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Role of Solid Lipid Nanoparticles in Oral Bioavailability Enhancement of Antihypertensive Drugs

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Review Article

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Abstract: Solid lipid nanoparticles (SLNs) are at the rapidly developed field of nanotechnology with a few potential applications in drug delivery, clinical medication and research, and additionally in other distorted sciences. Because of their small size-subordinate properties, lipid nanoparticles offer the likelihood to grow new therapeutics. The capacity to loaded drugs into nanocarriers offers another model in drug delivery that could be utilized for optional and tertiary levels of drug targeting on. Consequently, SLNs hold extraordinary advantage for achieving the objective of controlled and site specific drug delivery and henceforth have pulled in wide consideration of analysts. The current review describes the role of solid lipid nanoparticles on the pharmacokinetics of poorly soluble antihypertensive drugs. In the event that suitably examined, solid lipid nanoparticles may open new areas in treatment of hypertension with improved oral delivery.

Keywords: Solid lipid nanoparticles, antihypertensive, drug delivery, pharmacokinetics, poor soluble, oral bioavailability.

INTRODUCTION

Hypertension is a cardiovascular disorder, resulting in the elevated blood pressure. As per WHO, Geneva, in 2008, hypertension caused about 45% death due to ischemic coronary illness and 51% death as a result of stroke. In 1980, 600 million individuals were experiencing hypertension while in 2008 this figure was raised to 1 billion raising a major worry for its management [1]. Several studies over the past have shown an increasing prevalence of hypertension in India [2-4]. Kearney *et al.,* [5] in their paper predicted that the burden of hypertension in India is expected to double from 118 million in 2000 to 213.5 million by 2025.

For an adult of 45 years old without hypertension, the 40-year chance for creating hypertension is 93% for African Americans, 92% for Hispanics, 86% for whites, and 84% for Chinese grown-ups. In 2010, hypertension was the main source of death and incapacity balanced life-years around the world, and a more prominent supporter of occasions in ladies and African Americans contrasted and whites. Frequently ignored, the hazard for CVD increments in a log-direct form; from SBP levels <115 mm Hg to >180 mm Hg, and from DBP levels <75 mm Hg to >105 mm Hg. A 20 mm Hg higher SBP and 10 mm Hg higher DBP are each related with a multiplying in the danger of death from stroke, coronary illness, or other vascular malady. In people ≥30 years old, higher SBP and DBP are related with expanded hazard for CVD, angina, myocardial dead tissue (MI), heart disappointment (HF), stroke, fringe blood vessel malady, and stomach aortic aneurysm. SBP has reliably been related with expanded CVD [6].

Though there are plethora of conventional antihypertensive dosage forms, majority of them fail to treat hypertension due to their poor aqueous solubility thereby resulting in poor bioavailability (BA) [7]. Some of the drugs used to treat hypertension are the substrate of P-gp and exhibit significant first-pass metabolism leading to reduced bioavailability. The other challenges associated with antihypertensive therapy are their short half-life and high dosing frequency. One way to overcome those challenges associated to dosing frequency is to design an extended release formulation. On this regard, nanomedicine or nano-therapeutics provide a new avenue in delivering therapeutics to pathological sites and residing on it for increased period of time. Furthermore, nanomedicine also bypasses the hepatic first-pass metabolism, P-gp mediated efflux and target specificity allowing therapeutics to have extended circulation. In the early 2000s, various types of novel drug delivery systems such as buccal [8-10], gastro retentive [11-14], osmotic controlled [15, 16], solid dispersion [17] and liquisolid compacts [18].

RATIONALE FOR USING NANOCARRIERS

Oral route is the most favored route for the organization of the therapeutics. Be that as it may,

conveying therapeutics with low water solubility as well as permeability (BCS class II and IV) is an entangled assignment because of poor bioavailability caused by pH variety in the gastrointestinal tract (GIT) [19]. This wide distinction in the pH can seriously influence the pharmacological action of the medication by oxidation, deamidation, or hydrolysis of protein drugs. Oral bioavailability of medications like candesartan cilexetil is influenced as they experience synthetic debasement at acidic pH [20, 21]. Compounds like liver esterase and cytochrome P450 cause huge debasement of antihypertensives. Protease corrupts 94– 98% of orally regulated protein details. Intestinal mucosa is the other obstruction which impedes medicate penetration. Mucosal hindrance comprises of outward obstruction (microenvironment close to the region of bodily fluid layer) and inherent boundary (epithelial cell monolayer). Natural boundary is because of the nearness of tight intersection between nearby cells [22]. Distinctive instrument by which any particle can cross this obstruction incorporates transcellular, paracellular, and transcytosis. Transcytosis being dynamic transport pathway confines expansive measured and charged particles. At the point when the mucosal hindrance is penetrated, atoms need to cross lamina propria where blood vessels lie and particle can get section into the circulatory system [23]. Technique to defeat intestinal obstruction is to get ready mucoadhesive detailing which expands the home time of the definition with bodily fluid layers in this manner expanding drug focus at the site of assimilation. Mucoadhesive have the property of going about as saturation enhancer that can open tight cell intersection in this manner making the paracellular transport plausible [24].

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are type of colloidal carrier systems, in which particle size ranging in between 10 and 1000 nm are known as nanoparticles [25, 26]. Throughout the years, they have developed as a variable substitute to liposomes as medication bearers. The effective execution of nanoparticles for tranquilize conveyance relies upon their capacity to infiltrate through a few anatomical obstructions, managed arrival of their substance and their security in the nanometer measure. Be that as it may, the shortage of safe polymers with administrative endorsement and their high cost have constrained the across the board utilization of nanoparticles to clinical solution [27].

They have been explored in late decades for dermal, pharmaceutical and beautifiers thinks about [28]. Liposomes have one of kind points of interest as a pharmaceutical transporter, for example, assurance of medication against proteins debasement, low danger, adaptability, biocompatibility, completely biodegradability and non-immunogenicity. However, huge numbers of its applications are constrained because of a few burdens, for example, short timeframe of realistic usability, poor soundness, low epitome viability, fast evacuation by reticuloendothelial framework (RES), cell associations or adsorption and intermembrane transfer. Despite the way that liposomes have been the sign of lipid nanoparticles (LNPs) for site particular delivery of therapeutics, there is a need to create approaches for cutting edge control over drug release and drug delivery, which may not possibly stack into liposomes. One reason for this, aside from potential innovative issues, is the non-accessibility of a ' shoddy ' pharmaceutical liposome [29].

There are a few methods of preparations for SLNs, for example, hot homogenization followed by ultra sonication [30-33], high pressure homogenization [35, 36], solvent emulsification/evaporation [37], supercritical liquid extraction of emulsions [38], solvent injection method, micro emulsion method. Two procedures of the high pressure homogenization hot [39] and cool [40] procedures were produced. These are two essential creation strategies which in both, medicate is disintegrated or solubilized in the lipid being softened at around 5-10 °C over its liquefying point.

SLNs have strikingly extensive variety of properties which make them helpful for parenteral [41], dermal), nasal, ocular [42, 43], oral [44] and topical delivery of drugs [45]. These items have been created keeping in mind the end goal to diminish dangerous symptoms of the fused exceedingly powerful medications and increment the adequacy of the treatment. And in addition, they have exhibited great potential in quality exchange, restorative and nourishment industry. In any case, on account of said impediments and troubles identified with them, the aggregate number of items available is still limited. SLNs are widely used as vehicle for the delivery of poorly water soluble drugs. In turn, enhance the oral bioavailability (BA) of BCS class II drugs. The current review mainly focused on the role of solid lipid nanoparticles on the different kinetic parameters and their influence on enhanced oral BA.

SOLID LIPID NNAOPARTICLES OF ANTIHYPERTENSIVE DRUGS

Harshad *et al*., [46] reported the effect of SLNs on oral BA of poorly soluble drugs. In this review, we attempt to discuss updates in the oral BA of poorly soluble antihypertensive drugs.

Narendar and Kishan [47] developed the nisoldipine loaded SLLNs for improved oral bioavailability, using design of experiments approach. Nisoldipine is calcium channel blocker used in the treatment of hypertension. It has poor oral BA (5%) due to poor aqueous solubility and first pass metabolism. Hence, SLNs are reported to enhance the oral BA by 2.45-folds compared with suspension formulation. The half-life and MRT of SLNs also doubled compared with control formulation. This is evidenced the sustained release of the nisoldipine form the SLNs.

Similarly, comparative studies of nanostructured lipid carriers with SLNs for nisoldipine were reported. In this study, both nano carrier systems enhance the BA of poorly water soluble drug such as nisoldipine [34].

Similarly, candesartan cilexetil, angiotensin receptor 1 antagonist, prescribed for the treatment of hypertension. The bioavailability of candesartan cilexetil was less than 20% owing to poor solubility and pre-systemic metabolism. Therefore, an attempt was made to enhancement in the bioavailability using SLNs delivery system. SLNs of CC were prepared by using triglycerides as solid lipid matrices. The BA of CC loaded SLNs were increased by more than 2.85-folds compared with coarse CC suspension formulation in albino Wistar rats at a dose of 10 mg/kg [20]. Zhang *et al.*, 2012 also reported the improvement in oral bioavailability of candesartan was 12-folds more after incorporation into solid lipid nanoparticles [48].

Felodipine is an antihypertensive drug with poor oral bioavailability due to the first pass metabolism. Solid lipid nanoparticles as considered as alternative delivery system to improve the BA. Therefore, felodipine loaded solid lipid nanoparticles (SLNs) were developed using triglycerides as lipid matrices and prepared by hot homogenization followed by sonication method. Pharmacokinetics of felodipine-SLNs after oral administration in male Wistar rats was studied. The BA of felodipine loaded SLNs was increased by 1.75-folds when compared to that of a felodipine coarse suspension [49].

Lacidipine (LD) loaded solid lipid nanoparticles (LD-SLNs) were reported by Sandeep *et al*., [50] for improving the oral bioavailability. LD-SLNs were prepared in two steps. First step was hot homogenization and next by ultrasonication method, using triglycerides (tripalmitin and tristearin), monoglyceride and surfactants (Poloxamer 188 and egg lecithin E80). LD-SLNs prepared with Dynasan-116 (F3) having the size of 141.86nm, PDI of 0.293, P of -22.3m with 94.75% of EE was optimized and was stable for 60 days. Further, pharmacokinetic studies were conducted in Wistar rats. The relative bioavailability of LD in SLNs was 2.03-times when compared with that of the LD suspension. The results are indicative of SLNs as suitable lipid based carrier system for improving the oral bioavailability of LD.

Nimodipine (NMD) is highly lipophilic antihypertensive drug with log P value of more than 3 and 13% oral bioavailability. Hence, lipid delivery system is developed to increase the oral BA. Therefore, nimodipine loaded solid lipid nanoparticles (NMD-SLNs) were prepared to increase the oral BA by Chalikwar *et al*., [51] by using factorial design. The pharmacokinetic study of optimized nimodipine loaded SLNs showed 2.08-folds increase in relative bioavailability than that of NMD solution in male Albino Wistar rats, when administered orally. Due to enhanced bioavailability, these NMD-SLNs are considered to be promising vehicles for oral delivery.

Oral bioavailability of olmesartan medoxomil (OM) was improved by solid lipid nanoparticles delivery system. Nooli *et al*., [52] reported the enhanced oral BA of OM 2.32-times more in male Sprague Dawley rats compared with OM plain drug solution. Similarly, Arun *et al*., [53] reported the about 7.21-folds improvement and 3.52-folds improvement compared with OM coarse suspension and nanosuspension formulation, respectively. Recently, Pandya *et al.*, [54] developed the SLNs of OM to increase the oral BA by employing central composite design. From his findings, about 2.3-fold enhancement in the OM-SLNs were reported compared with marketed formulation.

Havanoor *et al.*, [55] and Thirupathi *et al*., 2017 [31] developed and reported the isradipine loaded SLN and exhibited a noticeable decrease in the mean systolic blood pressure for a period of 12 h. Such studies show the potential of SLN for antihypertensive drugs as a long circulating nanocarrier which markedly improves the oral bioavailability and residence time of the drug.

Carvedilol is a non-selective beta blocker and indicated for the treatment of mild to moderate congestive heart failure (CHF). It is practically insoluble in water (<0.01 mg/ml). After oral administration, Carvedilol is rapidly absorbed with an absolute bioavailability of 18-25% because of low solubility and extensive first-pass metabolism [56]. Therefore, the bioavailability of carvedilol is improved by solid lipid nanoparticle formulation. The bioavailability of carvedilol was enhanced by more than 5 fold intranasally compared with plain drug suspension [57]. Vanishetty *et al*., [58] developed the surface modified SLNs coated with N-carboxymethyl chitosan (MCC) to avoid intraduodenal administration and enhance oral BA of carvedilol. From this results, MCC coated SLNs showed 2-fold increase in oral BA compared with C-SLNs. Therefore, the results suggest that the SLN can be administered orally after coating with MCC to improve the bioavailability of drugs such as carvedilol.

CONCLUSIONS AND FUTURE PERSPECTIVES

New era antihypertensive medications, new novel sub-atomic targets and nanotechnology-based delivery framework are as of now in essential phase of preclinical trial and clinical trial and are indicating positive outcomes. Numerous novel molecular focuses for antihypertensive are under exploratory stage and are being tested with entrenched officially existing antihypertensive treatment to the extent their viability is concerned. In any case, there is still extent of change in treatment which can adequately control pulse. Solid

lipid nanoparticles are one of the promising methodologies in deciding a few impediments of antihypertensive.

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