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"Nanocarrier as an Antihypertensive Agent"

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INTRODUCTION

Hypertension is a serious cardiovascular event which refers to rise in the arterial blood pressure. Due to raised blood pressure, heart has to work harder in order to pump adequate amount of blood to cope up with normal body functioning. If the same is not treated, it may lead to heart-related problems and may damage the organs like kidney, brain, and eyes. It is as such not a disease in itself but is a risk factor for major cardiovascular events like heart stroke, ischemic heart disease, myocardial infarction, and heart enlargement. Several drugs in conventional dosage forms are available to treat hypertension but majority of the antihypertensive are poorly water soluble and therefore exhibits low bioavailability. These drugs are also substrate of P-gp and exhibit significant first-pass metabolism. The other challenges with these formulations are their short half-life and high dosing frequency. With the use of extended-release systems, these dosing frequencies can be reduced but as far as enhancement of bioavailability is concerned nanoparticles are far better approach. The associated benefits with nanoparticle include their capability of circumventing first-pass metabolism, P-gp mediated efflux and achieving targeting because entrapped drug in carrier is directly taken into the systemic circulation. Hindrance in the oral absorption of the drug includes extreme pH, poor intestinal permeability, and CYP 450-mediated enzymatic metabolism. Incorporation of the drug into nanoparticles can overcome these barriers. Proteins and peptides therapeutics including insulin glargine, etanercept, cyclosporine, decompressing, and jellyfish collagen protein (possess antihypertensive activity) are poorly bioavailable due to their charged nature, high molecular weight, low lipophilicity, and degradation by protease and peptidase secreted in the GIT. Nanoparticles have been reported which increase the uptake of drug through different mechanism which includes trans cellular absorption, paracellular transport by opening tight junction, P-gp inhibition, inhibition of gut wall metabolism by CYP450, and enhancement of lymphatic transport. Nanoparticles of size 100 nm have been considered ideal for lymphatic transport of lipid nanoparticle. Solutol HS 15, poloxamer 188, polyethylene glycol, and Cremophor RH 40 are some surfactants used in formulating nanoparticles and show inhibition of P-gp efflux and CYP450 activity. This review takes into account challenges associated with conventional antihypertensive formulations and role of oral nanoparticulate drug delivery system in overcoming such hurdles and enhancing the treatment of hypertension. The present review covers more recent and advanced technique for enhancing the efficacy of antihypertensive drugs. Most of the antihypertensive drug comes under BCS class 2 (low solubility and high permeability) which have low bioavailability as dissolution is the rate-limiting step. Drugs like amlodipine and Is radipine apart from having low bioavailability are also light sensitive apart from being a BCS class 2 drugs. Delivery of such drug in protected form is required to prevent their photodegradation. Both drugs were delivered by utilizing nano emulsion as a drug delivery system. Their pharmacokinetic data revealed the stability and enhanced bioavailability Chronotherapeutics can deliver drugs at the time when symptoms occur like during night and early morning as in the case with hypertension. Chronotherapeutics in Nano size range can further be more effective and

efficient in hyper- tension and has been discussed in liquid emulsion. Gene silencing is the recent technology where the use of small
interfering RNA is done to silence those receptors which are involved in the increase of blood
pressure. Intravenous route is mostly used for the delivery of SiRNA in treating hypertension.
Incorporation of SiRNA in delivery system is required to prevent their degradation by exonuclease activity present in blood. Oral delivery has been rarely studied for the delivery of
SiRNA for the treatment of hypertension. Researches are available for the oral delivery of SiRNA for other diseases has developed microencapsulated nanogel for the oral delivery of SiRNA to treat inflammatory bowel disease by targeting TNF-a. In another study, galactose modified trimethyl chitosan-cysteine conjugates with various galactose grafting densities were formulated to delivery vascular endothelial growth factor SiRNA orally for the treatment of hepatoma.

CLASSIFICATION

Nanocarrier containing Antihypertensive drugs classification

The first drug which was developed for treating hypertension was pentaquine in 1946 but it showed several side effects with little therapeutic efficacy. Soon in early 1950s, ganglionic blocking agent ‘‘hexamethonium’’ was introduced which was efficacious but was not convenient to use. Veratrum was introduced which had short onset of action but was toxic. Hydralazine developed soon after seeing the side effects of ganglionic blockers and is seldom
prescribed today. Reserpine, the most effective drug developed at that time, was also abandoned due to its side effects like depression and impotency. Breakthrough drugs like diuretics and b-blockers which are highly widely prescribed today are named as the modern era of antihypertensive which was started in 1960. In 1990s, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin blockers were introduced which are now prescribed as the first-line therapy either alone or in combination. Thorough understanding of Renin Angiotensinogen Aldosterone System (RAAS) has led to the development of several antihypertensive. There is dramatic progress in the development of novel therapeutics, the target of which is also related to RAAS

Figure 1shows the novel targets which have opened the new possibility for the successful development of the drug for treating hypertension which are currently under preclinical and clinical stages of development. Various antihypertensive drugs including novel antihypertensive with their class, mechanism of action, and the development stage are described inTable 1

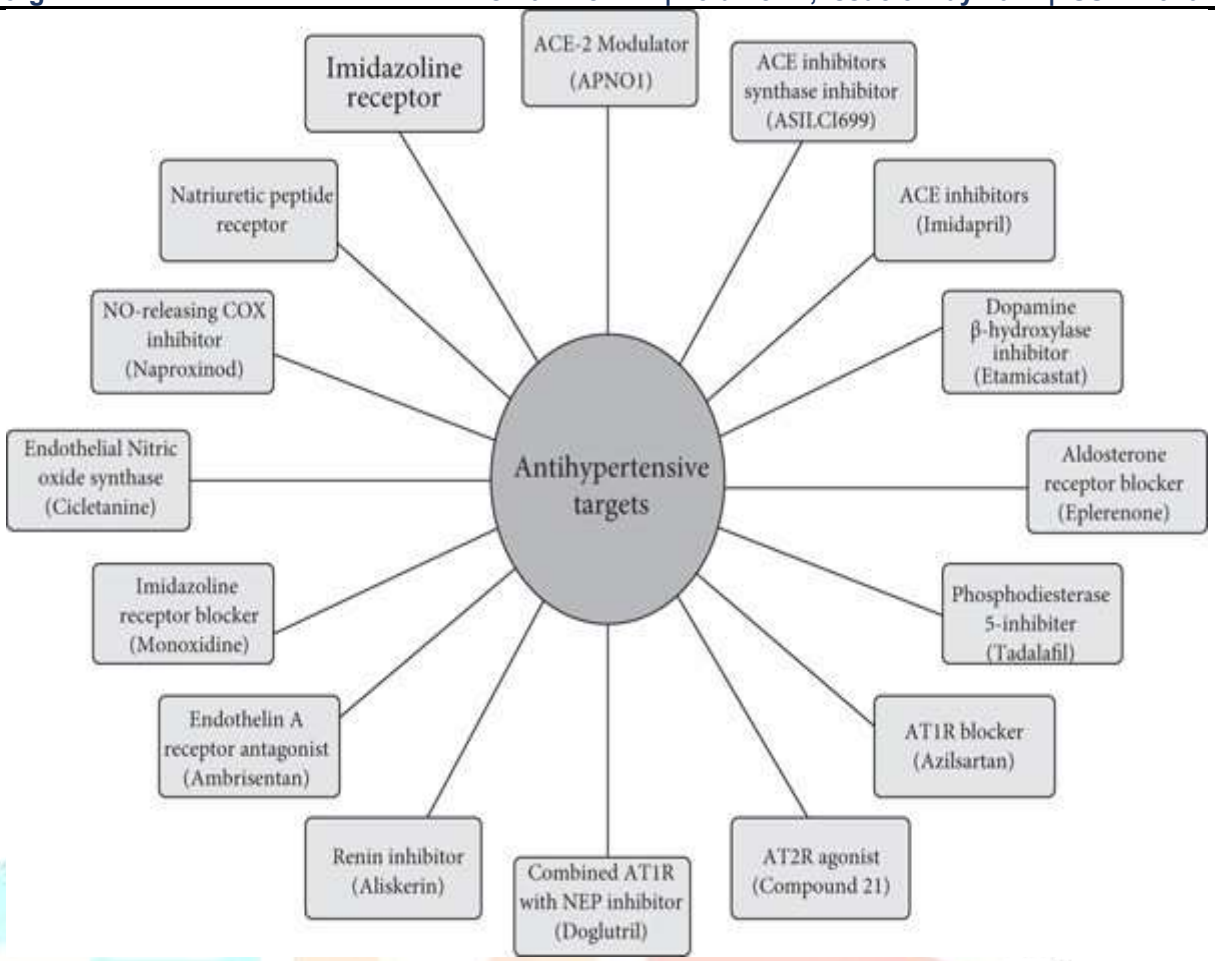


Figure 1. Novel molecular targets for antihypertensive.

Renin inhibitor

Renin is released from kidney and acts as a first step for the RAAS cascade. So, it acts as a target for antihypertensive therapy. In 2007, aliskiren the first-marketed renin inhibitor was introduced into the market. VTP27999 is a new molecule which is under Phase II clinical trial

Angiotensin II type 2 receptor agonist

AT2R has action opposite to that of AT1R. It opposes the AT1R-mediated vasoconstrictor action of angiotensin II. AT2R shows vasodilatory action which is formed of bradykinin, nitric
oxide, and cGMP. AT2R also mediates natriuretic Compound 21 is AT2R agonist which is under clinical trial for its antihypertensive action. It acts on the sodium/hydrogen exchanger 3
(NHE 3) and the Na+/K+- ATPase in the proximal tubules, thus showing natriuretic.

Phosphodiesterase 5 (PDE-5) inhibitor

PDE-5 causes degradation of cyclic GMP which is the intermediate step in vasodilatory action. PDE-5 inhibits cGMP degradation thereby causing vasodilatation. Tadalafil is recently approved PDE-5 inhibitor showing vasodilatory effect; KD027 is another PDE-5 inhibitor which is under phase II clinical trial of study.

Natriuretic peptide receptor a (NPRA) agonist

A trial and brain natriuretic peptides cause vasodilatory effect through cGMP by acting on NPRA. So, NPRA agonist like PL3994 which is under phase II trial of study causes increase in cGMP level leading to decrease in the blood pressure and induction of natriuresis.

Mas receptor modulator

Mas receptor like AT2 receptor causes release of nitrous oxide. Blockage of either Mas receptor or AT2 causes the blockage of other receptor due to their hetero-dimerization. Natural ligand for AT2 receptor is angiotensinogen, while for Mas receptor, it is Ang (1–7). Ang (1–7) has low bioavailability which can be enhanced by complexing it with hydroxyl-propyl b- Cyclodextrin. It is still under preclinical trial of study.

Angiotensin converting enzyme 2 (ACE2) modulatory

ACE 2 causes metabolism of angiotensin I and angiotensin II which are the key peptides for RAAS. Ang (1–7) is the metabolic product of ACE2 as described above. Angiotensin converting enzyme 2 (ACE2) modulators like APN01 (rhACE2) which are under Phase II clinical trial are showing promising results in controlling rise in blood pressure through this mechanism of action.

Endothelia a receptor (ETA) antagonist

Endothelia especially ET1 binds with endothelin receptor ETA and/or ETB expressed on cell membrane and produces effects like systemic and pulmonary vasoconstriction apart from oxidative damage, atherosclerosis, fibrinogenesis, and salt and water retention. Macitentan and Ambrisentan are recently approved Endotheline A receptor (ETA) antagonist for pulmonary hypertension which shows its effect by preventing the binding of ET1 to both ETA and ETB.

Combined AT1R blocker and NEP inhibitory [9][15]

Neutral endopeptidase also called as neprilysin, vasopeptidase, or enkephalinase degrades various peptide hormones into inactive fragments. These hormones are angiotensin I, II, and endothelin (vasoconstrictor). NEP also degrades vasodilators like natriuretic peptides and kinins. NEP inhibition increases the bioavailability of Natriuretic peptides which contribute to lowering of blood pressure but at the same time level of vasoconstrictor also gets increased. So, the strategy is to design a drug with AT1R or ACE blocking activity.

Imidazoline-receptor blocker [9]

Imidazoline receptors are of 3 types: I1, I2, and I3. I1 imidazoline receptor mediates the sympathoinhibitory actions to lower blood pressure. I1 receptors present in the rostral ventrolateral medulla oblongata (RVLM) are stimulated by clonidine, a first-generation imidazoline. But this drug also show binding capacity for alpha 2 receptor thus producing side effects. Second-generation centrally acting antihypertensive like monoxidine are more selective for I1 than for alpha 2 receptor thus comparative less toxic than firstgeneration antihypertensive. Endothelilal nitric oxide synthase (eNOS) coupler Patients with pulmonary artery hypertension have low levels of a substance called nitric oxide (NO) which maintains the normal tone of blood vessel. Endothelial nitric oxide synthase (eNOS) is the enzyme required for the production of NO.this result in enhanced vasoconstriction. Cicletanine which is a thiazide like diuretic also acts as eNOS coupler which makes eNOS active thus increasing NO production and decreasing ROS formation.

NO-releasing cyclooxygenase (COX) inhibitory [4][9]

Naproxcinod is non-steroidal anti-inflammatory drug which acts as cyclooxygenase inhibiting nitric oxide donor (CINOD). NO so produced has vasodilatory effect which developed the interest of the researcher to test it for blood pressure lowering effect and is currently under phase III trial of study.

Aldosterone synthaseinhibitor [11]

Mineralocorticoid receptor antagonists are not effective in reducing non-genomic effect of aldosterone. So, aldosterone synthase has drawn the attention toward mediating the blood pressure. Aldosterone synthase is cytochrome P450 enzyme involved in the biosynthesis of aldosterone. Inhibitor of this enzyme ASI LCI699 (in phase II trial) results in disruption of RAAS to keep rise in blood pressure under check.

Dopamine b-hydroxylase (DbH) inhibitor [7]

DbH is the enzyme which hydrolyzes the neurotransmitter dopamine into nor-adrenaline in sympathetic nervous system which acts on a-receptor to produce vasoconstriction. DbH inhibitor, etamicastat, causes vasodilation, natriuresis, and diuresis.

Table 1. Some novel antihypertensive with their development phase and mechanism of action.

Mechanism	Drug	Development phase	Company	References
Aldosterone-receptor blocker	Eplerenone	Marketed	Pfizer, USA	ACE 2 modulator
Phosphodiesterae 5 inhibitor	Tadalafil KD027	Marketed Phase II	Eli Lilly, USA Kadmon Pharmaceuticals	ACE 2 modulator; Adis Insight
Dopamine b-hydroxylase inhibitor	Etamicastat	Phase I	Bial, Portugal	McLendon et al. (2015)
ACE 2 modulator	APN01 (rhACE2)	Phase II	Apeiron-biologics	Morrell et al. (2013)
Aldosterone synthase inhibitor	ASI LCI699	Phase II	Novartis, Switzerland	Muller et al. (2000)
ACE inhibitor	Imidapril	Marketed	Mitsubishi Tanabe Pharma	Nolte et al. (2011)
AT1R blocker with PPAR- gractivity	Azilsartan (TAK-491)	Marketed	Takeda Pharmaceuticals, Japan	Novartis' new heart failure medicine LCZ696, now called
AT2R agonist Combined AT1R blocker and	Compound 21 LCZ696	Phase I Phase III	Vicore, Sweden Novartis, Switzerland	Nunes et al. (2010) O'Driscoll& Griffin (2008);
NEP inhibitor	Daglutril	Phase II	Solvay, Belgium	Ohara-ch [Online]
Renin inhibitor	Aliskiren VTP27999	Marketed Phase II	Novartis, Switzerland, and Vitae Pharmaceuticals, USA	ACE 2 modulator; Oparil& Schmieder(2015)
Endothelin A receptor antagonist	Macitentan (PAH)	Phase II	Actelion Pharmaceuticals	Palatin Technologies, Inc [Online];
	Ambrisentan (PAH)	Phase II	Gilead	Paulis& Unger (2010)
Imidazoline-receptor blocker	Monoxidine	Phase II	Eli Lilly, USA	Paulis et al. (2015)
Natriuretic peptide receptor agonist	PL3994	Phase II	Palatin Technologies, USA	Pridgen et al. (2014)

Endothelila nitric oxide synthase coupler	Cicletanine	Marketed	Gilead Sciences, Inc	Antal et al. (2015); Ranpise et al.
NO-releasing COX inhibitor	Naproxcinod	Phase III	NicOx, France	Selvamuthukumar Velmu

Constraints with oral delivery of antihypertensive [16][17]

Generally, solubility and permeability are the prerequisite for the oral absorption of the drug. Certain antihypertensive like deltiazem, nicardipine, and Nifedipine are the candidate for the P-glycoprotein (P-gp)-mediated efflux transporter present in the intestinal wall apart from Cytochrome P450-mediated enzymatic metabolism Drugs which are under BCS class 2 show variable absorption pattern and low bioavailability. Most of the antihypertensive comes under BCS class 2, some of which are mentioned in which represents that drug metabolism, solubility, permeability (log P), and P-gp are the critical parameters which determine the bioavailability of the antihypertensive. Nanoparticles seem to be the better approach to remove the constraints related with oral delivery of antihypertensive. Different nanoparticulate systems like polymeric nanoparticle and lipid-based nanoparticles (nano emulsion, SLN, NLC, liposomes) have been studied to overcome limitations associated with the oral delivery of antihypertensive.

Table 3 shows the advantages of using nanoparticle over conventional therapy.

Types of delivery system	**Therapeutic system**	**Excipients used**	**In- vivo study model**	**Mechanism**
Polymeric nanoparticle	Ramipril	lecithin/chitosan	Male Wistarrats	1.6-fold decrease in systolic Blood pressure
	Nifedipine	PCL PLAGA Eudragit RL/RS	MaleadultSH R	Initial fall in systolic blood pressure was rapid for PEG solution followed by with PCL NP and PLAGA NP. Blood pressure was within normal range after 10 h of dosing with all three NPs while PEG solution failed to achieve such sustained effect.
	Felodipine	PLGA,Plu ronicF-68	MaleWistarrat s	Systolic blood pressure normalized and elevated ST segment of ECG became normal upto a period of 3 days as compared to drug suspension.
	Lercanidipi ne	HPMC, T PGS	Male Sprague–Dawleyrats	2.47 increase in oral bioavailability than raw drug without TPGS
	Aliskiren	Magnetite , poly (D, L-lactide), PluronicF -68	Male Wistarrats	Significant decrease in mean systolic blood pressure by aliskiren nanoparticle as compared to aliskiren suspension
Solidnanop article	Nisoldipine	Trimyristi n (TM; Dynasan- 114; glyceryltri myristate) , egg lecithin,	MaleWistarrat s	2.17timesincreaseinoralbioavailabil ity,significant reduction in systolic blood pressure for a period of 36 h

		Poloxame r-188		
	Candesartan	GMS, soy lecithin,T ween80	MaleSprague–Dawleyrats	12 times increase in oral bioavailability
	Isradipine	Trimyristi n or GMS, poloxame r 188	Wistarrats	Significant decrease in the systolic blood pressure with SLN formulation using two differentlipids
Nano Structured Lipid Carrier	Lacidipine	GMS, Linoleic acid and poloxame r 407	Wistarmalealb inorats	3.9 times enhancement in the relativebioavailability
	Lercanidipi ne	Labrafil 2130M, GMS, linseed oil and Tween 80	MaleSprague–Dawleyrats	24 h control on the blood pressure by NLC as compared to plaindrug
Nano emulsion	Ramipril	Sefsol 218, Tween80, carbitol	Wistarmalealb inorats	229.62% increase in relative bioavailability of Ramipril nanoemulsion as Compared to ramiprol marketed capsule and 539.49% increase in bioavail- ability of formulation as compared to drug suspension.
	Amlodipine	DE (Labrafil m 1944 CS and Dextrin)	MaleSprague–Dawleyrats	In vitro release studied showed higher release of amlodipine from DE than powdered drug. 2.6 to 2.9 times increase in C_{max} and AUC (0– 24h) from DE than powder. Marked reduction in photodegradation of drug in DE than powdered drug (5.6% versus 66.9%)
	OlmesarnM edoxoil	SNEDDS (SNEOFa ndCSNE OF)	MaleSprague–Dawleyrats	After 0.5 h of dosing, significant reduction in arterial blood pressure (180 to 189 mm Hg)
	Valsartan	S- SNEDDS (Capmul MCM, Labrasol, Tween 20)	MaleWistarrat s	3–3.5 time increase in the rate of dissolution, significant reduction in the mean systolic blood pressure after 0.5 h and 2 h of dosing of S- SNEDDS as compared to valsartan suspension showing faster onset of action of SSNEDDS thus showing it to have the potential of the bioavailability enhancement of valsartan
Liposomes	Lacidipine	Cetyl alcohol andTween 80	Adult malehumanvo lunteer	540.11% increase in relative bioavailability of enteric-coated capsule of lipotome as compared to Motens tablet

TABLE NO-3Novel delivery system of antihypertensive and their positive outcome

PCL: poly-e-caprolactone, PLAGA: polylactic and glycolic acid, PEG: Polyethylene glycol, NP: Nanoparticle, SHR: systolic hypertensive rat, DE: Dry emulsion, SNEDDS: Self- Nano emulsifying drug delivery system, S-SNEDDS: solid self-Nano emulsifying drug delivery system, HPMC: Hydroxypropyl methyl cellulose, TPGS: D-a-tocopheryl polyethylene glycol1000 succinate, SNEOF: Self Nano emulsifying oily formulation, CSNEOF: Cationic Self Nano emulsifying oily formulation, GMS: Glyceryl monostearate.

Nanotechnology-based oral delivery of antihypertensive [1][18]

Rationale for using Nano carrier Oral route is the most preferred route for the administration of the drugs. But the delivery of drug exhibiting low aqueous solubility and/or permeability (BCS class II or IV) is very challenging as bioavailability of these drugs is very low and pH of the GIT also varies from acidic in stomach to basic in the intestine. The pH of the GIT varies from 1 in stomach to 8 in the intestine. This wide difference in the pH can severely hamper the pharmacological activity of the drug by oxidation, deamination, or hydrolysis of protein drugs. Oral bioavailability of drugs like candesartan cilexetil is affected as they undergo chemical degradation at acidic pH. Enzymes like liver esterase and cytochrome P450 cause significant degradation of antihypertensive as shown inTable 2. Protease degrades 94–98% of orally administered protein. Intestinal mucosa is the other barrier which hinders drug permeation. Mucosal barrier consists of extrinsic barrier (microenvironment near the vicinity of mucus layer) and intrinsic barrier (epithelial cell monolayer). Intrinsic barrier is due to the presence of tight junction between adjacent cells. Different mechanism by which any molecule can cross this barrier includes transcellular, paracellular, and transcytosis. Transcytosis being active transport pathway restricts large sized and charged molecules. When the mucosal barrier is permeated, molecules have to cross lamina propria where blood capillaries lie and molecule can get entry into the blood stream. Strategy to overcome intestinal barrier was to prepare mucoadhesive formulation which increases the contact time of the formulation with mucus thereby increasing drug concentration at the site of absorption. Many muco adhesive have the property of acting as permeation enhancer which can open tight junction and paracellular transport becomes possible. Another way to enhance GI permeability is transport through M cells. M cells have less quantity of protease enzyme and lacks mucus secretion. Lipophilic molecules have improved M cell transport Lipid nanoparticles like SLN and NLC are transferred through intestinal barrier by clathrin mediated transport. SLN is also trans cytosed by caveolae-mediated endocytosis. The materials used in the preparation of nanoparticles must be nontoxic and biodegradable. Application of different nanoparticle for oral delivery has been discussed in the upcoming sections. NLC is transported by paracellular transport through tight

junctions. Different nanoparticulate systems have been investigated to circumvent firstpass metabolism through lymphatic transport and includes nano emulsion, liposome, SLN, and NLC.Sizerangeof100–500nm has been proposed to be ideal in the lymphatic uptake but rate of absorption is faster when size is below 100 nm. Negatively charged nanoparticles show higher lymphatic uptake than positively charged and neutral nanoparticles. Lipophilicity acts as an add-on for lymphatic uptake of drug. NLC of hydrophilic drugs acts as a better approach for enhancing the uptake of such drugs Furthermore, efflux transporter like P-glycoprotein present on the intestinal wall causes efflux of several antihypertensive leading to poor oral bioavailability. Drug encapsulated in nanoparticle can avoid all these constraint and sustained action can also be achieved leading to dose reduction and frequency of dosing.

Currently used nanoparticles utilized in the treatment of Hypertension [16]

Figure 2 gives an overview of currently used nanoparticles for the treatment of hypertension. The materials used in the preparation of nanoparticles must be nontoxic and biodegradable. Application of different nanoparticle for oral delivery has been discussed in the upcoming sections.

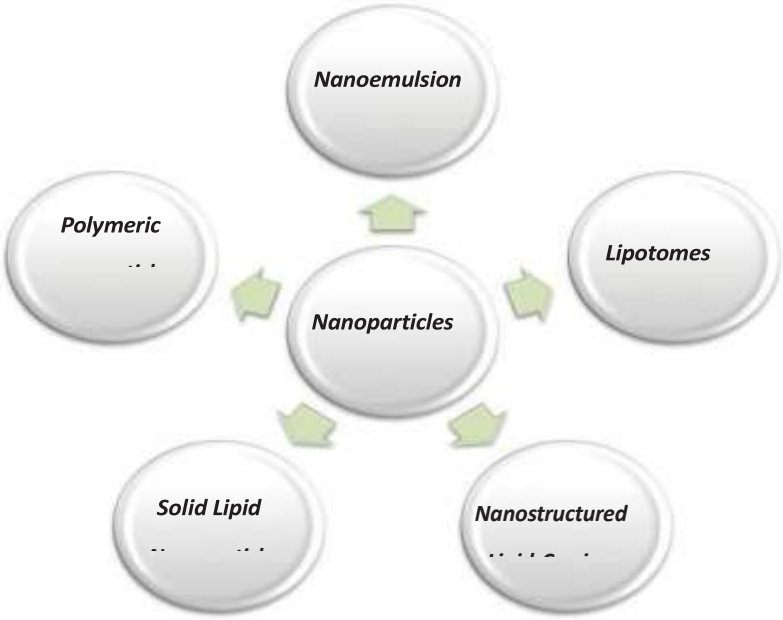


Figure.2 currently used nanoparticles utilized in the treatment of hypertension

Polymeric nanoparticles [19][16]

Polymer-based nanoparticles which have been extensively studied for oral antihypertensive include polylactide-co-glycoside (PLGA), poly-e caprolactone (PCL), Eudragit RL/ RS, hydroxyl propyl methyl cellulose (HPMC), and chitosan. Drug release from these nanoparticles is influenced by the method of preparation, particle size, surfactants, molecular weight of polymer, and polymer architecture. Some drugs are pH sensitive like artemether, erythromycin, and candesartan cilexetil and to prevent acidic degradation they need to be targeted in intestine or colon- specific region. The pH-sensitive polymers can target drug at specific area of GIT. For drugs which are degraded in acidic environment, methacrylic acid, copolymers like EudragitS100/L100, can be used to target the colon while drugs which are susceptible to degradation at lower part of GIT Eudragit L100-55 can be used for the drug delivery at controlled rate. Application of these polymers is wide which include tissue targeting,

delivery of bio therapeutics, and enhancing drug solubility. Rate of drug release from these polymers is fast. Drug release at the site of absorption creates the concentration gradient which helps in permeation of drug from the site of absorption thus causing increase in the drug bioavailability. Nepolean et al. prepared Nisoldipine Eudragit S100 nanoparticle. It was studied that the release of drug from the polymer was pH responsive and was evident to occur at the pH of the colon. There was avoidance of drug metabolism mediated by cytochrome P450 in the liver and gut wall. Thus, it was concluded that the formulation has the capability to enhance oral bioavailability of the drug prepared three different NPs of PLGA, PCL, and Eudragit for delivering Nifedipine. Initial fall in systolic blood pressure was rapid for PEG solution (193 ± 3 mm of Hg to 102 ± 2 mm of Hg) compared to Eudragit nanoparticle (189 ± 2 mm of Hg to 156 ± 2 mm of Hg) while significant reduction in blood pressure was seen with PCL NP (189 ± 2 mm of Hg to 124 ± 2 mm of Hg) and PLGA NP (113 mm of Hg ± 2 mm of Hg). After 10 h, blood pressure with PEG solution of Nifedipine was returned to normal while there was still significantly reduced blood pressure with all three NPs.

PLGA [Poly (lactic-co-glycolic acid)] are made up of lactic acid and glycolic acid monomer which are endogenous and are degraded easily, so the toxicity associated with these NPs is minimal. PLGA is US FDA and EMA approved. They are available in different form depending upon the ratio of the monomer. They can entrap both hydrophilic and hydrophobic drug and can provide sustained release profile from days to years depending upon the ratio of the monomer. They can also be used to target specific tissue or organ after modifying their surface prepared PLGANPs of felodipine. Systolic blood pressure normalized and elevated ST segment of ECG came under control for a period of 3 days when compared with drug suspension.

In another study, Alis Kiren magnetic nanoparticles were prepared using magnetite (Fe_3O_4) as magnetic material and poly (D, L-lactide) as polymer. Decrease in systolic blood pressure to 153.8 ± 3.9 mm of Hg as compared to placebo and alis kiren suspension having mean systolic blood pressure of 203.4±4.3mmofHga nd178.7±1.8mmofHg, respectively, revealed the success of the study in treatment of hypertension.

Chitosan nanoparticle.[20]

Chitosan is natural biodegradable, biocompatible, and nontoxic to human body. Chitosan is bio adhesive linear polysaccharide which is used as sustained release and site- specific delivery system for many drugs, including antihypertensive. Chitosan nanoparticles have enhanced the oral bioavailability of antihypertensive by preventing first- pass metabolism and degradation at acidic pH at upper GIT as chitosan are degraded by colonic microbes where pH is basic prepared Ramipril-Ø-Cyclodextrin complexed nanoparticles of lecithin/chitosan. In vivo result showed 1.6 times decrease in systolic blood pressure of deoxycorticosterone acetate salt induced hypertensive rats. Chitosan nanoparticles emerged as a solution for oral administration of antihypertensive which are poorly soluble

Hydroxypropyl methyl cellulose (HPMC) nanoparticle.[21]

HPMC is nonionic water-soluble derivative of cellulose ether used for preparing controlled release dosage form. They are available in different viscosity depending upon the concentration of methoxy and hydroxypropyl group (16.5–30% of methoxy and 4.0– 32.0% of hydroxypropyl groups) Swelling and erosion of HPMC depends upon the pH and ionic strength of release media has been used to deliver several antihypertensive showing poor bioavailability as tablet dosage form. This property of the HPMC was utilized in conjunction with TPGS as surfactant to enhance the dissolution and bioavailability of lercanidipine which was estimated tobe2.47 times to that of pure lercanidipine.

Lipid-based nanoparticles [22]

Several antihypertensive have been prepared using lipid- based delivery system as mentioned in Table 3. Lipid-based nanoparticles are ideal candidate for drug delivery of antihypertensive showing low solubility and high permeability. Lipid-based excipients can entrap greater amount of lipophilic drug than hydrophilic drug. Lipid nanoparticles (LNs) entrapped drug which are poorly soluble; the dissolution step is not needed as the drug is generally solubilized in lipid excipients. This solubilization is generally maintained throughout the gastrointestinal passage. The excipients used in preparing LNs include surfactants and co- surfactants apart from lipid which can promote permeability across intestinal wall. The mechanism underlying the enhancement of drug absorption includes increase in membrane fluidity, opening of tight junction, inhibition of P- glycoprotein efflux transporter, alteration of intestinal metabolism mediated by cytochrome P450, and lymphatic uptake thus by-passing hepatic first-pass metabolism. Various lipid- based nanoparticles which have been used in loading antihypertensive drugs are discussed below.

Nano emulsion.[23][24]

Nano emulsion is thermodynamically stable drug delivery system which c a n solubilize higher amount of drug. It is rapid acting, has higher shelf-life, and can be targeted. This system can achieve high oral bioavailability. Marketed formulation of cyclosporine (sand immune neural) in micro emulsion form resulted in improved absorption of drug due to formation of mixed micelle after oral administration prepared Olmesartan medoxomil nano emulsion to overcome low solubility of the drug apart from its conversion to less poorly permeable-form Olmesartan which decreases the oral bioavailability of the drug. The pharmacokinetic study on rat showed 2.8 times increase in AUC and 3 times reduction in the dose prepared amlodipine besilatenanoe- emulsion and the concentration of the drug in heart and blood after 24 h of study was found higher for nano emulsion formulation than drug suspension. Also, the C_{max}, AUC0,

and % relative bioavailability for the formulation were found to be 4.78, 2.2, and 475%, respectively. Jang D-J et al. enhanced the stability of amlodipine against photo degradation by formulating dry emulsion. Also, there self-Nano emulsifying oily formulation (SNEOFs) was 2.9 times enhancement of bioavailability of the formulation of amlodipine.

Solid lipid nanoparticles.[11][23]

SLNs are composed of the· excipients which are biocompatible and include solid lipid and surfactants/co-surfactants. Lipid excipiėnts used are mono-glycerides, diglycerides, and triglycerides of fatty acid with different chain length. More complex lipids are combination of these fatty acids with more imperfect crystal to accommodate more amount of drug into it. There are four different models of SLN which include SLN matrix, compound enriched shell, drug enriched core, and mixed type. Type of SLN formed depends upon the nature of drug and solid lipid used. The release of drug from SLN is biphasic, initial burst release followed by sustained release. The burst release can be minimized by decreasing manufacturing temperature and surfactant concentration. SLNs enhance the drug bioavailability by preventing first-pass metabolism as they undergo lymphatic uptake developed Nisoldipine SLN. C_{max} and AUC_{total} of developed formulation is 12.55 ± 0.6 mg/mLand96.15 ± 3.92 mg/mL/h while C_{max} and AUC_{total} of oral drug suspension is 7.53± 0.13 mg/mL and 44.13 ± 2.90mg/mL/h. The oral bioavailability of the formulation was found to be 2.17 times higher than suspension. The researchers hypothesized that nano size particle which adheres to the GI membrane increases residence time of SLN. The surfactants phosphatidyl choline and poloxamer enhance the permeability across the GI tract, apart from this the lipid used enhances the lymphatic uptake thereby circumventing the first-pass metabolism. Further pharmacodynamics study showed that SLN of Nisoldipine significantly decreases the mean systolic blood pressure for a period of 36 h, revealing the sustained effect of formulation showed enhancement in the C_{max} andAUC_{0-t}from0.64±0.15mg/mland3.51±0.87mgh/mL for candesartan suspension to 17.17 ± 2.40 mg/ml and 42.61 ± 7.53 mg h/mL for SLN of candesartan.

The AUC value indicates 12 times increase in oral bioavailability of the drug. T_{max} of SLN decreases to 0.42 ± 0.17 h from 2.75 ± 0.50 h. Such decrease indicates rapid drug absorption of the SLN than suspension thus making onset of action faster. The factor contributing to such an improved pharmacokinetic parameter was bio adhesiveness of SLN, intestinal permeation of SLN due to surfactant Tween 80, and nano size range apart from lymphatic uptake. Prepare disradipine SLN and showed a marked 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.

Nanostructured lipid carrier·[11]

SLN has some limitation associated with it like expulsion of drug due to organization of solid lipid into more perfect crystal with time, which results in decrease in entrapment efficiency and loading capacity with time. This drawback associated with the SLN led to the development of NLC which is composed of liquid lipid apart from solid lipid. Liquid lipid is present within the solid lipid and does not undergo modification into stable structure; also, solubility of drug in liquid lipid is higher than solid lipid, this results in enhancement of entrapment efficiency and loading capacity NLC is generally of three types namely high imperfect matrix, multiple O/F/W type, and non-crystalline amorphous type based on the method of preparation. Prepared NLC of poorly water-soluble drug lercanidipine hydrochloride having relative bioavailability of just 10%. There was significant reduction in blood pressure to 117.23 ± 1.61 mm of Hg after 8 h and 130.13 ±1.97 mm of Hg after 24 h while plain drug administered to rats showed reduced blood pressure of 2.51 mm of Hg at 4 h and then rats developed hypertensive stage again. The reason behind such an effective result by NLC was its uptake by lymphatic route or payer's patches, in another study by showed better absorption of Lacidipine NLC. AUC and C_{max} of Lacidipine NLCs and Lacidipine suspension was 8225 mg/ml/h, 813 mg/ml, and 2064.75 mg/ml/ h, 571.77 mg/ml respectively. This high

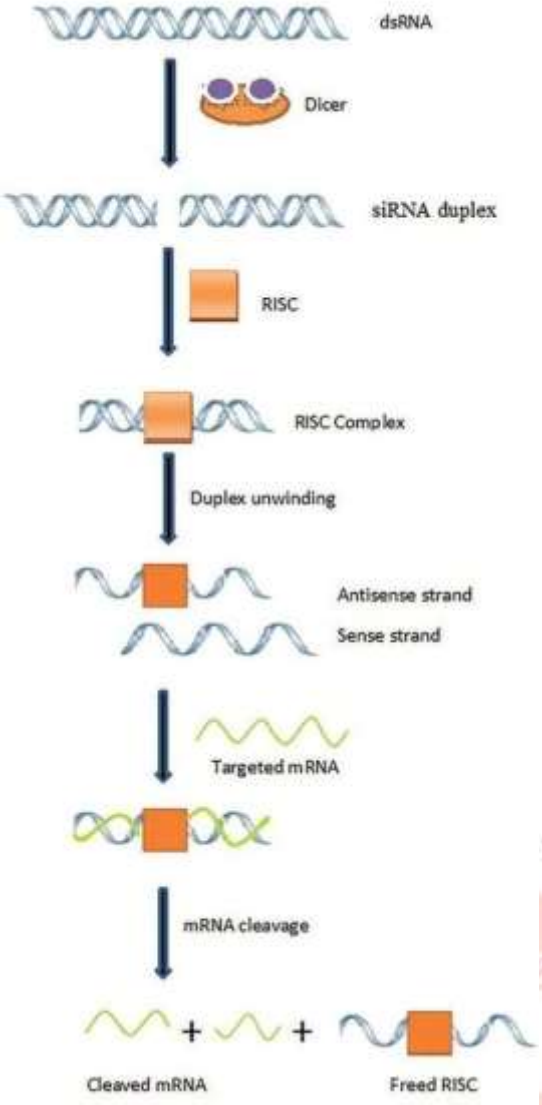
C_{max} and AUC value of NLC shows better drug absorption and increased relative bioavailability of around four times. These results show that NLC is a versatile Nanocarrier and has the potential to incorporate antihypertensive with different physicochemical properties. NLC could be used as an alternative drug carrier in the antihypertensive drug delivery.

Liposomes. [19]

This is another lipid-based novel dual-functioning Nanocarrier developed by for Lacidipine, a poorly soluble drug. Lipotomes were prepared using lipid acetyl alcohol and surfactant Tween 80 by thin film hydration technique. Its dual function as claimed by the researchers is enhancement of drug solubility and bypassing first-pass metabolism of drug. Researcher compared enteric-coated lipotomes with enteric-coated lipid formulation without Tween 80 and marketed tablets. Theyfound significant increase in the value of C_{max} of lipotomes (7.66 ± 3.52 mg/ml) than Tween 80 control preparation (3.62 ± 1.19 mg/ml), and marketed preparation (2.11 ± 0.81 mg/ml) showing efficacy of the lipotomes being absorbed efficiently. Also the relative bioavailability of lipotomes was 5 .4 as compared to Tween control formula (relative bioavailability 3.68). This result shows that the application of lipid excipient and surfactant Tween 80 individually plays vital role in enhancing clinical performance of the drug. The reason provided was thatTween80 increases GI permeability, and lipid entrapped drug is circumvented by first-pass effect apart from its lymphatic uptake Thus, nanotechnology plays a big role in improving therapeutic efficacy of many therapeutics whether synthetic molecules or peptides. They enhance drug performance by either protecting their degradation or providing sustained release. Several challenges come in the way of Nano formulation such as scale-up, production cost, reproducibility, stability, and regulatory issues that still remain unaddressed.

Nanoparticle-mediated gene therapy of hypertension [6]

Principle behind gene therapy is gene silencing. This refers to making target mRNA nonfunctional by its cleavage. The mechanism of gene silencing is shown in Figure 3. Small interfering RNA (SiRNA) is produced by RNAse III, and endonuclease also called Dicer. SiRNA duplex isin corporate into RISC (RNA-induced silencing complex), a nuclease resulting in RISC complex. SiRNA duplex undergo unwinding by RNA helicase resulting in antisense strand which remains with RISC (called activated RISC) while sense strand is degraded by exonuclease. This activated form of RISC binds with target mRNA and then RNAse activity is initiated by antisense strand of activated RISC. mRNA is cleaved into inactive fragments which become nonfunctional for protein synthesis. Thus, gene silencing occurs, and receptor protein is not synthesized. Activated RISC becomes free to further destroy mRNA



Figuer 3- Nanoparticle-mediated gene therapy

Gene therapy in hypertension refers to gene silencing of receptors which regulates the blood pressure. Small interfering RNA causes sequence-specific gene silencing thus receptor protein, which is the target of interest here is not synthesized. For example, AT1147siRNA was used by, the subtype of angiotensin receptor, thus angiotensin II binding to this receptor is affected. SiTRPC3 was another siRNA which decreased the expression of calcium-permeable transient receptor potential channel (TRPC). In another study, adeno-associated virus (AAV)-siRNA decreased the expression of AT1a receptor and mineralocorticoid receptor. siRNA effect was also seen in a1D-adrenergic receptor. The protein level of which was decreased by using siRNA. These studies show promising approach using siRNA for treatment of hypertension. The basic problem with siRNA is its rapid degradation upon administration. So, a delivery system is required prevent degradation of siRNA by endo- and exonuclease present in the blood, serum, and cells. Lipoplex, a cationic liposome made of DOTAP (N-[1-(2, 3- dioleoyloxy)]-N- N- N trimethyl ammonium propane), reduces the expression of b1-adrenoreceptor and controls the blood pressure for 12 days when given through intravenous route.

Nanocarrier containing drugs as antihypertensive [26]

] Ramipril Medical uses

Indications for its use include:

- High blood pressure
- Congestive heart failure
- Following heart attack in patients with clinical evidence of heart failure
- Susceptible patients over 55 years: prevention of heart attack, stroke, cardiovascular death, or need of revascularization procedures
- Kidney damage due to diabetes with protein in the urine (In low doses it is used as a prophylaxis for developing nephropathy and related secondary cardiovascular events.)

Contraindications

Contraindications to its use include renovascular disease (impaired blood flow in the kidneys), severe renal impairment (especially in patients with one kidney or with bilateral renal artery stenosis), volume-depleted patients, a history of angioedema while on an ACE inhibitors, pregnancy, and hypotension.

Adverse effects

- Shakiness
- Dry cough
- Dizziness and light-headedness due to low blood pressure
- Fatigue, especially in the early stages
- Mouth dryness in the early stages
- Nausea
- Fainting
- Signs of infection (e.g., fever, chills, persistent sore throat)
- Chest pain
- Neutropenia (low white blood cells)
- Impotence (erectile dysfunction)

Mechanism

ACE inhibitors inhibit the actions of angiotensin converting enzyme (ACE), thereby lowering the production of angiotensin II and decreasing the breakdown of bradykinin. The decrease in angiotensin II results in relaxation of arteriole smooth muscle leading to a decrease in total peripheral resistance, reducing blood pressure as the blood is pumped through widened vessels. Its effect on bradykinin is responsible for the dry cough side effect.

Ramipril, a prodrug or precursor drug, is converted to the active metabolite ramiprilat by carboxyl esterase 1. Ramipril is mostly excreted by the kidneys. Its half-life is variable (3–16 hours), and is prolonged by heart and liver failure, as well as kidney failure.

Nifedipine Medical uses

High blood pressure

The approved uses are for the long-term treatment of hypertension (high blood pressure) and angina pectoris. In hypertension, recent clinical guidelines generally favour diuretics and ACE inhibitors, although calcium channel antagonists, along with thiazide diuretics, are still favoured as primary treatment for patients over 55 and African American patients.

Sublingual Nifedipine has previously been used in hypertensive emergencies. It was once frequently prescribed as needed to people taking MAOIs for real or perceived hypertensive crises. This was found to be dangerous, and has been abandoned. Sublingual nifedipine causes blood-pressure lowering through peripheral vasodilation. It can cause an uncontrollable decrease in blood pressure, reflex tachycardia, and a steal phenomenon in certain vascular beds. There have been multiple reports in the medical literature of serious adverse effects with sublingual nifedipine, including cerebral ischemia/infarction, myocardial infarction, complete heart block, and death. As a result of this, the FDA reviewed all data regarding the safety and efficacy of sublingual nifedipine for hypertensive emergencies in 1995, and concluded that the practice should be abandoned because it was neither safe nor efficacious. An exception to the avoidance of this practice is in the use of nifedipine in the treatment of hypertension associated with autonomic dysreflexia in spinal cord injury.

Early labor

Nifedipine has been used frequently as a tocolytic (agent that delays premature labor). A Cochrane review has concluded that it has benefits over placebo or no treatment for prolongation of pregnancy. It has also benefits over beta-agonists and may also have some benefits over atosiban and magnesium sulphate, although atosiban results in fewer maternal adverse effects. No difference was found in the rate of deaths among babies around the time of birth, and data on longer-term outcomes were limited.

Other

Raynaud's phenomenon is often treated with nifedipine. A 2005 meta-analysis showed modest benefits (33% decrease in attack severity, 2.8-5 reduction in absolute number of attacks per week); it does conclude that most included studies used low doses of nifedipine.

Topical nifedipine has been shown to be as effective as topical nitrates for anal fissures.

Nifedipine is also used in high-altitude medicine to treat high altitude pulmonary oedema.

Other uses include painful spasms of the esophagus such as from cancer or tetanus. It is also used for the small subset of people with pulmonary hypertension.

Side effects

Nifedipine rapidly lowers blood pressure, and patients are commonly warned they may feel dizzy or faint after taking the first few doses. Tachycardia (fast heart rate) may occur as a reaction. These problems are much less frequent in the sustained-release preparations of nifedipine.

Extended release formulations of nifedipine should be taken on an empty stomach, and patients are warned not to consume anything containing grapefruit or grapefruit juice, as they raise blood nifedipine levels. There are several possible mechanisms, including the lowering of CYP3A4 activity.

Mechanism of action

Nifedipine is a calcium channel blocker. Although nifedipine and other dihydropyridines are commonly regarded as specific to the L-type calcium channel, they also possess nonspecific activity towards other voltage-dependent calcium channels.

Nifedipine has additionally been found to act as an antagonist of the mineralocorticoid receptor, or as an anti-mineralocorticoid.

Isradipine Medicinal Use

Isradipine is used to treat high blood pressure. Isradipine is in a class of medications called calcium channel blockers. It works by relaxing the blood vessels so your heart does not have to pump as hard.

High blood pressure is a common condition and when not treated, can cause damage to the brain, heart, blood vessels, kidneys and other parts of the body. Damage to these organs may cause heart disease, a heart attack, heart failure, stroke, kidney failure, loss of vision, and other problems. In addition to taking medication, making lifestyle changes will also help to control your blood pressure. These changes include eating a diet that is low in fat and salt, maintaining a healthy weight, exercising at least 30 minutes most days, not smoking, and using alcohol in moderation

Side effect

- Dizziness
- Nausea,
- Headache,
- Tiredness
- Flushing
- swelling of the ankles/feet

Mechanism

Isradipine is explain by calcium channel blocking activity, especially dilating effects in arterioles which reduce systemic resistance and lower blood pressure, with a small increase in resting heart rate. Although like other dihydropyridines calcium channel blockers, Isradipine has negative inotropic effects in vitro, studies conducted in intact anesthetized animals have shown that the vasodilating effect occurs at doses lower than those which affect contractility. In patients with normal ventricular function, Isradipine afterload reducing properties lead to some increase in cardiac output.

Medicinal use Candesartan

Candesartan is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Candesartan belongs to a class of drugs called angiotensin receptor blockers (ARBs). It works by relaxing blood vessels so blood can flow more easily.

This medication is also used to treat heart failure.

Side effects

The most common side effects of candesartan are:

- headache,
- dizziness,
- fatigue, abdominal discomfort,
- diarrhoea, and
- Upper respiratory infections.

Other important side effects include:

- hyperkalaemia,
- impotence,
- reduced renal function, and
- Allergic reactions.

Mechanism of action

Candesartan is a synthetic, Benz imidazole-derived angiotensin II receptor antagonist prodrug with antihypertensive activity. Candesartan selectively competes with angiotensin II for the binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle, blocking angiotensin II-mediated vasoconstriction and inducing vasodilatation. In addition, antagonism of AT1 in the adrenal gland inhibits angiotensin II-stimulated aldosterone synthesis and secretion by the adrenal cortex; sodium and water excretion increase, followed by a reduction in plasma volume and blood pressure.

Lacidipine Medicinal use

- Lacidipine is used to treat high blood pressure (hypertension).
- It is a type of medicine called a calcium channel blocker.
- It is used to relax your blood vessels so that they get wider and blood can flow through them more easily, lowering your blood pressure.
- In general this drug is used to reduce high blood pressure (hypertension), either alone or in combination with other drugs

Side effect

- Fatigue
- Ankle swelling
- Headache
- Nausea
- Oedema
- Dizziness
- Palpitations

Mechanism of action

By blocking the voltage-dependent L-type calcium channels, it prevents the transmembrane calcium influx. Normally, calcium ions serve as intracellular messengers or activators in excitable cells including vascular smooth muscles. The influx of calcium ultimately causes the excitation and depolarization of the tissues. Lacidipine inhibits the contractile function in the vascular smooth muscle and reduce blood pressure. Due to its high membrane partition coefficient, some studies suggest that Lacidipine may reach the receptor via a two-step process; it first binds and accumulates in the membrane lipid bilayer and then diffuses within the membrane to the calcium channel receptor. It is proposed that Lacidipine preferentially blocks the inactivated state of the calcium channel.

Amlodipine Medicinal Uses

Amlodipine is used with or without other medications to treat high blood pressure.
Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems.

Amlodipine belongs to a class of drugs known as calcium channel blockers. It works by relaxing blood vessels so blood can flow more easily.

Amlodipine is also used to prevent certain types of chest pain (angina). It may help to increase your ability to exercise and decrease the frequency of angina attacks. It should not be used to treat attacks of chest pain when they occur. Use other medications (such as sublingual nitro-glycerine) to relieve attacks of chest pain as directed by your doctor.

Side effect

- pounding heartbeats or fluttering in your chest;
- worsening chest pain;
- swelling in your feet or ankles;
- severe drowsiness; or
- A light-headed feeling, like you might pass out.

Common amlodipine side effects may include:

- dizziness;
- feeling tired;
- stomach pain, nausea; or
- Flushing (warmth, redness, or tingly feeling).

Mechanism of action

Amlodipine is an Angio selective calcium channel blocker and inhibits the movement of calcium ions into vascular smooth muscle cells and cardiac muscle cells which inhibits the contraction of cardiac muscle and vascular smooth muscle cells. Amlodipine inhibits calcium ion influx across cell membranes, with a greater effect on vascular smooth muscle cells. This causes vasodilation and a reduction peripheral vascular resistance, thus lowering blood pressure. Its effects on cardiac muscle also prevent excessive constriction in the coronary arteries.

Negative inotropic effects can be detected in vitro, but such effects have not been seen in intact animals at therapeutic doses. Among the two stereoisomers [R(+), S(–)], the (–) isomer has been reported to be more active than the (+) isomer. Serum calcium concentration is not affected by amlodipine. And it specifically inhibits the currents of L-typeCav1.3 channels in the zonaglomerulus of the adrenal gland.

The mechanisms by which amlodipine relieves angina are:

- Stable angina: amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, thereby lowering myocardial oxygen demand, at any given level of exercise.
- Variant angina: amlodipine blocks spasm of the coronary arteries and restores blood flow in coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A2analog in experimental animal models and in human coronary vessels in vitro.

Amlodipine has additionally been found to act as an antagonist of the mineralocorticoid receptor, or as an anti-mineralocorticoid.

Future Clinical Prospects

New generation antihypertensive drugs, new novel molecular targets and nanotechnology- based delivery system are currently in pivotal stage of preclinical trial and clinical trial and are showing positive results. Many novel molecular targets for antihypertensive are under exploratory phase and are being challenged with well-established already-existing antihypertensive therapy as far as their effectiveness is concerned. But there is still scope of improvement in therapy which can effectively control blood pressure. Nanotechnology is promising approach in resolving several constraints of antihypertensive. Targeted nanoparticle can effectively take antihypertensive to its site of action whether it is kidney, heart, or smooth muscle. Chronotherapeutic in conjunction with nanotechnology can effectively regulate the high blood pressure which can not only just modify the release pattern of drug but can also increase the bioavailability of drug. Gene silencing technology is innovative therapeutic tool which could definitely play a major role in future to treat hypertension. The challenges in gene delivery like cellular uptake and pharmacokinetics could be overcome by the use of suitable Nanocarrier. However, oral drug delivery system of siRNA is still under its infancy for hypertension. But, several researches on different disease state using siRNA technology are developing very fast from preclinical to clinical trial level. Ultimately, success of the treatment depends upon the versatility of the nanoparticulate system which can entrap a wide variety of molecule including peptides and proteins and its targeting potential apart from its stability in external environment and in physiological condition

In this review, we summarized the properties of selected Nanoparticles and the results of preclinical studies using the Nanoparticles in animal models of PAH. Drug-incorporated nanoparticles for local delivery might optimize the efficacy and minimize the side effects of drugs.

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