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Review Article

NANOTECHNOLOGY-DRIVEN INNOVATIONS IN HYPERTENSION MANAGEMENT: FORMULATION STRATEGIES, CHALLENGES, AND FUTURE DIRECTIONS

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ABSTRACT

Hypertension creates a worldwide public health challenge that significantly increases risks for cardiovascular diseases, strokes, and kidney failure. The standard therapeutic treatments comprising angiotensin-converting enzyme inhibitors and beta blockers struggle with several problems, including limited solubility together with short half-life duration along with unwanted effects causing reduced patient treatment adherence. Drug delivery systems powered by nanotechnology offer innovative solutions to address the problems through techniques, such as nanoparticles together with liposomes and microneedles (MNs). Nanotechnology-based drug delivery systems enhance drug effectiveness and improve stability while enabling precise drug distribution, which leads to reduced first-pass metabolism and lowered systemic side effects. Drug delivery according to circadian rhythms achieves better therapeutic effects at reduced risks. Researchers have developed two new approaches for medication delivery that utilize intranasal systems together with dissolvable MN patches for providing fast and easy administration capability. Hypertension management through nanotechnology applications delivers a transformational method that addresses numerous limitations of existing treatment approaches. Although the pre-clinical data holds promise, the clinical implementation of such innovative systems faces substantial obstacles. The implementation of nanotechnology in regular clinical practices will reshape hypertension treatment through performance-enhanced approaches that offer tailor-made patient-centered management.

Keywords: Hypertension, Nanotechnology, Liposomes, Solid lipid nanoparticles, Targeted drug delivery, Chronomodulated therapy, Microneedles for antihypertensive therapy.

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INTRODUCTION

Hypertension, meaning high blood pressure, is a chronic condition having a major impact on cardiovascular health, as well as myocardial infarctions, cerebrovascular accidents, renal failure, and cognitive deterioration. The heart has trouble circulating blood as it faces the effect of chronic hypertension which forces excessive pressure on arterial walls increasing the possibility of severe vascular complications. Clinical term for hypertension is blood pressure measurement which is above 140/90 mmHg all the time. In fact, this disease affects more than 1.13 billion people worldwide and is projected to affect more than 3 million people worldwide by 2020. Factors, such as urbanization, aging demographics, and dietary and physical inactivity choices are expected to cause the number of people exceeding 1.5 billion by 2025. In each drug class, the mechanisms that are specifically targeted are within or associated with the renin-angiotensin-aldosterone system (RAAS) to reduce blood pressure. Many antihypertensive medications are poor water-soluble resulting in poor bioavailability and therapeutic efficacy of many conventional treatments [1]. These drugs, however, are prone to severe first-pass metabolism and may also be substrates of P-glycoprotein (P-gp), limiting their effectiveness. They find that the need for frequent dosing. Due to their short half-lives, this will decrease patient compliance. Furthermore, dosing frequency is high and systemic side effects include hypotension, electrolyte imbalances, and fatigue [2]. These limitations can be overcome by the use of nanotechnology-based drug delivery methods: Nanoparticles, nanoemulsions, and nanogels. Encapsulation of antihypertensive drugs in nanoparticles improves their bioavailability, stability, and solubility. The nanoparticles serve to counteract the effects of first-pass metabolism and protection from drugs by P-gp-mediated efflux, by reducing drug degradation and promoting entry into the bloodstream. This controlled and targeted release of antihypertensive agents affords enhanced efficacy, less side effects, and greater therapeutic effect than conventional formulations. Nano systems can be bypassed by the severe pH and enzymatic activity but rarely decomposes orally administered medications of the digestive system. In addition, nanometer-sized nanoparticles can pass through tight cellular spaces. That produces junctions that increase absorption and deliver targeted treatment to particular organs or tissues, such as the heart or kidneys where hypertension causes the most harm. In addition, nanotechnology can be exploited for chrono therapeutics for the management of hypertension [3]. One study shows that secondary metabolite compounds in *Centella asiatica*, including Madecassoside, have renin inhibitor activity, similar to commercial drugs, such as aliskiren, suggesting *C. asiatica* extract as a natural hypertension management alternative through nanotechnology [4]. The body's circadian rhythms are aimed at when blood pressure usually increases during the night and early morning and the chronotherapeutic systems administer drugs at this time. Synchronizing drug release with endogenous physiological periods allows chronotherapeutic nano formulations to augment therapeutic efficacy, optimize diurnal blood pressure regulation, and reduce the probability of adverse events, critical temporal windows. Nanotechnological strategies for hypertension management, for example, gene silencing techniques (especially small interfering RNA [siRNA] delivery systems) targeting specific proteins involved in blood pressure regulation, such as within the RAAS pathway, are novel. Angiotensinogen, a pre-cursor to angiotensin I (AI), can be inhibited by siRNA to obstruct the cascade resulting in angiotensin II (AII) and its hypertensive consequences [5]. Targeted nanoparticle delivery systems are crucial for effective siRNA-based therapies, as the primary challenge lies in preserving siRNA stability and preventing degradation by nucleases in the bloodstream. Numerous limitations of conventional therapies are mitigated through the application of nanotechnology in antihypertensive treatment. Substantial advancements in hypertension treatment are achievable through enhanced bioavailability, targeted delivery, reduced dosing frequency, and the potential for chronotherapeutic and gene-

silencing applications. This review aims to examine the limitations of traditional antihypertensive formulations and explore how advanced nanotechnologies can improve therapeutic outcomes for more effective blood pressure regulation and reduce cardiovascular risks [6].

PATHOPHYSIOLOGY: PHYSIOLOGICAL MECHANISMS

RAAS

Renin release

When blood pressure falls, the kidneys release renin, an enzyme that converts angiotensinogen (produced by the liver) into AI.

AII formation

AI is converted into AII by the enzyme angiotensin-converting enzyme (ACE). AII is a potent vasoconstrictor that increases blood pressure by narrowing blood vessels.

Aldosterone secretion

AII stimulates the release of aldosterone from the adrenal glands, which promotes sodium and water retention by the kidneys, increasing blood volume and pressure [7].

Sympathetic nervous system (SNS)

Increased activity

The SNS regulates blood pressure through the release of catecholamines (e.g., norepinephrine) that cause vasoconstriction and increased heart rate. Chronic activation of the SNS can lead to sustained hypertension [8].

Endothelial dysfunction

Impaired vasodilation

Endothelial cells lining the blood vessels produce substances, such as nitric oxide (NO) that help dilate blood vessels. Endothelial dysfunction reduces NO production, impairing vasodilation and contributing to increased vascular resistance and blood pressure [9].

Vascular remodeling: Structural changes

Chronic hypertension can cause structural changes in blood vessels, such as thickening of the vessel walls (hypertrophy) and increased collagen deposition. These changes reduce the elasticity of blood vessels and increase resistance, further elevating blood pressure [10].

Kidney function and fluid balance

Altered sodium handling

Impaired renal function can lead to abnormal sodium and fluid balance, increasing blood volume and pressure. The kidneys play a crucial role in long-term blood pressure regulation by controlling fluid and electrolyte balance [11].

CONVENTIONAL DRUGS FOR THE TREATMENT OF HYPERTENSION [12-15]

NOVEL DRUG DELIVERY FOR HYPERTENSION

- Nanoparticle-based therapies in hypertension
- The lipid-based drug delivery system (LBDDS)
- Polymeric-based drug delivery system
- Intranasal drug delivery systems in the management of hypertension
- Chronomodulated drug delivery system
- Microneedles (MNs) and their application in transdermal delivery of antihypertensive drugs.

NANOPARTICLE-BASED THERAPIES IN HYPERTENSION

The LBDDS

Antihypertensive medications frequently have low solubility, large molecular weight, limited membrane permeability, and substantial first-pass metabolism in the liver, which makes oral bioavailability difficult. These problems are addressed by LBDDS, which enhance drug solubility, stability, and targeted delivery [16].

The bioavailability of poorly soluble antihypertensive medications is improved by LBDDS systems, such as solid lipid nanoparticles (SLNs), liposomes and transferosomes, and self-nano emulsifying drug delivery

S. No.	Drug classification	Mechanism of action	Drugs	Adverse effects
1	Thiazide and thiazide-like diuretics	Blockage of the sodium-chloride (Na/Cl) channel in the proximal segment of the distal convoluted tubule	hydrochlorothiazide (HCTZ), chlorthalidone, indapamide	Hypokalemia, Hyponatremia, Hypercalcemia
2	Angiotensin-converting enzyme inhibitors	Block the conversion of angiotensin I to angiotensin II (AII)	Benazepril Captopril. Enalapril, Fosinopril. Lisinopril, Moexipril Perindopril, Quinapril.	Dizziness, Fainting, Low blood pressure
3	Angiotensin receptor blockers	Block the activation of AII AT_1 receptors	Candesartan, Irbesartan Losartan, Olmesartan Telmisartan, Valsartan	headache and fatigue
4	Direct Renin inhibitor	Binding to the active site of renin	Aliskiren	Hyperkalemia, Severe hypotension
5	Calcium channel blockers	Block calcium channels and inhibit calcium ion influx into vascular smooth muscle and myocardial cells	Amlodipine, Diltiazem Felodipine, Nicardipine, Nifedipine, Nimodipine, Verapamil	Palpitation, Nausea
6	Beta-blockers	Block the receptor sites for epinephrine and norepinephrine on adrenergic beta-receptors	Atenolol, bisoprolol Carvedilol, Labetalol, metoprolol, propranolol, and sotalol.	Fatigue, Swelling, Breathing difficulties
7	Alpha-blockers	Inhibit the binding of norepinephrine to the α_1 receptors on vascular smooth muscle cells	Doxazosin, Prazosin Terazosin, Alfuzosin Tamsulosin, Silodosin Phenoxybenzamine Phentolamine, Tolazoline Labetalol	Dizziness, Diarrhea.

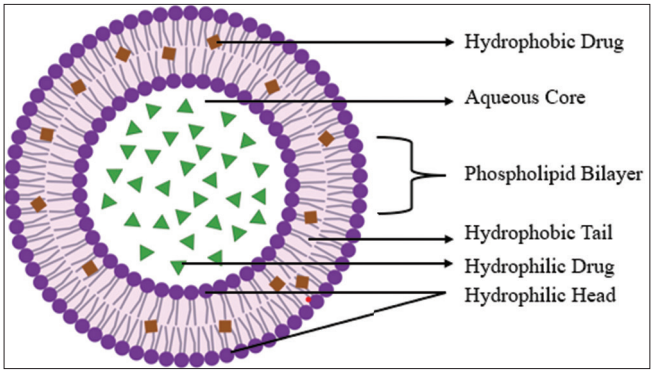

Fig. 1: Liposome

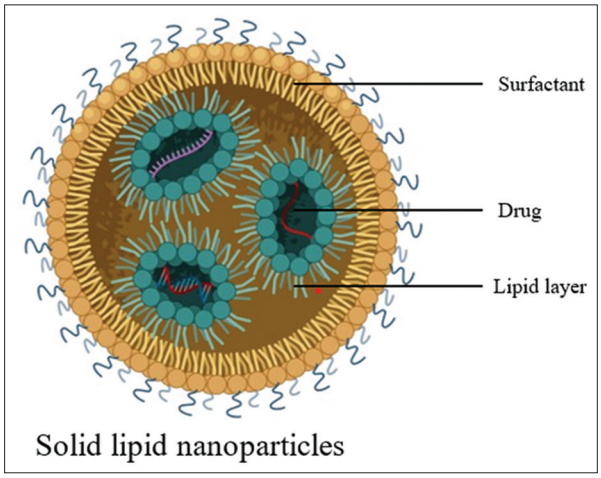

Fig. 2: Solid lipid nanocarriers

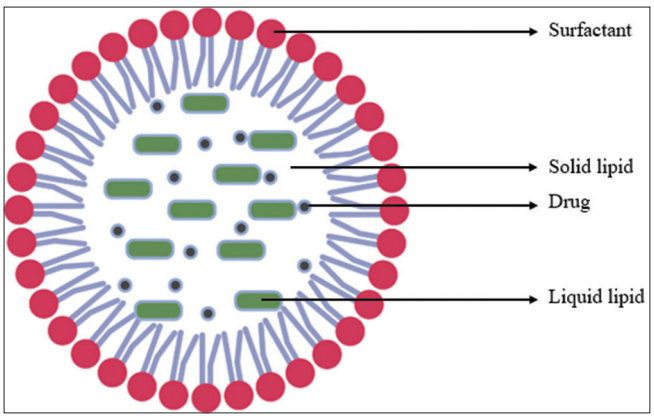

Fig. 3: Nano-structured lipid carriers

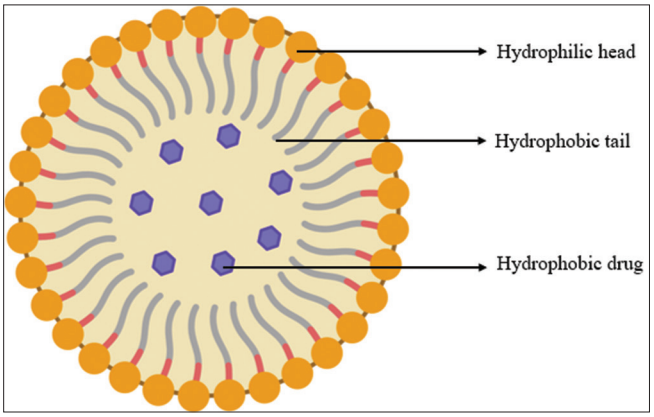

Fig. 4: Nanoemulsions

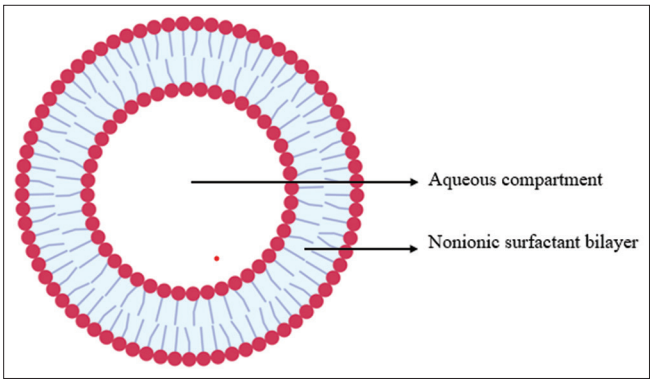

Fig. 5: Niosome

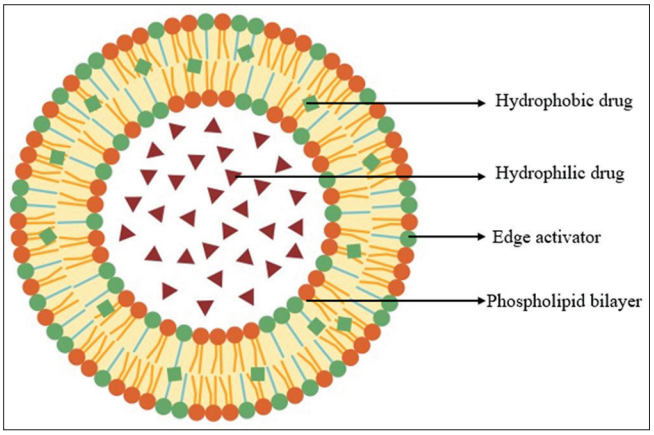

Fig. 6: Transferosome

systems [17]. These methods enable site-specific delivery by avoiding the liver's first-pass metabolism and increasing medication absorption through the lymphatic system [18].

The performance of LBDDS has greatly improved due to recent developments in nanotechnology and tailored drug delivery, which enable more precise drug release patterns, lower toxicity, and more effective therapy. With precision medicine techniques that concentrate on treating hypertension, the future of LBDDS in this regard seems bright [19].

Liposomes

Liposomes have shown potential as carriers and as an effective system for improving the physical-chemical properties of drugs that are either chemically unstable or have poor solubility. Hence, applying thin film hydration is common in liposome preparation; this involves dissolving cholesterol and phosphatidylcholine in an organic solvent. The above solution is then gently evaporated to leave a thin lipid film, which is then hydrated with a drug-containing aqueous solution. Lipid bilayers organize themselves during the hydration process to provide the structure for the liposome drug delivery system. Sonication or homogenization techniques lower the particle size (PS) of the drug to the nanometre range, which is preferred for use in site-specific drug delivery or intravenous application [20].

Liposomes are advantageous to drugs in their delivery due to the structural properties of these sphere-like structures that can carry both hydrophilic and hydrophobic in a bilayer that mimics biological membranes. The cells consist of a lipid bilayer that preserves the

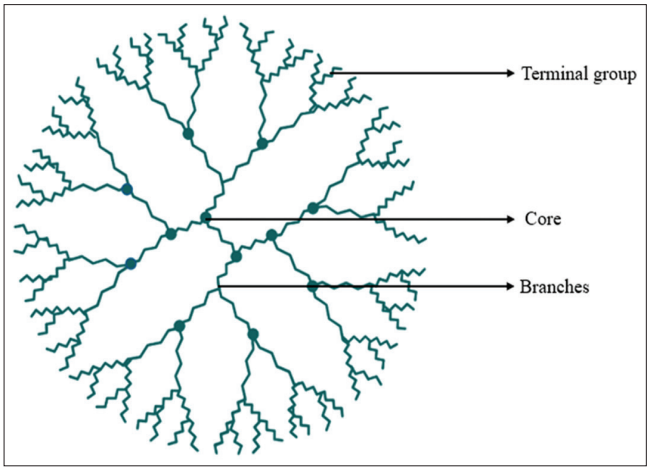

Fig. 7: Dendrimer

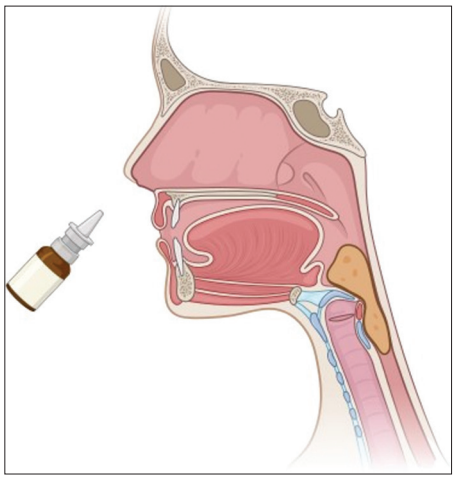

Fig. 8: Intranasal drug delivery systems for hypertension

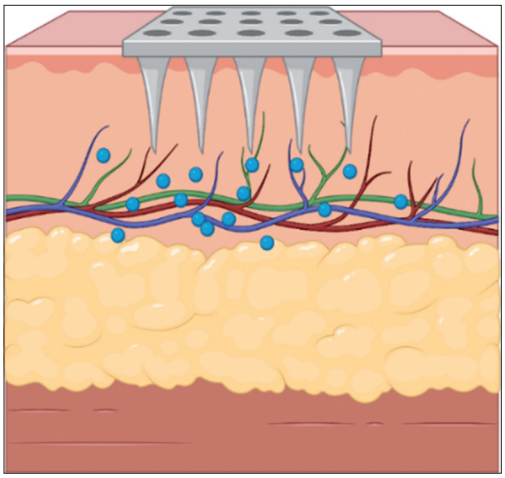

Fig. 9: Microneedles in transdermal delivery of antihypertensive drugs

drug from enzymatic degradation and provides steady and gradual liberation. Liposomal encapsulation can also overcome biological barriers, such as gastrointestinal and hepatic metabolism and enhance the overall bioavailability of the drug. The given structure also has an advantage in delivering drugs to the targeted tissues or cells; it is even more effective when ligand conjugation is added to the liposomes. For example, conjugation with vitamin A enhances the cell uptake of liposomes in hepatic stellate cells in liver-targeted formulations and improves the treatment of liver fibrosis [21].

The research team developed pulmonary arterial hypertension (PAH) treatment using optimized inhalable Epigallocatechin gallate (EGCG), the main ingredient in green tea and nano-liposome showed excellent lung deposition with high stability and above 90% encapsulation efficiency. The formulated EGCG solution performed better in transforming growth factor beta signaling blockade than unformulated EGCG while showing stability after nebulization at these concentrations. Experimental results established the aerodynamic qualities that make the formulation suitable for inhalation into and deposition in the lungs of patients diagnosed with PAH [22].

The strategy developed a dual-purpose liposomal formulation named Tf-Pen-Lip-pACE2 to deliver human ACE2 into the brain for fighting treatment-resistant hypertension. The animal study demonstrated that this drug formulation effectively reached the brain by penetrating through the blood-brain barrier along with showing promising therapeutic results [23].

The application of nanoethosomal gels represents an important discovery that advances hypertension management through transdermal lercanidipine HCl administration. As a third-generation calcium channel blocker lercanidipine demonstrates weak oral bioavailability at around 10% because of its high metabolism in the first-pass phase combined with its low water solubility. The encapsulation of lercanidipine into nanoethosomes proves more effective than standard oral pills as it improves drug absorption and transport rates and overall bioavailability [24].

Liposomal encapsulation enhanced the bioavailability of the antihypertensive medication lercanidipine by 2.75-fold relative to conventional formulations. Liposomal ascorbic acid formulations demonstrated enhanced blood pressure regulation and vascular responsiveness in animal models of hypertension compared to non-liposomal ascorbic acid. The results indicate that liposomal encapsulation enhances drug concentrations in target tissues and prolongs therapeutic effects [25].

A notable instance of liposomal advancement in drug delivery is illustrated in a study by Nahar *et al*., which concentrates on the treatment of PAH. This study employed peptide-coated liposomes as an innovative therapy to improve the targeting of drug-laden liposomes to pulmonary arterial endothelial cells, which exhibit overexpression of specific receptors in PAH [26].

By conjugating the cyclic peptide CARSKNKDC to the liposomal surface, the researchers targeted liposomal fasudil to specific cells, achieving a 35–40% reduction in pulmonary arterial pressure without significantly impacting systemic blood pressure representing a notable enhancement compared to unencapsulated fasudil. Liposomal fasudil showed an elongated half-life and regulated release, which relieved the requirement of frequent dosing. The results suggest this formulation has promise as an improved way to target, release, and clear the drug to improve patient outcomes with fewer drug side effects. This formulation should be examined regarding long-term efficacy and safety and its applicability to other forms of hypertension [27].

In conclusion, liposomes serve as a flexible delivery vehicle to overcome the limitations inherent to conventional drug delivery, particularly pathologies characterized by chronic nature, for instance, hypertension and liver fibrosis. The use of liposomes as a vehicle, however, fosters targeted and sustained drug release through increasing bioavailability and therapeutic efficacy, decreasing dosage frequency and side effects as well as reducing patient burden. The results of several studies demonstrate great promise that liposomes can serve as an efficient drug delivery system for a variety of future pharmacotherapeutic advances, notably for drugs that require specific targeting and controlled release.

SLNs

The application of drug-loaded SLNs formulates a novel means of treatment that is beneficial for patients suffering from hypertension as it helps in ensuring that stable therapeutic levels are maintained. It poses a major challenge to public health and is an important risk factor for cardiovascular illnesses; antirheumatic drugs, such as candesartan are known to be effective, yet their bioavailability is often low because of the high degree of first-pass metabolism and poor solubility. Candesartan SLNs can provide solutions to these problems through much-needed prolonged action and enhanced stability without adverse side effects [28].

SLNs retain the efficacy of oral dosage forms since lipid-based systems minimize metabolism by the liver providing a more direct route through lymphatic Biopharmaceutical aspects of SLNs are very important to maintain therapeutic levels in systemic circulation SLNs are constructed through fusion: slurry is prepared which is sonicated to further reduce PS by emulsifying It. Lipophilic drugs can be absorbed much easier if administered together with SLNs that are bound to Candesartan with glyceryl monostearate, Tween 80, and Span 20 [29].

Improving the drugs' therapeutic action requires the utilization of experimental techniques such as the central composite design for the SLNs containing olmesartan whilst the Box-Behnken design is meant for candesartan SLN bottles. These designs permit effective control of essential parameters (e.g. drug-to-lipid ratio, surfactant concentration) which allow appropriate nanoscale PSs and improved stability, which may also be verified by measuring zeta potential (ZP) indicating that SLNs are suitable for prolonged circulation and delivery to the target sites [30].

Adneno-associated virus carrying SLNs increases the bioavailability of the drug by staying on the intestinal wall and enhancing lymphatic transport and thus, bypasses the first-pass metabolism of the liver. The lipid matrix encasing the drug allows a time-release of the drug in a consistent manner. SLN's drug encasing with liposomes helps in the time-released version as stabilization of the drug is achieved, but sustaining the release of lipid matrix as it slowly gets degraded, assures a maintained medicinal level for extended time period. Studies employing dialysis for SLNs have shown that these systems are better in delivering drugs than conventional systems with SLN exhibiting more sustained drug release mechanism due to the lipid matrix's structure stability. By introducing SLNs, dialysis research has shown that drug release from SLNs is more uniform than from traditional formulations, and the slow release is attributed to the stability of the lipid matrix structure [31].

Investigations of SLNs for medications such as candesartan and olmesartan show them to be promising for efficacious antihypertensive treatment. The entrapment efficiencies of both formulations were found to be >80%, indicating effective drug encapsulation in the lipid matrix. The average PS of candesartan SLNs was 87.7 nm, which is suitable for extended circulation and targeted delivery. The bioavailable of olmesartan SLNs has been investigated *in vitro* and *in vivo* with marked enhancement in the bioavailability as the plasma concentrations from SLNs were 2.3 times higher than the conventional formulations in rat models. This enhancement highlights the ability of SLNs to enhance the therapeutic efficacy of antihypertensive agents [32].

Recent research in SLN has included studies of cyclodextrin incorporation into the SLN matrix to improve stability and solubility, with special emphasis on pediatric formulations. Our evaluation of the sustained release characteristics and the improved bioavailability of hydrochlorothiazide from cyclodextrin complexes in SLNs demonstrates that analogous modifications for other antihypertensive medications might be advantageous [33]. SLNs offer several advantages for the delivery of poorly soluble antihypertensive drugs, such as candesartan and olmesartan, including controlled release, improved bioavailability through lymphatic uptake, and reduced first-pass metabolism. The SLNs have these characteristics that make SLNs feasible for use in long-term drug management of conditions such as hypertension and perhaps other chronic conditions requiring sustained levels of drugs. SLNs are a promising treatment for human pathologies of hypertension due to their good safety profile and potential effectiveness, so future clinical research is needed to assess their long-term safety and effectiveness in human populations and to standardize them as a good drug delivery system.

Nano-structured lipid carriers (NLCs)

Oral administration of drugs has its advantages, which explains its popularity, but it also has some disadvantages, such as low bioavailability and first-pass metabolism, which is substantial for drugs that are poorly soluble. Problems of this nature have been resolved by the use of liposomal carriers including NLCs which are able to address such problems as poor bioavailability in lipophilic drugs, poor solubility as well as problems of target drug delivery and stability. NLCs are generally produced using high-pressure homogenization which is a common method. It consists of heating a mixture of solid lipids and liquid lipids containing an active agent that should typically be heated to temperatures of about 60–80°C dispersing this mixture within a surfactant solution that has high shear forces [34].

An alternative method called solvent evaporation disperses drugs and lipids that have been previously solubilized in an organic solvent at elevated temperatures into an aqueous phase which is then evaporated to remove the solvent. Other experimental designs, mostly models, such as the Box-Behnken accurate models, including lipid concentration, includes pressure, and the number of cycles of homogenization, are usually used to improve the formulation. The combination of both solid lipids together with liquid lipids helps in the formation of a disordered lipid matrix thus helping prevent crystalline formation which helps to enhance and promote prolonged drug release. In the solvent evaporation process, the drug and lipids are dissolved in an organic solvent at some higher temperature, and then dispersed into an aqueous phase, evaporating the solvent afterward [35]. Recent advancements in NLC research include tailored lipid blends and co-encapsulation methods for multi-drug formulations. Ongoing experimental research on drug candidates such as carvedilol and lercanidipine continues to demonstrate promise, underscoring sustained interest in NLCs as a potential therapy for chronic diseases [36,37]. This summary emphasizes the preparation techniques, drug release mechanisms, and findings of recent studies concerning liposome-based drug carriers for hypertension. NLCs demonstrate potential as an oral drug delivery system, particularly for antihypertensive medications. Their benefits – namely enhanced sustained release, improved bioavailability, and reduced systemic side effects – suggest significant potential for improving treatment outcomes. Future research should concentrate on clinical validations and the enhancement of production techniques to facilitate broader application.

Nano emulsions

Nanoemulsions are sophisticated, stable, formulation based on nano-sized droplets (20–200 nm) containing oil, water, and surfactants. Co-surfactant was frequently used to enhance stability. In drug delivery, these emulsions are important because they tackle important issues in drug absorption regarding hydrophobic drug solubility and bioavailability. The permeability of nanoemulsions is enhanced. It also provides stability to active compounds, rendering drugs to cross biological barriers to attain better therapeutic efficacy [38].

Olmesartan has been reformulated into a nanoemulsion to enhance bioavailability, regulate release, and its therapeutic efficacy will have to be optimized if it is to be effective. The formulation of an efficient nanoemulsion starts with the selection of components based upon the solubility characteristics. The nano-emulsion mainly consist of an oil phase (e.g., clove, soybean oil), a water phase, a surfactant (e.g., Tween 20) and co-surfactant this is usually used to keep the system stable. This is usually (e.g. polyethylene glycol) to keep it stable. Different techniques,

such as spontaneous emulsification generate nanoemulsions or high-energy methods such as ultrasonication and high-pressure homogenization [39]. Researchers validated a reliable method for estimating rosuvastatin calcium and fenofibrate using ultraviolet-spectrophotometric analysis, demonstrating precision, robustness, and accuracy, and successfully undergoing forced degradation experiments which further developed as a nanoemulsion formulation [40].

Statistical design methodologies, most commonly Box-Behnken, are often used to optimize these emulsions to enhance component ratios, stabilize average droplet size, and promote well-controlled drug release. Nano-sized droplets in nanoemulsions markedly improve the bioavailability of hydrophobic pharmaceuticals by augmenting surface area for absorption. In transdermal drug delivery nanoemulsions improve skin permeability thus promoting drug deeper penetration through the skin layers. Nanoemulsions enhanced the solubility in gastrointestinal fluids of oral formulations, promoting greater systemic absorption through the intestinal lining. These advantages are shown by the research: A clove oil-derived nanoemulsion of olmesartan showed a 2.8-fold improvement in Nanoemulsions enhance drug stability in physiological conditions and improve permeability, as evidenced by *in vitro* and *in vivo* testing of optimized formulations [41].

These emulsions exhibit stability under thermodynamic stressors, such as heating, cooling, and centrifugation, facilitating more consistent and prolonged drug release. Nanoemulsions for olmesartan facilitated a controlled release profile, providing prolonged antihypertensive effects that may decrease dosing frequency, enhance patient adherence, and minimize side effects. Nanoemulsions are advantageous for the administration of poorly soluble pharmaceuticals, facilitating controlled release and enhancing therapeutic outcomes. To offer bioavailability compared to traditional oral formulations in a hypertensive rat model. Nanoemulsions enhance drug stability in physiological conditions and improve permeability, as evidenced by *in vitro* and *in vivo* testing of optimized formulations [42].

Thermodynamic stressors, such as heating, cooling, and centrifugation do not induce destabilization of these emulsions and improve drug release stability and predictability. Adsorbed nanoemulsions of olmesartan yielded a controlled release profile, which offered prolonged antihypertensive effects for delivery as single 2 mg doses, potentially reducing the need for dosing frequency, maintaining patient adherence, and reducing side effects. Administering poorly soluble pharmaceuticals in nanoemulsions, results in improved controlled delivery and drug outcomes. Chronic conditions such as hypertension which demand consistent medication use such as the case, olmesartan nanoemulsions show significant advantages. For this purpose, customized innovations are being made in nanoemulsions, such as a tadalafil nanoemulsion mist customized for application in pediatric pulmonary hypertension. This formulation offers enhanced pulmonary absorption by providing the nebulizing mist formulation. Medication delivery systems are an emerging area in pharmaceuticals and nanoemulsions are emerging methodologies [43,44].

Niosomes

Niosomes are microscopic vesicles formed of non-ionic surfactants that form bilayers just like liposomes. In fact, in the pharmaceutical landscape, they are not uncommon, especially for drug delivery. Niosomes improve the stability and bioavailability of drugs and can be used for targeted delivery, all with a low toxicity level. This makes them a relatively attractive drug delivery system. They can be particularly useful in settings where delivery needs to be controlled or localized, such as in the case of hypertension. This can enhance the effectiveness of therapy and lessen harmful side effects [45].

Thin-film hydration is one of the common approach for producing niosomes. Hence, here is how it works: You mix surfactants like Span 60 with cholesterol in an organic solvent. We then evaporate the mixture in a round-bottom flask under reduced pressure to give a thin film. Aqueous-phase addition to a film causes expansion and vesicle formation. After hydration, the vesicles are sonicated to decrease their size and produce more homogenous niosomes with enhanced encapsulation efficiency and drug stability. To discover the perfect conditions for encapsulation and controlled release, researchers play with many factors such as the ratio of surfactant to cholesterol and how long they hydrate it. For example, it has been shown that captopril and quercetin-loaded niosomes offer this critical advantage of allowing enhanced drug retention and release timings [46,47].

The niosomes release drugs through different mechanisms like pushing together of membranes in a progressive dissolution of surfactant bilayer ensuring that benevolent therapeutic actions prolong and speaking of captopril-quercetin it's an exciting mixture. Captopril is an ACE inhibitor that controls blood pressure by blocking the conversion of angiotensin to angiotensin 2, while quercetin is an anti-inflammatory and antioxidant molecule that reduces oxidative stress induced by hyperserotonemia through the nuclear factor kappa B pathway. They work very well in combination to treat people with high blood pressure. The *in vitro* and *in vivo* studies on these niosomal preparations have provided optimal results. The retention of about 87% of the active substance within these captopril-quercetin niosomes is notable. They also enable a slow release of the drug for 24 h instead of the rapid release given by the free molecule. That means they can sustain therapeutic levels much more consistently. Animal studies suggest that these niosomes are able to lower blood pressure more effectively than their traditional counterparts, likely due to better targeting and longer drug retention in the blood. Therefore, niosomes seem to improve the action of drugs or pharmaceuticals such as captopril by improving bioavailability, prolonging release action, and sparing toxicity. Two important studies show the potential benefits of captopril and quercetin for antihypertensive therapy. In the future, research should primarily deal with refurbishing multiple therapeutic agents into niosomes for developing multifunctional therapies for atherosclerosis and other chronic oxidative stress-associated disorders [48].

Despite their various advantages, there is still a gap for oral and injectable delivery of niosomal formulations that could extend their application. Recently, there have been some interesting advances in niosomal formulations, in particular niosomes containing both captopril and quercetin designed for the treatment of hypertension. Unlike conventional treatments, this innovative approach offers a viable solution as it includes both ACE inhibition and antioxidant properties to effectively regulate blood pressure and should concentrate on incorporating multiple therapeutic molecules into niosomes to limit adverse effects. Overall, the captopril-quercetin niosome system continues to show great *in vivo* performance, enhancing drug performance *in situ* and remember, niosomes are also going places – including potentially delivering anti-cancer drugs, anti-inflammatory meds, and antibiotics, due to their stability and targeting capabilities. Long before, we got around to using niosomes for hypertension.

Cubosomes

Cubosomes can be defined as a lipid-based nanostructure that consists of lipid bilayers and aqueous channels which has the dual advantage of being entirely sophisticated while also being a potential candidate for a drug delivery system. Both such structures facilitate the encapsulation of hydrophilic, lipophilic, and amphiphilic drugs, hence, rendering them suitable in increasing the bioavailability and controlled release of poorly soluble drugs, such as carvedilol and verapamil. The drug to be incorporated was mixed with glyceryl monooleate wherein cubosomes are synthesized through the melt dispersion emulsification method. This is then isolated from the Poloxamer 407. The lipid phase is heated to a temperature of 70°C, after which an aqueous phase, such as Polyvinyl Alcohol or Cremophor RH 40 (RH40) is added gradually. To create a stable dispersion, this combination is emulsified by vertexing it while putting it in a high-speed agitation. Following this instability, the emulsion underwent cooling, hence creating a stable dispersion-

aimed mixture. The procedures, such as optimal or factorial design are utilized wherein parameters, such as PS, polydispersity index, ZP, and drug entrapment efficiency are enhanced to guarantee proper formulations [49].

Cubosomes encapsulate and deliver drugs through a unique orthogonal biocompatibility/controlled release scheme. Enzymes and other inhibitors that cause erosion of the drug's active ingredients are readily and easily dissolved in the hydro-phobic zones of the lipid bilayers while the drug release is prolonged by the presence of aqueous channels. Hydrophilic P407 stabilizers contribute to improving dispersion stability through the formation of a shell that hinders aggregation and maintains overall uniformity in the particle distribution [50]. More recent studies with carvedilol-loaded cubosomes have shown promising results with the best-formulated samples containing particle sizes of 105–140 nm, high encapsulation efficiency (up to 93.6%), and controlled drug release during a period of 24 h. When *in vivo* studies were performed with hypertensive rat models, significant drops in blood pressure were observed in comparison to standard formulations [51].

Cubosomes loaded with verapamil aimed for intranasal delivery displayed better drug permeation and increased bioavailability. These formulations also achieved extended drug delivery along with lower overall systemic side effects, thus indicating that cubosomes can serve a number of purposes through different delivery routes. New trends in cubosome construction include the cross-linking of stabilizers with RH40, which was developed to target the reduction of hepatic first-pass metabolism to enhance bioavailability [52].

Intranasal cubosome systems, exemplified by verapamil, exhibit promise for non-invasive delivery, enhancing patient adherence and directing treatment to specific therapeutic locations. The incorporation of biodegradable polymers into cubosome formulations has improved their accuracy, stability, and utility in systemic and localized drug delivery. Cubosomes serve as an efficient and adaptable medium for the administration of antihypertensive medications. Their biocompatibility, capability to encapsulate various drug types, and potential for prolonged drug release render them an invaluable asset in pharmaceutical sciences. Subsequent research must prioritize the expansion of production and the execution of clinical trials to substantiate their efficacy and safety for extensive application.

Transferosomes

Transferosomes represent a cutting-edge method for transdermal drug delivery, enhancing skin permeability and drug bioavailability, particularly for medications with suboptimal oral absorption, such as antidiabetic and antihypertensive agents. These ultra-deformable vesicles, composed of phospholipids and edge activators such as Span 80, Tween 80, and sodium deoxycholate, can alter their shape to penetrate narrow pores, thereby bypassing the stratum corneum, the skin's natural barrier, unlike conventional liposomes, which are typically restricted to surface layers. The standard preparation method involves dissolving the drug, phospholipids, and surfactants in a solvent mixture, employing rotary evaporation to form a thin film, and subsequently hydrating with a buffer solution. Sonication is subsequently employed to achieve the optimal vesicle size for skin penetration [53].

Recent studies indicate the efficacy of transferosomes for medications such as cilnidipine and eprosartan mesylate, with cilnidipine-loaded transferosomes exhibiting enhanced bioavailability and transdermal flux, thereby facilitating hypertension management. This ongoing study underscores the potential of transferosomes to transform transdermal therapy, particularly for patients requiring long-term, non-invasive drug delivery [54,55].

POLYMERIC BASED DRUG DELIVERY SYSTEM

The use of polymeric nanoparticles enables targeted and sustained delivery of therapeutic agents, which could solve the hypertension's problem. Among the dietary polyphenols, the barriers, including quercetin, curcumin, and resveratrol, enhance endothelial function and oxidative stress. They increase the stability, solubility, and the specific deposition of these substances at the target tissues thereby increasing the potency of such drugs. Curcumin-containing nanoparticles described have been proved to improve vascular endothelial function in hypertensives by quenching reactive oxygen species and increasing the NO levels. However, resveratrol nanoparticles also increased bioavailability and extended the release time, thus improving blood pressure control and reducing vascular damage [56].

Dendrimers

Dendrimers are branched tree-like polymeric constructs that are primarily used for drug delivery due to their specific geometry, multivalency, and the presence of tailored surface chemistry. Poly(amidoamine) PAMAM dendrimers are the most preferred dendrimers as they are synthesized through stepwise controlled methods that allow functional tailoring according to the targeted application. Hydrophobic drugs are encapsulated within the cores of these dendrimers or conjugated to the chemical groups of the dendrimer, achieving targeted delivery for improvements in pharmacokinetics. Dendrimers function through several primary mechanisms: encapsulating drugs within their core, conjugating drugs to surface moieties, functionalizing with ligands or antibodies for targeted delivery, and modulating drug release through surface chemistry and dendrimer generation. PAMAM dendrimers have shown efficacy in improving the solubility and bioavailability of poorly soluble pharmaceuticals, such as ramipril and hydrochlorothiazide while facilitating cellular uptake through endocytosis and promoting intracellular drug release. The outcomes of utilizing dendrimers in pharmaceutical delivery are encouraging. PAMAM dendrimers markedly improve solubility and dissolution rates, with ramipril and hydrochlorothiazide exhibiting solubility enhancements of 4.91-fold and 3.72-fold, respectively. In cardiovascular models, co-administration of cardioprotective agents, such as Losartan, epidermal growth factor, or S-nitroso-N-acetyl penicillamine has been effective in reducing PAMAM cardiovascular toxicity associated with ischemia/reperfusion injuries [57].

Not only this drug has also been efficacious when administered in delivery systems targeting therapeutic genes such as vascular endothelial growth factor (VEGF), promoting myocardial tissue regeneration and vascularization. New findings in dendrimer technology introduce drug-loaded hybrids containing ramipril-hydrochlorothiazide for the treatment of hypertension which increases the solubility of the drugs and their stability in the body. In cardiovascular settings, Dendrimer-based gene conjugates have been able to induce hypoxia-regulated expression of the VEGF gene for applications toward myocardial infarction therapy. Significant improvements have been seen with PEGylated dendrimers that reduce hemolysis and cytotoxicity, yet still achieve a high degree of gene and drug transfection [58].

Dendrimers play an essential role as a versatile and efficient drug delivery system with enhanced solubility, controlled release, and targeted therapy. Their applications in cardiovascular disease, in particular in angiogenesis and gene therapy, show great clinical promise. Obstacles such as toxicity and the intricacies of functionalization persist, requiring ongoing progress in surface modifications and hybrid formulations to fully achieve their potential [59].

INTRANASAL DRUG DELIVERY SYSTEMS FOR HYPERTENSION

Nasal drug administration has been an alternative technique due to the fact that it allows for direct absorption through the nasal mucosa and bypasses the first hepatic pass metabolism. This method is effective in treating the oral bioavailability of antihypertensive drugs that are usually administered orally. This means that drugs such as olmesartan, medoxomil, valsartan, and carvedilol, which have a low oral bioavailability can be utilized if they are used in the nasal formulations which are intended to enhance the active ingredients. Nanoparticles/nanostructured carriers of the drugs are usually made to increase solubility and absorption of the drugs across the mucosal layers which can be very effective in nasal routes. Research has often employed techniques, such as solvent evaporation, emulsification, and ionic gelation. The chitosan nanoparticles that were loaded with olmesartan and formed by ionic gelation were further optimized to achieve improved drug entrapment and preservation of the formulation. The absorption of the drug through the nasal cavity is mainly due to the highly vascularized nasal cavity: the nasal epithelium which readily facilitates drug absorption. Because of bio adhesive polymers such as chitosan, which can be found in nanoparticles, there is an increase in drug contact time and absorption since the nanoparticles can stick to the nasal mucosa. These formulations allow for a drug, such as carvedilol to be able to cross the nasal barrier with more ease and therefore present a significantly increased bioavailability in comparison with other methods of oral use. There have also been reports on the improved clearance of bioavailability with nasal formulations. It has been reported that when carvedilol SLNs were delivered nasally, the percentage of bioavailability switched from 24.11% in oral administration to 50.63%. Chitosan nanoparticles yielded up to 11.3 times increase in bioavailability along with an observed decrease in the blood pressure of hypertensive rats in comparison with oral cyclophosphamide negative chitosan nanoparticles and SLNs offer an ability of extending the time frame of release while facilitating easy intake for hypertensive patients, increasing the effectiveness of the treatment. There have been recent developments in delivering nasal formulations that work within seconds and provide an effective solution for the management of high blood pressure. Studies on olmesartan-loaded chitosan nanoparticles show that these particles increase systemic distribution and absorption while reducing mucosal irritation in animal models. Moreover, carvedilol SLNs in an in situ nasal gel formulation have prolonged the residence time in the nasal cavity, thereby augmenting the drug's antihypertensive effectiveness. This gel-based SLN system signifies a notable progression, highlighting the innovative capabilities of nasal drug delivery systems in the management of cardiovascular diseases [60-62].

CHRONOMODULATED DRUG DELIVERY

The technique takes into account physiological oscillations to optimize therapeutic outcomes and coordinates the times of drug delivery with the natural 24-h cycles of the body. In the case of hypertension treatment which has a circadian trend in which blood pressure is usually highest in the morning hours, this approach has been able to show improved efficacy as well as decreased side effects. Blood pressure is said to reach its peak in midmorning and decrease at night, this leaves people open to greater chances of having multiple cardiovascular incidents including strokes in the early morning hours. Circadian Treatment is an appealing strategy to handle hypertension effectively because the surge in blood pressure at dawn can be countered with the release of medication at this time. The suprachiasmatic nucleus located in the ventral hypothalamus of the brain is the primary site of action for these biological clocks as it is the site where physiological processes and hormones are regulated. This control system not only helps in the normalization of biological systems, such as blood pressure but also alters the pharmacokinetics and pharmacological action of the drug; hence, the importance of chronomodulated approaches. Circadian deviation is often associated with increased cardiovascular risk and greater allostatic load, this makes such interventions timely. Novel approaches using chronomodulated systems for the treatment of hypertension have included the concepts of creating a pulsatile release system of delivery and a mini-tablet formulation. One new method involves the use of response surface methodologies to incorporate valsartan an antihypertensive drug within nanocrystals. Containment of this formulation in a system that expands the drug release time effectively addresses the problem of high levels of blood pressure in the early morning hours. Factors such as the size of the particles, the type of coating materials, for example, ethyl cellulose hydroxypropyl methylcellulose, and the freeze-drying conditions are all relevant factors to the stabilization of drugs and their precise controlled release, hence increasing the efficacy of the formulation. It has been noted that controlled-release systems are ideal during times when the blood pressure is most likely to rise, that is, in the morning when most cases of hypertension can be expected. Therefore, these systems developed mitigate the risk of overdosing while improving drug efficacy and safety. Some of the advancements include CODAS® and VERELAN PM® systems which enable reliable release of the combination drugs in a specified time frame which otherwise would be unsuitable for hypertensive patients. In addition, the further development of Vitrimer polymers and nanotechnology will also improve the pulsatile release systems in terms of better efficacy and practicality for patients with hypertension. In brief, chronomodulated controlled drug release is clearly a major breakthrough in the treatment of hypertensive patients as it manages to focus the release of the drug whenever the body needs it, which is ideal in this case due to the blood pressure pattern throughout the day. This development will minimize any potential negative effects bringing further improvement to what has previously been achieved. However, further research has to be conducted to improve the control to the timing of the release mechanism so that greater complementariness can be achieved to the body's natural processes so as to make the treatment more effective for all hypertensive patients [63-65].

MNs AND THEIR APPLICATION IN TRANSDERMAL DELIVERY OF ANTIHYPERTENSIVE DRUGS

MNs possess potential benefits compared to traditional hypodermic needles for the administration of drugs and vaccines. MNs are engineered with distinct dimensions to prevent nerve stimulation and minimize patient discomfort. MNs can be utilized without clinical expertise, as they are designed as cost-effective disposable patches to enhance the pharmacokinetic profile of therapeutic component delivery. For instance, disposable MN patches may diminish HIV transmission by promoting self-administration of tests and treatments. An antihypertensive dissolving MN was developed using concurrent medications, specifically sodium nitroprusside in conjunction with sodium thiosulfate. Dissolvable MNs were fabricated through centrifugal casting utilizing SNPs and ST. SNPs were securely encapsulated within the MNs and swiftly administered into the systemic circulation through this method. The antihypertensive MN therapy rapidly and markedly decreased blood pressure. It satisfied the clinical criteria for the management of hypertensive emergency blood pressure. The simultaneous administration of ST effectively mitigated the adverse effects (e.g., organ damage) resulting from SNP consumption. This study illustrated a proficient and user-friendly biodegradable patch for the regulated administration of pharmaceuticals in antihypertensive treatment [66,67].

STRATEGIES FOR NANO-FORMULATION AND THEIR IMPACT ON THE BIOAVAILABILITY AND EFFECTIVENESS OF ANTIHYPERTENSIVE DRUG CANDIDATES [68-75]

Drug candidate	BCS class	Absorbent/ Polymers/ Excipients	Lipid/Oils	Surfactant	Formulation approach	Outcome
Valsartan	Class II	Neusilin US2	Capmul MCM	Kolliphor HS-15	S-SMEDDS	1.6-fold increase in bioavailability
Telmisartan	Class II	Carbopol 934	Labrafil M2125CS	Acrysol EL135	SNEDDS	7.5-fold enhancement in oral bioavailability
Olmesartan	Class II	Silicon dioxide	Capmul MCM	Tween 80	SEDDS	Better handling potential and improved release
Candesartan	Class II	Lauryl Glycol 90	Soybean oil	Tween 80	Nanoemulsion	10-fold AUC increase with significant improvement
Carvedilol	Class II	Castor oil	Kolliphor RH40	TPGS	L-SNEDDS	Increased dissolution and stability
Losartan	Class II	Magnesium stearate	Capryol 90	Cremophor RH40	SLNs	Enhanced lymphatic absorption
Nifedipine	Class II	HPMC E15	Glycerol monostearate	Poloxamer 188	SLNs	Sustained release, reduced dose frequency
Ramipril	Class II	Maltodextrin	Safsol 218	Cremophor EL	Nanoemulsion	Enhanced stability and targeted delivery
Sacubitril-Valsartan	Class II	Kollidon VA64	Glyceryl monostearate	Kolliphor ELP	NLCs	Dual-drug delivery system for hypertension
Amlodipine	Class II	Aerosil 200	Medium-chain TGs	Tween 20	Nanoemulsion	Improved solubility and reduced systemic toxicity
Propranolol	Class I	Polyvinyl alcohol	Soybean oil	Span 60	Niosomes	Prolonged effect with reduced side effects
Nebivolol	Class II	PEG 4000	Labrafac WL1349	Kolliphor RH40	SNEDDS	Improved absorption in the GI tract
Bisoprolol	Class II	Silica gel	Capmul PG-8	Cremophor RH40	SEDDS	Enhanced oral delivery
Metoprolol	Class I	Guar gum	Medium-chain TGs	Tween 80	Nanoemulsion	Reduced dose frequency and better compliance
Furosemide	Class IV	Cross-linked chitosan	Stearic acid	Poloxamer 188	SLNs	Controlled release and improved stability
Atenolol	Class III	Sodium alginate	Lauric acid	Span 20	Liposomes	Targeted delivery and reduced systemic toxicity
Diltiazem	Class II	Hydroxypropyl cellulose	Caprylic acid	Tween 20	Nanoemulsion	Faster onset of action and better stability
Clonidine	Class II	Maltitol	Captex 355	Labrasol	Transferosome	Transdermal delivery with prolonged release
Labetalol	Class II	Polyacrylate crosspolymer	Oleic acid	Tween 60	Nanoemulsion	Enhanced absorption with reduced side effects
Hydralazine	Class III	Xanthan gum	Medium-chain TGs	Cremophor EL	SNEDDS	Improved solubility and bioavailability
Lisinopril	Class II	Polycaprolactone	Glycerol monostearate	Polysorbate 80	NLCs	Sustained release and improved targeting
Spironolactone	Class II	PVP K30	Glyceryl behenate	Poloxamer 407	SLNs	Prolonged effect and reduced toxicity
Nicardipine	Class II	Carbomer 940	Coconut oil	Tween 80	Nanoemulsion	Faster onset and better patient compliance
Enalapril	Class III	Polyvinylpyrrolidone	Stearic acid	Poloxamer 188	SLNs	Controlled release and improved stability
Eprosartan	Class II	Sodium starch glycolate	Medium-chain TGs	Span 60	Nanoemulsion	Enhanced solubility and reduced side effects
Olmesartan Medoxomil	Class II	Kollidon CL	Lauryl alcohol	Labrafac WL1349	Nanoemulsion	Improved systemic bioavailability
Aliskiren	Class II	HPMC K4M	Glyceryl trimyristate	Poloxamer 407	NLCs	Reduced dosing frequency and enhanced efficacy
Fosinopril	Class II	Microcrystalline cellulose	Cetyl alcohol	Cremophor RH40	Nanoemulsion	Better compliance and faster absorption
Trandolapril	Class II	Precipitated silica	Stearic acid	Tween 20	NLCs	Improved bioavailability and patient adherence
Benazepril	Class II	Chitosan	Oleic acid	Kolliphor ELP	SLNs	Enhanced release profile and absorption
Felodipine	Class II	Transcutol HP	Cinnamon Oil	Tween 60	SNEDDS	Effective release observed when compared to a drug suspension

SLN: Solid lipid nanoparticles, SNEDDS: Self-nanoemulsifying drug delivery systems, NLC: Nano-structured lipid carrier, L-SNEDDS: Liquid self-nanoemulsifying drug delivery system, S-SMEDDS: Solid-self-microemulsifying drug delivery system

CONCLUSION

Hypertension therapy has benefited tremendously from nanotechnology implementations which create novel drug delivery options beyond standard treatment methods. Four major delivery systems created through nanotechnology including liposomes and SLNs and MNs allow pharmacological agents to be released in controlled amounts while enhancing drug solubility together with drug targetability and availability. The biological membrane-imitating delivery systems shield antihypertensive medications from enzymes while providing stability and enhanced bioavailability to substances, such as candesartan and olmesartan. Rapid drug absorption combined with elevated bioavailability becomes possible through intranasal delivery systems featuring dissolvable MN patches that avoid hepatic drug breakdown. Collaborative timing between medication release and blood pressure rhythms through chronomodulated drug release serves to mimic the pattern of hypertension at the peak morning increases. Reliable drug release technologies called CODAS® and VERELAN PM® systems provide timed dosage control that follows human physiological patterns. Nanotechnologies represented by dendrimers nanoemulsions and transferosomes represent the forefront of drug delivery scientific progress by enabling targeted delivery and sustained drug release through multifunctional platforms. Across their insolubilizer functions, dendrimers maximize drug dissolving capability because nanoemulsions maintain hydrophobic medications' availability by improving stability across all delivery routes while transferosomes pierce skin layers to administer antihypertensive agents through the skin surface. Multiple factors requiring clarification need to be validated through extensive clinical trials before the implementation of these advances in clinical practice. The validation process must address scalability and cost-effectiveness along with long-term safety. The combination of contemporary nanotechnological methods and conventional drug delivery approaches shows promise to transform hypertension disease management while providing better treatment results alongside reduced worldwide impact.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT:

Udaya Kiran Sahoo: Conceptualization, Investigation, Writing – Original Draft, Visualization.

S. Vidyacharan: Resources.

Pritam Kayal: Resources.

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