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Review Article

ENHANCING OF ORAL BIOAVAILABILITY OF POORLY WATER-SOLUBLE ANTIHYPERTENSIVE DRUGS

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ABSTRACT

Among various routes of drug delivery, Oral administration is the most convenient route because of its high patient compliance. Although oral drug delivery is effective for drugs with high aqueous solubility and epithelial permeability; however for poorly aqueous soluble drug the membrane permeability, chemical, and enzymatic stability of drugs are the major limitations in successful oral drug delivery. Almost 70% of the new drug candidates which shows poor bioavailability, the antihypertensive drugs are among those. Novel drug delivery systems are available in many areas to overcome the problems associated with hydrophobic drugs and the nanotechnology-based drug delivery system is the most potential to beat the challenges related to the oral route of administration with some important advantages such as the colloidal size, biocompatibility, lowered dose size, reduced toxicity, patient compliance and drug targeting. The foremost common nanotechnology-based strategies utilized in the development of delivery systems are nano-emulsions, nano-suspensions, dendrimers, micelles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, carbon nanotubes, Self-Nano-emulsifying Drug Delivery System, proliposomes, nano-crystals, and so forth, which give controlled, sustained, and targeted drug delivery. The appliance of those systems within the treatment of hypertension continues to broaden. This review focuses on various nano-carriers available in oral drug administration for improving solubility profile, dissolution, and consequently bioavailability of hydrophobic antihypertensive drugs.

Keywords: Nanoparticles, Anti-hypertension, Hydrophobic drugs, Oral bioavailability, Nanocarriers

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INTRODUCTION

Oral delivery of a drug is the most convenient, common, and widely used route of administration for compliance like effortless administration, no assistance, patient conformity as compared to the other routes; for example intravenous, pulmonary, and intramuscular drug delivery. Because of the low bioavailability and low absorption upon oral administration several compounds failed and did not succeed in the research and development [1]. The drugs which have poor oral bioavailability are not capable to reach the minimum effective concentration to exhibit the therapeutic action [2]. The reasons for the poor bioavailability of the drugs depend on some parameters like dissolution rate, permeability, aqueous solubility, susceptibility to efflux mechanisms, first-pass metabolism. In recent years, almost 70% of new drug candidates are showing poor bioavailability [3]. Among these drugs, some antihypertensive drugs show poor bioavailability.

Presently available anti-hypertensive drugs can be classified into the following categories-(a) ACE inhibitors, (b) Angiotensin antagonist, (c) Calcium channel blocker, (d) Diuretics, (e) Central sympatholytics, (f) α-Adrenergic blocker, (g) Vasodilator, (h) β-Adrenergic blocker [4]. The majority of these drugs bear a few significant drawbacks like low permeability, low bioavailability, comparatively short half-life, and undesirable side effects. To overcome such types of challenges related to antihypertensive drug therapy, novel drug delivery systems present an opportunity for formulation scientists which can provide the following characteristics: (1) Enhanced bioavailability, (2) Low dosing frequency, (3) Reduced side effects, and (4) Increased selectivity [5].

Oral drug delivery confrontation

Although oral drug delivery is effective for drugs with high aqueous solubility and epithelial permeability, efficient oral administration of the poorly water-soluble drug may be a challenge. Presently, most of the new chemical entities are lipophilic and consequently have poor aqueous solubility [6]. On the idea of the biopharmaceutical classification system (BCS), a variety of latest therapeutic entities are characterized under BCS class II (low solubility and high permeability) or BCS class IV (low solubility and low permeability). Besides, the oral bioavailability of certain drugs is also suffering from their poor gastrointestinal permeability. To achieve effective therapeutic action, these drugs need to be given at a high dose for example antiviral drugs. Moreover, chemical and enzymatic barriers presented by the gastrointestinal tract (GIT) also affect the oral administration of medicine. The change in GIT pH and the presence of sort of enzymes significantly affect the oral bioavailability of medicine like antihypertensive, antibiotics, antihyperlipidemic agents, and so forth. Furthermore, drugs with high first-pass metabolism such as repaglinide, -blockers, calcium channel blockers, and ACE inhibitors even have low oral bioavailability. These drugs also present a challenge in formulation development for oral administration [7].

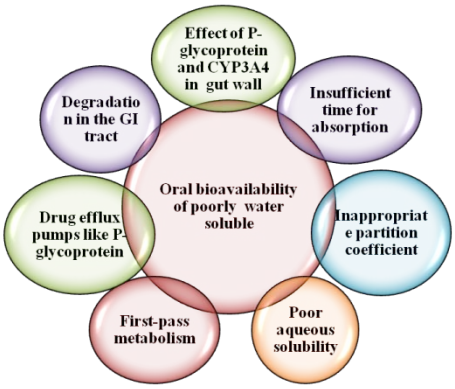

Fig. 1: Reasons for poor oral bioavailability of poorly water-soluble drugs

Nanotechnology in delivery of poorly soluble drugs

Drugs with poor solubility possess difficulty in formulation by applying conventional approaches as they show problems like slow

onset of action, poor oral bioavailability, lack of dose proportionality, failure to realize steady-state plasma concentration, and undesirable side effects. The traditional dosage forms thus may end in over-or under medication and poor patient compliance [8]. These type of challenges can be overcome by applying novel drug delivery systems, offering benefits such as reduction in dose frequency, enhanced permeability, lowering of dose size, site-specific targeting, and improvement in oral bioavailability [9-11]. Nanotechnology is a promising strategy with the advancement in drug delivery systems especially for those potent drugs whose clinical development failed; credit to their poor solubility, inadequate bioavailability, low permeability, and other poor biopharmaceutical properties [12-14]. The foremost common nanotechnology-based strategies utilized in the development of delivery systems are nanoemulsions, dendrimers, micelles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, carbon nanotubes, and so forth, which give controlled, sustained, and targeted drug delivery. The nanotechnology-based systems have extensively been investigated for improvement of the bioavailability of antihypertensive drugs [15]. This review provides an insight into varied nanotechnology-based approaches having the potential in improving the oral bioavailability of poorly soluble antihypertensive drugs.

Solid lipid nanoparticles (SLNs)

Lipid nanocarriers have gained significant attention in oral drug delivery within a previous couple of decades. The SLNs are a submicron colloidal carrier that consists of physiological lipid, dispersed in water or an aqueous surfactant solution [16]. SLNs offer benefits like biocompatibility, non-toxicity, and stability against coalescence. Solid lipid nanoparticles are often applied for the delivery of hydrophilic also as hydrophobic drugs [17]. Venishetty *et al.* (2012) have shown carvedilol-loaded solid lipid nanoparticles (SLNs) as a promising strategy to reinforce the bioavailability of such poorly soluble drugs. They prepared methyl carboxy chitosan (MCC) coated carvedilol-loaded SLNs to enhance its bioavailability and to protect it from an acidic environment [18]. In another study, Kumar *et al.* (2007) have demonstrated a three to fourfold increase in bioavailability of nitrendipine solid lipid nanoparticles upon intraduodenal administration. Nitrendipine has oral bioavailability between 10% and 20% due to high first-pass metabolism. The SLNs of nitrendipine were characterized for zeta potential, particle size, crystalline behavior of lipid and drug, and drug encapsulation efficiency. The results of *in vitro* and *in vivo* drug release study indicated solid lipid nanoparticles as a possible carrier for enhancing the bioavailability of nitrendipine [19]. Chalikwar *et al.* (2014) have shown an increase in oral bioavailability of nimodipine, a calcium channel blocker, by formulating solid lipid nanoparticles (SLNs).

Nimodipine is very lipophilic with only 13% bioavailability. SLNs of nimodipine were prepared by 23 factorial design and factors like lipid, surfactant, and cosurfactant concentration were studied. In another investigation, Ekambaram and Sathali (2011) have developed solid lipid nanoparticles (SLNs) of ramipril to extend its bioavailability. Ramipril may be a water-insoluble drug and its oral bioavailability is merely 28%. The SLNs were prepared by employing glyceryl monooleate and glyceryl monostearate with poloxamer 188, Span 20 and Tween 80, as stabilizers. The formulation containing glyceryl monooleate and Span 20 has shown an increase in the bioavailability [20]. The investigation reveals that SLNs present an effective alternative carrier system for drug delivery. Parmar *et al.* (2011) have studied *in vitro* and ex vivo characteristics of valsartan-loaded solid lipid nanoparticles which showed SLNs as a promising system to improve solubility and bioavailability, to bypass the first-pass metabolism and enhance lymphatic absorption [21].

Dendrimers

Dendrimers are innovative polymeric carriers attracting attention thanks to their advantages that include three-dimensional structure, nanometer size, narrow polydispersity index, and controlled molecular structure and also are accompanied with multiple functional groups/multivalency. The word "dendrimers" springs from the Greek word "Dendra," which means like a tree [22]. Dendrimers have a size ranging between 1 and 100 nm with three distinct domains:

- A core, which is at the middle containing atom or a molecule with a minimum of two identical chemical functions;
- Branches, which are the units repeated in the geometric progression that results in radially concentric layers known as "generations"; and
- Terminal functional groups at the surface determines the properties of dendrimers.

Different types of dendrimers are available on the idea of different polymers like polyamidoamines (PAMAMs), polyamines, polyamides (polypeptides), poly(aryl ethers), polyesters, carbohydrates, and DNA. PAMAM dendrimers are most ordinarily used. Dendrimers are applied as a flexible drug delivery system for delivery of medicine, gene, proteins, peptides, then forth [23-24]. For various pharmaceutical purposes, dendrimers have also been formed as conjugates by linking to different carriers like liposomes, CNTs, and nanoparticles [25]. A number of the applications of dendrimers include solubilization, gene therapy, and immunoassay. However, the conjugation and encapsulation of drugs with dendrimers have provided a platform for oral delivery of hydrophobic drugs like antihypertensive drugs or anticancer drugs [26-28].

The development in solubility through dendrimers depends upon dendrimer temperature, concentration, generation size, pH, terminal functionality and core. Candesartan cilexetil may be a calcium channel blocker utilized in the treatment of hypertension. The permeability of candesartan cilexetil depends on its aqueous solubility and lipid-protein partition coefficient about the corneum. Gautam and Verma (2012) investigated that the fabricated polyamidoamine (PAMAM) dendrimers containing candesartan cilexetil and the results of the investigation have shown a significant increase in water solubility of candesartan cilexetil within the form of PAMAM dendrimers [29]. To increase the aqueous solubility; Dendrimers of lomerizine have also been developed [30].

The studies also recommend that conjugation of drug to dendrimer enables bypassing of the efflux transporter which increases the solubility of the drug and therefore the bioavailability of the drug increases. A known substrate of the P-glycoprotein (P-gp) efflux transporter (propranolol), has been conjugated to lauroylG3 dendrimers. This conjugated propranolol has shown increased solubility [31]. PAMAM dendrimers have significantly enhanced the water solubility of nifedipine [32]. However, the appliance of dendrimers in oral delivery is in its infancy but may emerge as a rewarding strategy within the future [24, 33].

Nanosuspensions

Nanosuspensions are biphasic, colloidal dispersions of drug particles that are stabilized by using surfactants. Nanosuspensions contain particles dispersed in an aqueous vehicle with the dimensions of the particle about 1 μm. Nanosuspensions can overcome the issues associated with the delivery of poorly water-soluble drugs thanks to their nano-size particle range. Often Nanosuspensions are formulated with high solid content (40%), which improves patient compliance by reducing their dose size. For converting nanosuspensions to pellets/tablet-like dosage forms, various methods like freeze-drying, spray drying, and extrusion-spheronization are applied. Patel *et al.* (2014) have described an approach to develop a nanosuspension of a poorly water-soluble antihypertensive drug to enhance bioavailability and the optimized batch was converted into a solid dosage form. Telmisartan (TLM) was selected as a model drug. The TLM-loaded nanosuspension was optimized by applying a 3^2 full factorial design. The concentration of stabilizer and amount of milling agents were taken as the principal component of the study (PCA). The Lyophilization process was wont to develop tablets of nanosuspension. The *in vitro* drug release study was administered an over-optimized batch of TLM-loaded tablets, marketed tablets (Sartel 20), and conventional tablets in 0.1 M HCl as a dissolution medium. The results of *in vitro* drug release have demonstrated a higher value of cumulative percentage release (CPR) for nanosuspension-loaded tablet formulation as compared to two other formulations [34]. The *in vivo* pharmacokinetic study was performed in TLM-loaded tablets against marketed tablets in Wistar rats and also revealed improvement in the rate of absorption from

nanosuspension. Thus, the study indicated improvement in the rate and extent of oral absorption of TLM from nanosuspension-loaded tablets as compared to marketed formulations. This effectiveness was attributed to the nanometer size of particles in nanosuspension with subsequent increase in area and absorption.

The other properties of nanosuspensions like higher level of saturation solubility, the rapid onset of action, better adhesiveness to gastrointestinal epithelium, and enhanced area also cause better oral absorption and bioavailability of lipophilic drugs. Liu *et al.* (2014) have shown that by developing an osmotic pump capsule of carvedilol, increases the oral bioavailability and the nanosuspension's *in vivo* studies on beagle dogs have shown significant improvement in bioavailability as compared to marketed products [35]. The nanosuspensions are also reported to possess a superb disintegration profile which increases dissolution rate with complete dissolution in minutes [36]. Thadkala *et al.* (2015) have shown that by developing oral nanosuspension tablets, dissolution rate and absorption of nebivolol hydrochloride can be improved. Nebivolol hydrochloride is a lipophilic drug that is β1 receptor antagonist and comes under class II in BCS. The solvent displacement/nanoprecipitation method was used to formulate the nanosuspension of nebivolol and the *in vitro* dissolution studies of optimized formulation showed a maximum drug release of 98.93% within a quarter-hour which followed first-order release kinetics. After that the *in vitro* drug release of optimized formulation and innovator product (Nebilet) was compared; which showed the drug release of 98.37% and with pure drug 27.34% within an hour and concluded that nanosuspension formulation has shown increased drug release rate as compared to the other two [37].

Proper selection of the surfactants and/or stabilizers which will reduce the challenges in fabricating nanosuspensions for oral administration and therefore the method of preparation can produce physically stable nanosuspensions with long-term storability. Rajalakshmi *et al.* (2012) have reported promising alternative strategy with improved stability and biopharmaceutical efficacy of nanosuspensions for poorly water-soluble drugs. Nanosuspension of valsartan was prepared by employing soya lecithin and poloxamer as stabilizers and the *in vitro* drug release study showed higher release from nanosuspension [38]. During a pioneer study, Sahu and Das (2014) have reported the increased solubility and oral bioavailability of felodipine within the sort of physically stable nanosuspension [39]. A report of another study on the candesartan cilexetil has also revealed a nanosuspension system as an efficient alternative strategy to enhance the oral bioavailability of poorly water-soluble antihypertensive drugs. The results of this study have shown a significant lowering in high vital signs upon administration of nanosuspension as compared with a plain drug suspension and, thus, the investigation showed a significant raise in antihypertensive activity of candesartan within the sort of nanosuspension and also showed that it might be effectively transformed from laboratory scale to pharmaceutical market and could be an efficient approach to increase bioavailability of poorly soluble drugs, especially to drugs which are simultaneously insoluble in organic and aqueous media [40].

Nanoemulsions

Nanoemulsions are oil-in-water (o/w) emulsions with droplet sizes within the range of 100 and 500 nm. The advantages of Nanoemulsions are

- ✓ Solubilization of hydrophobic molecules in the oily phase,
- ✓ Modification of oil droplets with polymers to prolong circulation time, and
- ✓ Targeting tumors passively and/or targeting ligands actively.

The most ordinarily used methods to organize nanoemulsions are low-energy emulsification and high-energy emulsification [41]. Ghai and Sinha (2012) have developed nanoemulsions as an emulsified drug-delivering carrier for selective -1 adrenoreceptor blocker of talinolol. The talinolol nanoemulsion is comprised of fifty (w/v) Brij-721 ethanolic solution, triacetin, and water in ratio of 40:20:40 (%w/w). After that the polydispersity index, droplet size, *in vitro/in vivo* release of nanoemulsion, and surface morphology were investigated. The results of the study have revealed a significant increase in drug release and bioavailability, which showed an increase in solubility of drug from nanosized emulsion [42]. Gorain *et al.* (2014) have proved nanoemulsion as a promising approach for increasing bioavailability. The oil-in-water (o/w) nanoemulsion of Olmesartan medoxomil (OM) was prepared using sefsol 218, soya bean oil, and Solutol HS15. The physicochemical characterization of nanoemulsion has shown to be thermodynamically stable with nanometer droplet size, increase in permeability from the CaCo-2 cell line, and low polydispersity index. Also the pharmacokinetic study showed increase in area under the curve (AUC0–27) to 2.8-fold which has enhanced control over hypertension by reduction in dose to 3-fold [43]. Guan *et al.* (2014) have compared the pharmacokinetic properties of nitrendipine submicron emulsion with conventional nitrendipine solution in rats. The ultra-performance liquid chromatography including mass spectrometry detection (UPLC-MS/MS) was applied for analysis of plasma concentration. The AUC, *C*max, and *t*1/2 for nitrendipine emulsion and nitrendipine solution were found to be 900.76±186.59 versus 687.08±66.24 ngh/ml, 854.54±159.48 versus 610.59±235.99 ngh/ml, and 2.37±1.99 versus 2.80±2.69 h. as compared to nitrendipine solution, the nanoemulsion showed improved bioavailability and therapeutic efficacy [44].

Self-nanoemulsifying drug delivery system (SNEDDS)

SNEDDS are nanoscale oil-in-water (O/W) nanoemulsion, which is an anhydrous isotropic mixture of surfactant, oil, and drug that get converted into nanoemulsion when introduced into aqueous phase with gentle agitation. The digestive motility of the alimentary canal provides required agitation for the formation of nanoscale emulsions. The SNEDDS retain benefits related to nanoemulsions like increased oral bioavailability, increased permeation of drug, improved chemical and enzymatic stability, and simple fabrication and scale-up. The SNEDDS of a poorly water-soluble drug has shown improvement in solubility. Rajinikanth *et al.* (2012) have demonstrated that a significant increase in the dissolution rate of valsartan by forming its SNEDDS by using Tween 20, Labrasol (oil), and PEG 400 when compared to marketed valsartan tablet and powder. From the results, it's going to be concluded that SNEDDS of poorly soluble drugs presents a promising drug formulation system for oral delivery of antihypertensive drugs [45]. Similarly, another investigation has also shown the development in the drug release of valsartan and olmesartan within the sort of SNEDDS [46].

Polymeric nanoparticles

With a particle size of 10 to 100 nm, the polymeric nanoparticles are considered as colloidal drug delivery carriers. The most advantages of nanoparticles are

- ✓ Enhanced bioavailability,
- ✓ Increased specificity and targeting to the desired site, and
- ✓ Reduced toxicity and dose.

All these benefits enable the safe delivery of drugs especially to focus on sites without affecting normal tissue. Polymeric nanoparticles are successfully developed for different applications like tumor targeting and gene delivery [47]. These types of nanoparticles are prepared by employing synthetic, biodegradable, and natural polymers which therapeutic effect significantly depends on biodegradation of polymers and the drug release. The drug release from nanoparticles follows erosion mechanism, diffusion mechanism, or both erosion and diffusion together [48]. A number of the foremost commonly employed polymers in the development of nanoparticles are poly (D, L-lactide-coglycolide), polycaprolactones, and poly(D, L-lactide) [49-50]. The polymer relative molecular mass, method of preparation, particle size, and sort of stabilizer significantly affect the oral drug delivery through nanoparticles. The polymeric nanoparticles are often effectively employed for increasing oral bioavailability of medicine with poor solubility, chemical/enzymatic stability, and poor permeability [51, 52].

The investigation of valsartan-loaded nanoparticles has shown prolonged release of drug by decreasing its frequency of dose, side

effects and dose size [53]. Moreover, the therapeutic use of isradipine, an antihypertensive agent (a calcium channel blocker), is hampered thanks to its rapid and intense vasodilator effect. But when isradipine in its nanoparticles form is given orally, it has shown prolonged antihypertensive effect and initial slow release [54]. For oral bioavailability of hydrophobic drugs, they need to be dissolved in gastrointestinal fluids. Zhang *et al.* (2010) have synthesized mesocellular foam (MCF) nanoparticles of Telmisartan. The MCF is formed with an endless 3D pore system using Pluronic 123 as a surfactant including cetyl trimethyl ammonium bromide (CTAB) as a cosurfactant. Telmisartan in mesocellular form has shown high dissolution rate and high drug loading [55]. The commonly used nebivolol presents the problem of poor bioavailability and solubility and thus frequent dosing. Jana *et al.* (2014) have studied nebivolol loaded nanoparticles using Eudragit RS 100 by the solvent evaporation process. Differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy studies have shown drug-polymer compatibility and the *in vitro* drug release data have shown prolonged drug release with low initial burst release [56]. Zhu *et al.* (2014) have developed felodipine-loaded poly(l-lactic acid) nanoparticles. Felodipine which has much less solubility in water and thus low bioavailability could also be the second generation of 1,4-dihydropyridines (1,4-DHPs). The nanoparticles were prepared by emulsion solvent evaporation technique and the investigation results have revealed effective *in vitro* compatibility and controllable drug release [57]. Kumar *et al.* (2015) have demonstrated that oral bioavailability of valsartan can be improved by preparing its nanoparticles with optimization and developing by full factorial design [58]. A report of *in vitro/in vivo* study of nifedipine loaded nanoparticles also showed increased patient compliance by a decrease in the frequency of administration and due to their improved oral bioavailability and long-lasting action, the polymeric nanoparticles have shown an increase in antihypertensive activity [59].

Carbon nanotubes (CNTs)

Presently, carbon nanotubes are gaining tremendous attention as novel drug delivery carriers. CNTs offer features like

- ✓ High cellular uptake,
- ✓ Enhanced transmembrane penetration accumulation thanks to the needlelike shape of CNTs, and
- ✓ The ability of high drug loading due to their increased surface area.

Several *in vivo* and *in vitro* studies on CNTs have proven them to be an efficient drug delivery system. The poly(amidoamine)-(PAMAM-) functionalized multiwalled carbon nanotubes (MWNTs) loaded with poorly water-soluble carvedilol was developed to enhance the drug loading capacity and dissolution. PAMAM-MWNTs have shown a marked increase in solubility. From the study, it is concluded that MWNTs present a bigger area for proper dispersion of drugs and PAMAM modifies drug loading capacity and improves the solubility of medicine [60]. However, despite these advantages in drug delivery, CNTs are still not considered safe for clinical application [61].

Nanocrystals

Nanocrystals are comprised of aggregates of a huge number of atoms with sizes between 10 nm and 400 nm. The steps involved in the formation of nanocrystals involve the formation of nanosuspension, followed by wet milling, high homogenization, nano crystallization, and eventually spray drying to obtain nanosized crystals [62]. The decrease in drug particle size to nanoscopic crystals leads to an increased surface area to volume ratio [63]. Hecq *et al.* (2005) have investigated the nanocrystals of nifedipine which indicated that there was the retention of crystalline state upon particle size reduction and that leads to improvement in dissolution rate and enhancement of solubility of nifedipine [64]. Surface modification of nanocrystals also plays a crucial role in the *in vitro* and *in vivo* behavior of nanocrystals. In a study, chitosan (positively charged polymer) was employed to modify the surface of nanocrystals containing nitrendipine (negatively charged drug). The investigation results of modified nanocrystals showed improvement in physical stability and demonstrated remarkable improvement in bioavailability as compared to the traditional dosage form. On the idea of experimental data, it is often concluded that surface modification of the nanocrystals with some polymer would emerge as an efficient method for controlling *in vitro* and *in vivo* performance of the nanocrystals and thus increasing the bioavailability of poorly water-soluble drugs [65]. An investigation of nitrendipine nanocrystals has also revealed an increase and *in vitro* drug release profile. The *in vivo* study has shown a 15-fold and 10-fold increase as compared to the physical mixture and commercial tablet, respectively [66]. A study of nimodipine nanocrystals has also suggested nanocrystals as a successful delivery system for hydrophobic drugs [67].

Proliposomes

Proliposomes are defined as dry, free-flowing particles with a dispersed system and when it will come in touch with water, it will immediately form a liposomal suspension. Proliposomes exhibit more advantages in promoting drug absorption than conventional liposomes. Due to their solid properties, the physical stability of liposomes is often improved without influencing their intrinsic characteristics. Therefore, proliposomes would be a possible vehicle to assist improve the oral absorption of hydrophobic drugs [68]. Isradipine-loaded proliposomes were developed to reinforce the oral bioavailability and were compared with its oral suspension and when the pharmacokinetic parameters were evaluated in male albino Wistar rats it showed 2.4 times increase in bioavailability from the optimized proliposome batch as compared to regulate oral suspension [69]. Kim *et al.* (2008) have revealed the potential of proliposomal formulation in sustained drug delivery of propranolol. The characterization of proliposomal formulation has shown good flowability, particle size distribution, and well conversion into liposomes by hydration and desirable *in vitro* drug release [70]. Similarly, researchers have reported significant enhancement within the oral bioavailability of valsartan-loaded proliposomes [71]. Furthermore, several patents for preliposomal formulations also are available which contain poorly water-soluble antihypertensive agents.

CONCLUSION

Nanotechnology holds an excellent potential ineffective delivery of poorly soluble antihypertensive drugs by improving solubility and oral bioavailability. Moreover, novel drug delivery approaches have appeared as strategies to revitalize the event of the latest hydrophobic entities. Some important advantages of nanosystems are the colloidal size, biocompatibility, lowered dose size, reduced toxicity, patient compliance and drug targeting. Literature survey reveals various benefits of novel drug delivery system including enhancement of bioavailability, improved targeting, therapeutic efficacy, and production scalability provided by solid lipid nanoparticles, whereas SNEDDS provides an enhanced interfacial area for drug partitioning and improved bioavailability and doesn't require high-energy emulsification; thus it reduces the manufacturing cost. Besides, polymeric nanoparticles provide ease of manipulation of particle size and surface characteristics for both active and passive targeting. Dendrimers have gained interest, thanks to their unique properties like highly branched structure, multivalency, and versatile chemical compositions. Proliposomes contain free-flowing granular material that improved stability, enhanced solubility, and ease of handling. However, though liposomes provide controlled drug release and increased bioavailability but show a tendency to aggregate or fuse. Although significant advancements are made in nanotechnology, some challenges are encountered within the development of novel drug delivery systems like:

- ✓ Transformation of those nanocarrier systems from laboratory scale to the pharmaceutical market,
- ✓ Counting on factors like cost of fabrication, reproducibility of properties of formulation on a production scale, and
- ✓ Benefits to the human population due to large variation in pharmacokinetics.

However, despite these challenges, the event and benefits offered by novel drug delivery systems can't be ignored. Thus, nanotechnology

offers the opportunity for formulation scientists to increase research and development to overcome the challenges related to current antihypertensive drugs, thereby improving patient compliance and therapeutic efficacy.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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