has very low aqueous solubility and first-pass metabolism and were considered as major shortcoming in the therapeutic application and efficacy of RC as conventional oral dosage form. It has reported log P of 2.6. Low solubility of RC across the physiological pH range is reported to result in incomplete absorption from the GIT. Based on its solubility in physiologically relevant pH conditions and absorption characteristics, it was classified in the biopharmaceutics Classification System (BCS) as a class II drug. To overcome poor aqueous solubility, hepatic first-pass metabolism and to enhance oral bioavailability, nanocarriers are gaining tremendous interest and have shown remarkable advantages over
conventional dosage forms in oral drug delivery of RC. These drug delivery systems are needed which can provide the reduced dosing frequency, enhanced bioavailability, increased selectivity, and reduced side effects [5, 6]. Nanotechnology based oral drug delivery systems afford an alternative strategy to administer with improved bioavailability and therapeutic effect [7].

Nanotechnology in delivery of poorly water soluble drugs

In general, drugs with poor aqueous solubility, compromise difficulty in formulation development by conventional methods, as they present difficulties such as slow onset of action, poor oral bioavailability, lack of dose proportionality, failure to achieve steady state plasma concentration, and disagreeable side effects. The conventional dosage forms thus may result in over- or under medication and poor patient compliance. These defies can be overwhelmed by applying novel drug delivery systems that offer benefits like decrease in dose regularity, lowering of dose bulk, site precise targeting, enhanced permeability, and enhancement in oral bioavailability [8, 9]. Nanotechnology is a promising strategy in the development of drug delivery systems, especially for those potent drugs whose clinical utility failed due to their poor solubility, low permeability, inadequate bioavailability, and other poor biopharmaceutical properties. The most common nanotechnology based strategies used in development of delivery systems are nanoemulsions, dendrimers, niosomes, solid lipid nanoparticles, polymeric nanoparticles, nanostructured lipid carriers, and so forth, which provide controlled, sustained, and targeted drug delivery. The nanotechnology based systems have extensively been investigated for improvement of the bioavailability of antihypertensive drugs [10]. The present review provides an insight of the in vivo studies with various nanotechnology based approaches having potential in improving oral bioavailability of poorly soluble antihypertensive drugs.

Polymeric nanoparticles

Nanoparticles (NPs) have drawn increasing attention from every branch of medicine [11] for their ability to deliver drugs in the optimum dosage range, repeatedly resulting in better therapeutic efficacy of the drug, markedly less side effects and improved patient compliance. Small molecule drugs, proteins, or peptides can be encapsulated and protected from the severe harsh gastric environment by polymeric nanoparticles. Furthermore, nanoparticle surface characteristics can be designed to optimize mucoadhesion, cellular uptake, immune system interactions, and cell targeting. Particles synthesized from commonly used polymers, such as poly(lactic acid) (PLA), poly(sebacic acid) (PSA), poly(lactic-co-glycolic acid) (PLGA) and poly(acrylic acid) (PAA) may achieve mucoadhesion via hydrogen bonding, polymer entanglements with mucins, hydrophobic interactions, or a combination of these mechanisms [12]. The improved oral BA from NPs might be due to prolonging residence time [13], can also be attributed to protection from proteolytic enzymes, direct uptake of particles by intestinal cells [14].

Hippara et al., [15] developed the long-circulating PEGylated chitosan nanoparticles (NPs) of RC for improved pharmacokinetics and pharmacodynamics profile by oral route. Chitosan NPs of RC were prepared by carbodiimide mediated reaction, using a carboxylic acid derivative of PEG. Pharmacokinetic studies indicated that optimized NPs showed prolonged drug release over a period of 72 h. Pharmacodynamics studies in hyperlipidemic rat model demonstrated greater lipid-lowering capability of RC nanoparticles in comparison with pure RC. Thus, nanoparticles of RC demonstrated significant sustained delivery of the drug in-vivo along with improved therapeutic action, which might be prospective drug delivery modality for enhancement of poor oral BA of RC.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are sub-micron colloidal carriers with particle size range of 50-1000 nm. SLNs are made up of solid lipid, which is melting at corresponding melting points and stable as solid at room temperature [16]. SLNs have the advantage of sustained drug release [17], enhanced oral BA [18, 19], targeting effect [20], and also showed enhanced pharmacodynamics activity [21, 22].

Narendar and Kishan, [23] developed the RC loaded solid lipid nanoparticles to improve the oral BA. The optimized RC-SLNs were developed with Dynasan-112 using hot homogenization followed by ultra sonication method. RC-SLNs showed about 4.6-fold enhancement in the oral BA when compared with RC coarse suspension in Wistar rats. Further, the RC-SLNs also exhibited a decreased lipid profile upto 36 h, while suspension showed 24 h only. Therefore, these findings indicating that, SLNs are alternative delivery systems to increase the BA of RC. Suvarna et al., [24] also reported the influence of triglycerides on the improved oral BA of RC, using SLN approach. RC-SLNs were made with Dynasan-118 and particles are nearly spherical in shape. Pharmacokinetic studies were performed in albino Wistar rats and results showed that about 2.2-fold enhancement in the oral BA was observed with SLN formulation compared with suspension.

Surface modified SLNs of RC for LDL targeting receptors were developed using quality by design approach [25]. The prepared SLNs showed enhanced permeability, pharmacokinetic and pharmacodynamics activity.
Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers are similar to SLNs, but solid lipids are mixed with liquid lipids in a ratio of 70:30 up to a ratio of 99.9:0.1, whereas the surfactant content ranges 1.5%-5%. NLCs are a useful drug delivery system with high drug loading, encapsulation efficiency and stability. They may increase, bioavailability and stability of bioactive compounds, and shelf-life, consumer acceptability, functionality, nutritional value and safety of food systems, and provide controlled release of encapsulated materials. NLCs exhibit a prolonged residence time in the GIT when compared to other lipid-based formulations, and present a different release mechanism that can be modulated by tunnelling the lipids contained within their solid lipid matrix [26]. NLCs also provides enhancement in oral BA compared with SLNs [27].

NLCs of RC were prepared by using stearic acid and Compritol ATO 888 as solid-lipid, Oleic acid as liquid-lipid and Poloxamer 188 as a surfactant, by high shearm homogenisation followed by Ultrasonication technique. From the pharmacokinetic studies in rats, the bioavailability of NLC formulation (F3) exhibited 2-fold enhancement as compared to the marketed conventional tablet [28]. Agarwal et al., [29] also developed the RC-NLCs for improved pharmacodynamics activity by oral delivery. RC-NLCs were prepared by hot homogenization method with stearic acid and oleic acid as solid lipid and liquid lipid respectively. Pharmacodynamic studies in male wistar rats revealed that, reduction in lipid profiles were found to be significant compared with plain RC at a dose of 25 mg/kg body weight.

RC-loaded NLCs were developed and optimized for improved pharmacokinetic and pharmacodynamics activity. The RC-NLC was prepared using melt emulsification ultrasonication technique and optimized by Box–Behnken statistical design. The optimized NLC formulation was observed to be 150.3 ± 4.67 nm, 0.175 ± 0.022, –32.9 ± 1.36 mV and 84.95 ± 5.63%, respectively. Pharmacokinetic study on female albino Wistar rats showed 5.4-fold enhancement in BA with RC-NLC compared to suspension and also showed significant (p < 0.01) lipid lowering result in hyperlipidemia rats. Therefore, NLC signifies a pronounced impending for improved effectiveness of RC after oral delivery [30].

Self Emulsifying Drug Delivery System

Self-emulsifying drug delivery systems (SEDDS) or selfemulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants [31]. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil–in–water (o/w) emulsions or microemulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate–limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood–time profiles [32].

RC loaded self-nanoemulsifying drug delivery systems (RC-SNEDDS) were prepared and reported as nanocarrier system for enhanced oral BA. RC-SNEDDS were developed using cinnamon oil 30%; labrasol 60%; Capmul MCM C8 10% was –29.5 ± 0.63 with an average particle size distribution of 122 nm. The relative bioavailability of optimized RC-SNEDDS (CN 7) formulation showed an improved bioavailability of about 2.45-fold superior than that of RC coarse suspension [33].

RC loaded self-nanoemulsifying powder were developed by using SEDDS formulation to improve the oral BA as alternative approach [34]. RC-SEDDS formulations exhibited desirable physical characteristics of self-emulsifying systems with nano-sized globules in the range 119.8 to 228.9 nm, rapid emulsification in approximately 60 s and transmittance of close to 100 %. In-vitro dissolution studies on the developed formulations indicate a 4-fold increase in drug release in 10 min, compared to the pure drug RC. The pharmacodynamic results showed significant improvement in oral bioavailability by observing the decreased lipid profiles, compared to the pure drug in Wistar rats.

Abo and Abdel-Bar [35] was reported the solid supersaturated self-nanoemulsifying drug delivery system (sat-SNEDDS) as a carrier for the improvement of RC bioavailability by oral route. Different sat-SNEDDS were prepared by incorporating different ratios of RC into SNEDDS using tween80/PEG400 (77.2%) as surfactant/cosurfactant mixture and garlic /olive oil (22.8%) as oil phase. The prepared systems were characterized for an optimal system and further oral bioavailability study was performed. The adsorption of the stable positively charged nanocarrier RC sat-SNEDDS onto solid carriers provided free flowing amorphous powder. The carrier could alter the morphological architecture and in vitro release of the RC solid sat-SNEDDS. Hydrophobic carriers as microcrystalline cellulose 102 (MCC) showed superior physical characters and higher dissolution rate over hydrophilic carriers as
maltodextrin with respective T_{100}% 30 min and 45 min. The rapid spontaneous emulsification, the positively nanosized MCC-sat-SNEDDS improved oral bioavailability of RC by 2.1-fold over commercial tablets of RC. Solid MCC-sat-SNEDDS collective double benefits of sat-SNEDDS and solid dosage form was effectively raised to increase the oral BA of RC.

Hadel et al., [36] reported the enhanced oral BA of RC by using SNEDDS employing natural oil containing unsaturated fatty acid and omega 3. SNEDDS formulation of RC was developed using factorial design. The antihyperlipidemic effect of RC-SNEDDS was better than that of the commercial RC tablets and the pure drug on rats.

Karasulu et al., [37] developed the rosuvastatin calcium loaded self emulsifying drug delivery system (SEDDS) to improve the bioavailability and pharmacodynamic activity. RC-SEDDS were optimized and in vivo performance of RC-SEDDS was studied by pharmacokinetic and pharmacodynamics in Yorkshire pigs. The average droplet size of SEDDS ranged between 200-250 nm, were found to be stable and exhibited around 4-fold greater permeation than commercial tablet (Crestor® 20 mg tablet). In pharmacokinetic studies, RC-SEDDS exhibited enhanced bioavailability of RC than commercial tablet. Triglyceride and total cholesterol levels were significantly reduced with SEDDS formulation by 37% and 19% when compared to baseline values in pharmacodynamics study. However, these decreases with commercial formulation were only 6% and 2% respectively. Therefore, RC-SEDDS formulation could be potentially used to improve the oral bioavailability of RC.

RC loaded SNEDDS formulation converted to tablet dosage form considered as one of the delivery system to improve the BA. Initially, optimized SNEDDS formulations were developed using design of experiments. SNEDDS composed of 10% Labrafil, 80% Cremophore RH40 and 10% Propylene glycol gives the particle size of 15 nm. Further, SNEDDS were converted to solid dosage form by utilizing hydrophilic nano-silica, 3% Ac-Di-Sol and 30% Avicel as excipients. From the pharmacokinetic studies, more than 2.4-fold improvement in the oral BA was observed with nano formulation compared with the commercially available RC tablet [38].

CONCLUSION

Rosuvastatin calcium is a hypolipidemic drug and belongs to BCS class II drug with poor oral bioavailability due to poor aqueous solubility and first-pass metabolism. Enhancement of solubility and the bioavailability of the RC by four different nano carrier systems are presented in this review article. Polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers and self-emulsifying drug delivery systems were reported for RC delivery. These were considered to be potential strategies to enhance the solubility, subsequently bioavailability and pharmacodynamics activity of RC. Amongst them solid lipid nanoparticle delivery system seems to be better over other delivery systems.

REFERENCES


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