REVIEW ARTICLE

Advancements in Solubility and Bioavailability of Calcium Channel Blockers: A Comprehensive Review

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ABSTRACT
The present review addresses the challenges associated with the low aqueous solubility of Active Pharmaceutical Ingredients (APIs) focusing specifically on Calcium Channel Blockers (CCBs). These drugs are classified as Class II compounds in the Biopharmaceutical Classification System (BCS), characterised by high permeability but limited bioavailability. This low bioavailability constrains the therapeutic efficacy of CCBs as antihypertensive agents. Research efforts concerning solubility enhancement and modification of bioavailability of CCBs, dosage forms and their physicochemical properties pharmacokinetics are presented. This paper presents the latest updates and techniques in drug formulation, enabling researchers and formulators to develop strategies to address solubility issues and, hopefully, improve therapeutic indices in patients.
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INTRODUCTION

Active Pharmaceutical Ingredients (APIs) often exhibit low aqueous solubility despite demonstrating high permeability, underscoring the critical role of solubility in the drug discovery and development process[1]. Low solubility frequently leads to inadequate drug absorption and limited bioavailability[2], which remains a major obstacle to achieving optimal therapeutic efficacy[3]. Although advances in drug design such as combinatorial chemistry and high-throughput screening have enabled the creation of highly specific and structurally complex molecules targeting diverse biological receptors, these developments have also contributed to reduced solubility of many APIs. Consequently, researchers have adopted various formulation strategies to enhance both solubility and bioavailability. It is therefore imperative for pharmaceutical scientists and formulators to prioritize solubility considerations from the earliest stages of drug discovery to improve clinical outcomes.

The Biopharmaceutical Classification System (BCS) provides a widely accepted framework for categorizing pharmaceutical compounds based on their solubility and permeability characteristics. Within this system, Class II drugs are defined by low solubility and high permeability, properties that often result in compromised bioavailability.[4] The U.S. Food and Drug Administration (FDA) employs the BCS as a standard reference for conducting dissolution studies and evaluating in vivo bioequivalence.[5] As illustrated in Table 1, improving the aqueous solubility of Class II drugs can lead to a significant improvement in their oral bioavailability.

Among Class II drugs, Calcium Channel Blockers (CCBs) serve as a prominent example, demonstrating the challenges associated with low solubility. CCB act as inhibitors of extracellular calcium ion channels and are widely prescribed for the treatment of hypertension by promoting arterial dilation through the reduction of calcium influx into vascular smooth muscle cells, which ultimately leads to a decrease in blood pressure (BP).[6] Additionally, CCBs also have been used for treatment of chest pain and other conditions triggered by coronary artery disease. Oral administration of CCBs effectively reduces blood pressure across diverse patient populations regardless of ethnicity, race, or gender.[7] The most common subclasses of CCBs include L-type blockers, such as phenylalkylamines (e.g., verapamil), benzothiazepine (e.g., diltiazem), and dihydropiridines (e.g., isradipine). Despite their clinical efficacy, the low bioavailability of CCBs remains a major limitation to their therapeutic potential.

In this review, we comprehensively reviewed the techniques and methodologies employed to enhance the solubility and bioavailability of CCBs. Furthermore, we provide an overview of the history and discovery of CCBs, their physicochemical properties, pharmacokinetics, efficacy, and safety profiles. This study aims to offers valuable insights into formulation strategies that can enhanced improve the clinical performance of CCBs, thereby benefiting researchers and formulators in the

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pharmaceutical field.

METHODOLOGY

The authors conducted a comprehensive search using several databases, including SCOPUS, Cochrane Library, ScienceDirect, Springer, Web of Science, and PubMed, to identify related literature. A range of search terms and keywords was utilized, such as "discoveries of Calcium Channel Blockers," "pharmacokinetics," "physicochemical properties," and "methods and strategies for solubility enhancement". The scientific articles analyzed in this manuscript were published between April 2014 and September 2024, and current issues and the latest advancements concerning CCB bioavailability were thoroughly examined.

RESULTS AND DISCUSSION

Hypertension (Epidemiology)

Hypertension, commonly referred to as high blood pressure[9], is a prominent contributor to the development of cardiovascular disease (CVD), which accounts for one-third of all global deaths.[10] The American Heart Association's reports indicate that between August 2021- August 2023, prevalence of American adults aged 18 and above that had hypertension is 47% (equivalent to 122,000,000 individuals) with 77.4% of them having their blood pressure uncontrolled and not within the optimal range (i.e., 130 mm Hg systolic rate/80 mm Hg diastolic rate).[11] In Malaysia, CVD accounts for one-third of all fatalities, with a cardiovascular risk background that is higher than that of developed countries in both the West and Asia.[12] Consequently, hypertension has become a significant concern for medical practitioners and physicians, as it necessitates effective regulation, management, and awareness-raising among individuals and society as a whole.[13] Despite the various methods and treatments available to manage hypertension, it remains one of the most significant health challenges in many developed countries.

Classification and Risk Factor

Hypertension can be categorized into two main types: primary hypertension or essential hypertension, and secondary hypertension.[14] Essential hypertension is a condition defined by consistently high blood pressure caused by genetic and age-related factors. In developed countries, 25-35% of adults and 60-70% of those aged ≥ 70 years are diagnosed with essential hypertension.[15]

In contrast, secondary hypertension is typically caused by factors such as sleep apnea, familial relationships, and other underlying medical conditions. An article published in the American Journal of Hypertension 2017 reported that more than 35% of elderly patients with secondary hypertension do not achieve their targeted blood pressure levels, mostly due to the lack of early detection and treatment. Early intervention in young patients (i.e., ≤40 years) with hypertension has been shown to yield better treatment outcomes with antihypertensive drugs.[16] Additionally, age-related arterial stiffening is a significant contributor to secondary hypertension as morbidity and mortality rates increase with age.[17]

In addition to the aforementioned risk factors, sodium and potassium intake are also important factors that contribute to hypertension. Research suggests that the presence of potassium and sodium influences blood pressure through several mechanisms. Evidence from a meta-analysis indicates that reducing sodium intake lowers blood pressure. However, the scientific evidence for which contributes more to hypertension and blood pressure, potassium intake, sodium intake, or both, remains unclear.[18]

Symptoms

Hypertension, or high blood pressure often presents without symptoms and can go undiagnosed in over half of those affected. Even among those who are aware of their condition, many leave it untreated or undertreated. However, successful treatment of hypertension can significantly reduce the global burden of disease and mortality.[19] It typically takes years for hypertension to reach a level that is severe enough for symptoms to become evident that may lead to target organ damage (TOD). A hypertensive emergency is characterized by elevated blood pressure (i.e., >180/110 mmHg) accompanied by acute hypertension-induced organ damage. Patients may exhibit symptoms including dizziness, headache, chest pain, palpitations, shortness of breath, and hematuria, corresponding to the affected organs.[20] Desta et al. (2019), reported the prevalence of hypertensive emergency among hospitalized patients with hypertensive crises in Ayder Comprehensive Specialized Hospital (ACSH) from September 2018 to August 2019. The results revealed that among 141 patients experiencing hypertensive crises, 42 individuals (29.8%) were identified as having a hypertensive emergency. This highlights the necessity for careful management of hypertension, as implementing screening programs could reduce the risk of target organ damage.[21]

Additionally, individuals associated with high blood pressure may be more vulnerable to mental health issues such as depression and anxiety. Data from the National Health Interview Survey (NHIS), which included 63,985 participants from 2015 to 2018, indicated that a greater percentage of U.S. adults with hypertension reported experiencing depression compared to those without hypertension (42.9% vs. 37.5%). The findings also suggested a shared risk factor between hypertension and depression, notably stress.[22]

Treatment

The management of hypertension typically depends on its classification. For patients with primary hypertension, lifestyle modifications are recognized as the initial approach because these modifications can effectively lower blood pressure, often achieving results comparable to those obtained from a single antihypertensive medication. A notable example is the DASH (Dietary Approaches to Stop Hypertension) diet, which promotes the intake of fruits, vegetables, whole grains, and low-fat dairy products. This dietary regimen has been shown to significantly reduce blood pressure while also supporting weight management and improving metabolic health. Additionally, lifestyle changes generally result in fewer side effects compared to pharmacological treatments for hypertension.[23,24] In cases

Table 1: The biopharmaceutical drug classification system

Class	Description	Solubility	Permeability
I	High in dissolution and absorption	High	High
II	Low in dissolution but high in permeability rate	Low	High
III	Although permeability is the primary factor limiting drug absorption, these drugs exhibit rapid solvation	High	Low
IV	Have a poor bioavailability rate. Problematic for oral administration	Low	Low

of secondary hypertension, antihypertensive medications are typically prescribed if blood pressure remains elevated despite these interventions.

The prescription of antihypertensive medications often relies on a trial-and-error approach, wherein patients may need to experiment with various types and combinations of drugs until optimal blood pressure control is achieved. Antihypertensive agents are categorized according to their mechanisms of action, which include diuretics, beta blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs), alpha-2 agonists, and calcium channel blockers.[25]

Oparil et al. (2015), proposed a novel strategy for hypertension prevention that involves the use of emerging drug classes such as vasopeptidase inhibitors, soluble epoxide hydrolase inhibitors, natriuretic peptide A agonists, and aldosterone synthase agonists.[26]

Anti-hypertensive Agents

Diuretics

Diuretics, commonly referred to as water pills, rank as the second most frequently prescribed class of antihypertensive medications due to their established effectiveness in reducing blood pressure and maintaining lower morbidity and mortality rates among patients with hypertension.[27] Diuretics are used to treat conditions that impair the kidneys' ability to regulate and control the proportion of salt and water during the excretion process. By regulating the excessive amount of salt and water, diuretics stabilize blood pressure, making them effective antihypertensive medications, particularly for secondary hypertension.[28] Since the introduction of the first oral diuretic (Thiazide) in the 1950s, it has had a positive impact on hypertensive patients with acceptable side effects, providing them with a better quality of life.[29]

Diuretics can be classified into five categories: carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics, potassium-sparing diuretics, and osmotic diuretics. Each category promotes varying diuresis effects, eventually aiding in the treatment of hypertension by preventing fluid accumulation and subsequently lowering blood pressure. Diuretics have been proven beneficial, particularly for mild to moderate hypertensive patients, as they lower blood pressure significantly more than any other antihypertensive medication.[27,28] Generally, a combination of diuretics and other classes of hypertensive drugs, such as Beta blockers, CCBs, ARBs, and ACE inhibitors, are prescribed as first-line treatment for hypertension.[30]

However, the use of loop diuretics as first-line treatment for hypertension remains controversial, as they are more appropriate as secondary medications in specific conditions, such as fluid overload, fluid retention, and advanced renal failure.[31,32] Although diuretics have numerous benefits and advantages, they can also have unfavourable side effects such as dehydration, hypokalaemia, and hyperuricemia.[33] Loop diuretics have a threshold dose; if the dosage is below the appropriate level, the diuresis effect will not take place in the kidney's tubule.[32] The dosage for other diuretics, such as hydrochlorothiazide and chlorthalidone, depends on the patient and can range from 12.5 - 100 mg once daily and 500 - 1000 mg once daily, respectively.

Beta Blockers

Beta blockers, also known as adrenergic receptor antagonists, are recommended as first-line therapy for hypertension.[34] Each beta blocker is unique based on their selective adrenergic receptor and vasodilatory properties and they are categorized into first, second, and third generations. First-generation beta blockers are non-cardio selective and only inhibit epinephrine and norepinephrine from binding at β1 and β2 adrenergic receptors, while third-generation beta blockers, such as nebivolol, have vasodilatory effects that dilate arteries by stimulating endothelial nitric oxide production.[35,36] Beta blockers can be prescribed alone or alongside other blood pressure medications like diuretics and CCBs, to reduce the risk of illness and death related to hypertension. The concurrent administration of beta-blockers with non-dihydropyridine CCBs is typically discouraged due to the high risk of severe bradycardia and heart block. Research has demonstrated that diltiazem can elevate the plasma levels of propranolol by approximately 50%, while verapamil has been shown to decrease the clearance of both metoprolol and propranolol.[16]

While beta-blockers are a useful initial treatment for hypertension, improper administration can lead to serious complications. These medications are contraindicated in individuals with asthma, bradycardia, and chronic obstructive pulmonary disease (COPD), as they may worsen these conditions by obstructing airflow in the respiratory system, potentially resulting in respiratory failure.[37] Recent studies have indicated that the use of atenolol in older adults is associated with an increased risk of stroke compared to other antihypertensive agents; however, no significant change in risk has been observed for non-atenolol beta-blockers within the same demographic.[38,39] Furthermore, beta-blockers, including atenolol, have been linked to a higher incidence of atrial fibrillation when compared to losartan.[40] The appropriate dosages of beta-blockers are typically determined by healthcare providers based on individual patient characteristics such as age, sex, and specific health conditions. For instance, the recommended initial doses for metoprolol succinate and metoprolol tartrate are 25-100 mg/day and 100-450 mg/day, respectively.[41]

Angiotensin Converting Enzyme (ACE) Inhibitor

Table 2: The pharmacokinetic of calcium channel blockers

Drug	Absorption (%)	Bioavailability (%)	Time to peak (h)	Protein binding (%)	Elimination half-life (h)
Amlodipine	>90	60-65	6-12	95	35-45
Nicardipine	>90	35	1-4	>90	8.6
Felodipine ER	>99	20	2.5-5	99	10-17
Diltiazem CD	95	60-65	6-12	70-80	5-8
Isradipine CR	90-95	15-24	7-18	95	8
Nisoldipine CC	>90	5	6-12	>99	7-12
Nifedipine CC	>90	84-89	2.5-12	92-98	7
Verapamil SR	>90	20-35	5.2-7.7	>90	4.5-12
Lercanidipine	44	10-12	2-3	98	8-10

Abbreviation: SR: sustained release, CD: controlled delivery, ER: extended release, CR: controlled release, and CC: coat-core.

ACE inhibitors are widely recognized as one of the most effective antihypertensive medications that inhibit the secretion of ACE within the renin-angiotensin-aldosterone-system (RAAS). This inhibition leads to the prevention of the conversion of angiotensin I to angiotensin II, which in turn, inhibits vasoconstriction and promotes vasodilation by activating the bradykinin pathway. Consequently, water and sodium retention are reduced, leading to a reduction in blood pressure within the blood capillary.[42]

The RAAS system plays a critical role in maintaining the body's haemodynamic balance and electrolyte equilibrium. Under certain circumstances, this biological mechanism increases blood pressure and protects the body and cardiovascular system from collapsing due to hypotension, blood volume loss, and other traumatic conditions. The peptide hormone angiotensin II is essential in regulating the competence of the system, as it serves as a potent vasoconstrictor by impairing nitric oxide development in the arteries. Besides that, it also triggers the adrenal glands to release aldosterone, a hormone that enhances sodium reabsorption and potassium secretion in the kidney's tubules. Moreover, the presence of angiotensin II stimulates the release of antidiuretic hormone (ADH), leading to water reabsorption and an increase in blood volume in the capillary.[43]

Thus, the development of ACE inhibitors, which obstruct ACE secretion within RAAS, is a crucial step in regulating blood pressure, particularly among hypertensive patients. Scientists and medical practitioners have gained a more comprehensive understanding of angiotensin receptor stimulation in RAAS and the mechanism of ACE inhibitors since the introduction of oral ACE inhibitors in the 1980s.[44] Recent guidelines issued by the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) recommend the use of angiotensin-converting enzyme (ACE) inhibitors as a first-line antihypertensive therapy. This recommendation is particularly emphasized for patients with diabetes mellitus and those with cardiovascular diseases, reflecting the established efficacy of ACE inhibitors in these populations.[16,45]

The Antihypertensive and Lipid Lowering Trial in Heart Attack Trial (ALLHAT) also recommended the use of ACE inhibitors as initial therapy, either alone or in combination with thiazide diuretics.[46] However, ACE inhibitors have some disadvantages, such as the presence of alternative non-ACE pathways that can lead to the residual production of angiotensin II. Furthermore, blocking ACE can lead to excessive bradykinin levels, which can contribute to angioedema. This is due to the decreased proportion of angiotensin II, which is responsible for converting bradykinin into an inactive peptide.[43,47] Another adverse effect of ACE inhibitors is a dry cough, which is observed with most ACE inhibitors. Medical practitioners should be cautious in recognizing this side effect, as failure to do so can lead to unnecessary diagnostic tests, evaluation, and mistreatment of patients.[47]

Angiotensin receptor blocker (ARB)s and ACE inhibitors are two classes of RAAS inhibitors that act on the RAAS through a common mechanism.While they are believed to have similar outcomes in terms of mortality and morbidity reduction in hypertension, there is currently no solid evidence to indicate which is better.[48] Nevertheless, both ARBs and ACE inhibitors are considered vital in the treatment of hypertension, as they act on the RAAS and help control blood pressure.[48]

Angiotensin Receptor Blocker (ARB)

ARBs are antihypertensive medications that act in the renin-RAAS and are recommended by most national guidelines as initial or add-on medication for hypertension. ARBs inhibit the interaction of angiotensin II with angiotensin II type 1 receptors (AT1)[49] and have demonstrated positive outcomes in terms of hypertension modulation, when administered with other antihypertensive medications such as CCBs and thiazide diuretics. ARBs were developed with the aims to manifest the same medication properties as ACE inhibitors while overcoming certain adverse effects associated with ACE inhibitor, including the accumulation of bradykinin and tachykinin. This is due to the mechanism of action of ARBs, which does not involve the accumulation of bradykinin and tachykinin, as they could potentially lead to dry cough and angioedema.[50] In addition, ARBs have also been widely recognized for their effectiveness in the treatment of heart failure, diabetic nephropathy, and other cardiovascular diseases.[51] The blockade of AT1 receptors by ARBs leads to angiotensin II to bind to angiotensin II type 2 receptors (AT2), which shows contradictory outcomes compared to AT1 activation (e.g., vasodilation). However, to date, the clinical consequences of AT2 activation have not been

Table 3: The solubility enhancement of calcium channel blockers

Authors	Result Summary	References
Chaudhary et al., 2023	Nifedipine release was enhanced by the BPSF formulation, which achieved almost 70% drug release in 30 minutes as opposed to only 11% for control tablets.	[80]
Grewal et al., 2023	The crystalline structure of nifedipine was preserved while its dissolving characteristics were greatly enhanced by reducing its particle size.	[86]
Hamzah et al., 2022	An optimized microemulsion achieved a higher solubility of 112.54 mg/ml, whereas a solid dispersion with a 1:4 drug:polymer ratio had a solubility of 96.97 mg/ml.	[81]
Sarker & Rafe, 2021	Nanocrystal technology enhanced the solubility of nifedipine and other BCS class II and IV medications by generating 100% active pharmaceutical ingredient (API) particles, which increased dissolution rates.	[84]
Gaidhani et al., 2021	The supercritical precipitation (SAS) method achieved 90% drug release while maintaining a consistent particle size, but the conventional solvent evaporation (CSE) method only managed 11% release over the same period.	[82]
Alhagiesa & Ghareeb, 2021	The study demonstrated a significant increase in nimodipine solubility, achieving up to a 24-fold enhancement with complete dissolution in 90 minutes, compared to only 6% for pure nimodipine.	[87]
Mbah et al., 2018	The drug's maximum plasma concentration (Cmax) rose in response to glycerol and propylene glycol, suggesting improved solubility compared to controls.	[83]
Junyaprasert & Morakul, 2015	Drug solubility was improved by decreasing particle size, emphasizing the function of stabilizers and better drug distribution.	[85]

thoroughly explained by physicians and medical practitioners.

Angiotensin II receptor blockers (ARBs) offer a range of critical therapeutic benefits, particularly for patients with hypertension. Among these, telmisartan is noteworthy for its cardioprotective properties and is specifically indicated for reducing cardiovascular disease in patients with established atherothrombotic CVD. Clinical study has shown that telmisartan provides a comparable reduction in the composite endpoint of cardiovascular death, myocardial infarction (MI), stroke, and hospitalization due to heart failure when compared to the active comparator, ramipril. This conclusion is supported by findings from recent study, which, although it did not achieve its primary composite endpoint, demonstrated that telmisartan significantly lowered hospitalizations for cardiovascular reasons and reduced left ventricular hypertrophy. Furthermore, patients receiving telmisartan experienced fewer instances of combined macrovascular and microvascular events, as well as microalbuminuria.[52]

However, medical practitioners and researchers should pay crucial attention to several adverse effects that could be fatal to patients, such as mild headache, dizziness, mild increases in serum potassium and creatinine levels. Additionally, the intake of ARBs is not suitable for pregnant patients as it could have fatal adverse effects on the infant.[53] Therefore, it is essential for medical practitioners to carefully indicate a suitable dosage for patients before prescribing ARBs for the first time. Currently, eight types of ARBs have been widely commercialized, including losartan, candesartan, eprosartan, irbesartan, telmisartan, valsartan, olmesartan, and azilsartan.[54] Each type of ARBs has varying dosages, and some are more potent than others despite having a lower proportion. For example, candesartan cilexitil reduces a greater number of blood pressure for a lower amount of dosage (i.e., 16 and 32 mg per day) compared to losartan (i.e., 50 and 100 mg per day).[55]

Alpha-2 Agonist

There are generally two types of alpha agonists, namely alpha-1 (α-1) agonists and alpha-2 (α-2) agonists.[56] Alpha-2 agonists are categorized as selective direct-acting agonists that stimulate the α2 adrenergic receptor, activating inhibitory neurons and resulting in a significant reduction of central nervous system sympathetic outflow. This reduction decreases peripheral vascular resistance and subsequently reduces heart rate and blood pressure.[57] Alpha-2 agonists are among the adrenergic agonists recognized as potent antihypertensive medications. The intake of α-2 agonists, such as clonidine and guanfacine, has been proven to significantly reduce blood pressure either alone or in combination with a diuretic.[58]

One of the most common α-2 agonist drugs is clonidine. Although initially used for the treatment of nasal congestion, it is now used as an antihypertensive drug due to its ability to reduce systemic blood pressure through adrenergic stimulation. Moreover, clonidine can be administered orally and may also be used to treat attention-deficit hyperactivity disorder (ADHD).[56]

Calcium Channel Blocker

CCB is one of the most preferred antihypertensive medications for reducing blood pressure and vascular volume.[59] Usually, most CCBs can be easily differentiated from one another by considering their tissue specificity, ion selectivity, and chemical properties. Nonetheless, they all share the same pharmacological properties of inhibiting the influx of extracellular calcium ions through either ion-selective or voltage-gated channels.[60]

In 1883, Sidney et al. discovered the pivotal role of calcium in muscle contraction. In 1901, Stiles concluded that calcium and sodium ions are necessary for maintaining rhythmic contractions in a frog's esophagus. Around 60 years later, interest in intercellular calcium properties was

raised by Kamada (Japan) and Heilbrun (USA) in the 1940s, who discovered the role of intracellular calcium in muscle contraction. In 1961, Ebashi successfully proved the correlation of calcium in the contraction of the Actomyosin-system by demonstrating the relaxation state of the muscle in the presence of EDTA. Additional studies by Fabiato (1977 and 1979) and Winegrad and Shanes (1962) confirmed the importance of calcium in muscle contraction and the effect of the influx of extracellular calcium ions in the Actomyosin system.[9] The term "calcium antagonist" was not widely used until the early 1960s, when Godfraind analyzed substances with multiple properties, such as coronary dilators and angina pectoris treatments. The first series of coronary dilators identified included lidoflazine, which consisted of diltiazem, nifedipine, and verapamil.[61] In 1969, Fleckenstein and colleagues conducted an experiment on coronary vasodilators, which indicated significant properties for inhibiting calcium ion influx intracellularly. These properties contributed to the establishment of a new class of drugs called "Calcium Antagonists" or "Calcium Channel Blockers".[9] Experimental work on the screening of coronary dilators in the 1960s and 1970s became the integral factor leading to further understanding of the calcium-blocking mechanism and the role of calcium in the Actomyosin system.[61]

In the 80s, calcium antagonists were widely approved as a predominant hypertension medication driven primarily by their efficacy in lowering blood pressure and their low incidence of side effects. Calcium antagonists have also been extensively used to treat other diseases, such as Raynaud's phenomenon, cerebral vasospasm, and hypertrophic cardiomyopathy, among others. The development of CCBs has been viewed progressively for years to come, and several new drugs have been developed, such as felodipine control release and isradipine.[62] In the 1990s, the first T-type CCB, mibefradil, which was related to verapamil, showed compromising pharmacological effects and was widely commercialized in 1997. CCBs are extensively used because of their potent effect in lowering blood pressure and managing cardiovascular diseases.[9] Currently, researchers and medical practitioners are still developing new methods and types of CCBs to improve their efficacy. One of the latest developments in CCBs is the discovery of new L-type CCBs in the application of inflammation and neurodegenerative diseases, including Alzheimer's and Parkinson's disease.[62]

Types of Calcium Channel Blocker

CCBs consist of two subclasses: dihydropyridines and non-dihydropyridines. Despite their common mechanism of action, these subclasses bind and work at specific and unique locations.[63] Dihydropyridines are generally more effective as vasodilators than non-dihydropyridine (non-DHP) agents, though non-DHPs exhibit greater negative inotropic effects. Both subclasses are equally effective at lowering blood pressure, with non-DHPs offering potential benefits for patients with chronic kidney disease and diabetic nephropathy.[64] Dihydropyridines are preferred for managing CVD. Since their introduction in the 1960s, they have undergone significant improvement to optimize their efficacy and safety leading to the development of four generations of these drugs.

Nicardipine and nifedipine, which belong to the first generation of drugs, are known for their effectiveness in hypertension treatment, but their quick onset and short duration can result in a higher incidence of side effects[65] Second-generation dihydropyridines, such as benidipine and efonidipine, provide a slow-release and short-acting action, leading to better control of therapeutic effect and reduced adverse effects.[66] Third-generation dihydropyridines, such as amlodipine and azelnidipine, are usually more stable in terms of their pharmacokinetics, less cardio-selective, and better tolerated in patients with heart failure.[67] Fourth-generation dihydropyridines, such as lercanidipine and clinidipine, are highly lipophilic and offer a greater degree of reduction in adverse effects, broad therapeutic spectrum, and potential benefits in myocardial ischemia and congestive heart failure.[68] Headache, flushing, or reflex tachycardia are common symptoms associated with these drugs. Indications for dihydropyridines include arterial hypertension, angina pectoris, or Raynaud phenomenon.[69]

Phenylalkylamines, such as verapamil and gallopamil, have a strong myocardial depressant effect and a moderate vasodilator effect, but they are less potent than dihydropyridines [70]. Both classes can cause bradycardia, gingival hyperplasia, and even atrioventricular block. These medications are typically prescribed for arterial hypertension, supraventricular tachyarrhythmias, and angina pectoris.[70]

Chemical Properties

Calcium channel blockers are classified based on their selectivity towards voltage-gated Ca2+ channels in the vascular smooth muscle, chemical class, receptor binding affinity, structure, and lipophilicity.[71]

There are four subunits in voltage-gated calcium channels: a1, a2-d, b, and g. The a1 subunit is the most dominant, forming the pore structure for ion conduction. There are ten different a1 subunits with different ion conductance and distribution, which determine the channel properties of L-, N-, T-, P-, Q-, and R-type calcium channels.[71] Among these channels, L-type calcium channels are the preferred targets of CCBs. CCBs can be grouped into three subgroups: benzothiazepines (e.g., diltiazem and clenazem), dihydropyridines (e.g., nifedipine, nicardipine, felodipine), and phenylalkylamines (e.g., verapamil and gallopamil). Each of these classes has different chemical structures, causing heterogeneity in their actions.

Nakayama et al. (1996) showed that CCBs prevent calcium influx by binding to the a1 subunit, preventing cell excitability, and inhibiting calcium currents through L-type calcium channels.[9] Although the biochemical and therapeutic effects differ, the CCB binding sites are located on the alpha subunit of the oligomeric assembly that forms the voltage-gated calcium channel. The binding site of 1.4-dihydropyridines is also a target for a cluster of experimental drugs known as calcium channel activators. Although they have a similar structure to nifedipine, these drugs have completely different properties, such as opening calcium channels and having positive inotropic and vasoconstrictive effects.[72] Additionally, they possess

vasodilation properties, which can cause cardiac activation. Although nifedipine belongs to the dihydropyridine class, it can also cause cardio depression, limiting its use in patients with severe left ventricular dysfunction. Verapamil and, to a lesser extent, diltiazem both have vasodilation and cardiac depressant properties at therapeutic doses. In a normally functioning ventricle, this myocardial depressant effect is neutralized by a reduction in afterload.

Mechanism of Action

All CCBs act as vasodilators, meaning they have the same goal of reducing blood pressure. Much has been learned about the pharmacodynamic effects of calcium antagonists, and they have a broad spectrum of therapeutic applications, such as the following:

Anti-arrhythmic Action

When administered intravenously, CCBs have demonstrated effective treatment of paroxysmal re-entrant supraventricular tachycardia (PSVT) in most cases, a disorder characterized by an irregular, fast heartbeat that can start and stop abruptly. When CCBs are administered intravenously, the ventricular rate will slow down in atrial flutter and fibrillation, with an exception of converting to a sinus rhythm, especially if the arrhythmias are short-lived and the heart size is small.[73] Furthermore, oral verapamil is effective in reducing the response of the ventricle during resting periods and exercise in atrial flutter and fibrillation. They are also a great alternative to β-adrenoceptor blockers and digoxin.[74]

Vasodilator Properties

When administered orally or intravenously to hypertensive patients, CCBs effectively reduce systemic vascular resistance while increasing cardiac output, and stroke volume index, making them useful in the treatment of hypertensive emergencies with or without encephalopathy. Notably, dihydropyridines have shown efficacy in most cases. Several studies, including many blinded and placebo-controlled trials, have demonstrated that verapamil, nifedipine, and diltiazem can be as potent as diuretics in controlling mild to moderate systemic hypertension.[75] While there may not be a significant difference in efficacy among the agents, the rapid onset of action and potent vasodilator properties of dihydropyridines are advantageous in hypertensive emergencies compared to other CCBs.

Coronary Artery Spasm (CAS)

Huang et al. (2023) stated that, stable angina can result from coronary vasospasm, which can be prevented by CCBs.[76] The study stated that patients with coronary atherosclerosis and stable angina show signs of coronary vasoconstriction, which can be abolished by nifedipine. In addition, CCBs may play a role in angina amelioration, as demonstrated by a study showing that nifedipine increases myocardial perfusion in partially obstructed vessels. Nifedipine also prevents the elevation of left-ventricular end-diastolic pressure in patients with chronic stable angina. Under all these circumstances, CCBs can relieve pulmonary congestion symptoms by lowering ventricular diastolic pressure and stop tachycardia-induced angina by improving subendocardial perfusion. Therefore, CCB are considered the primary treatment for coronary artery spasm (CAS), and if CAS remains inadequately managed with CCB, long-acting nitrates or nicorandil may be employed as a secondary treatment.[77]

Pharmacokinetics

CCBs are nearly completely absorbed via oral administration. However, their bioavailability may be affected by first-pass metabolism by the liver. The reported bioavailability values vary between CCBs, with nifedipine having the highest value (50-60%), followed by diltiazem (40%), and verapamil (20-30%). Nifedipine, diltiazem, and verapamil exhibit high protein binding scores, with a value of 90% or more. The elimination half-life of these drugs is short, ranging from 3-6 hours, except for verapamil, which has a longer elimination half-life with long-term administration.

The total body clearance values for all CCBs range from 0.5-1L/h/kg. Nicardipine and amlodipine have lower clearance values. The volumes of distribution are also different among CCBs, with nifedipine ranging from 1-2L/kg, verapamil from 2.4-6.2L/kg and amlodipine at 21.4/L.kg. In healthy individuals, amlodipine is eliminated with a half-life of around 34 hours. The bioavailability of all CCBs is generally low, with amlodipine having the highest percentage at 64%, while the others range from 10% to 40%.[78] The newer CCB agents have high plasma protein binding, exceeding 90%. While they have a low bioavailability similar to older generations, studies using radioisotopes have found that they are better absorbed. However, due to the relationship between plasma concentration and effect, the newer agents only require twice-daily administration compared to the older generations' 3-4 times daily.[68] Amlodipine can be dosed once daily because of its prolonged elimination half-life, while nisoldipine needs to be administered several times daily due to its short half-life. Details and a summary of pharmacokinetic data for all calcium channel blockers are summarized in Table 2.

Solubility Issues

CCBs are one of the hypertensive drugs and their effectiveness in drug delivery is crucial. However, poor solubility of these drugs is a minor setback. Drugs with poor solubility can have an impact on absorption and bioavailability upon administration, preventing them from reaching the minimum effective concentration needed to exhibit therapeutic action. Poor solubility can also lead to difficulties in formulation leading to a slow onset of action, inconsistent dosing effects, and undesirable side effects, leading to reduced patient compliance towards the medication.

According to Resztak et al (2024), poor solubility of drugs depends on variables such as drug partition coefficient (Log p).[79] Drugs with a Log P value greater than 3 are considered poorly soluble, and this can be observed in CCBs such as verapamil and amlodipine. To facilitate absorption, drugs must be in a water-soluble state at the site where they are absorbed. In addition, first-pass metabolism can contribute to poor drug metabolism, leading to poor absorption and low drug bioavailability. The importance of solubility extends to parenteral formulations, where achieving the right drug concentration in the bloodstream is essential for

therapeutic effectiveness. Poorly soluble drugs often require larger doses to achieve therapeutic levels in the plasma after oral administration, underscoring the challenges of enhancing solubility in oral drug delivery systems.

Solubility enhancement strategies

A study was conducted to enhance the solubility of nifedipine through its dissolution in biodegradable porous starch foam (BPSF). The dissolution profile of the nifedipine/BPSF formulation was analyzed, revealing an immediate release of nifedipine from the BPSF tablets. Notably, the formulation with a nifedipine to BPSF ratio of 1:10 achieved approximately 70% drug release within 30 minutes, in contrast to the control nifedipine tablets, which exhibited only 11% drug release during the same timeframe.[80] Other methods such as, solvent evaporation method & microemulsion technique was used to enhance solubility of CCBs particularly amlodipine besylate. Hamzah et al. (2022)[81] observed that a solid dispersion (SD) with a drug: polymer ratio of 1:4 attained the maximum solubility of 96.97 mg/ml ± 0.92, while the solubility of the optimized microemulsion was determined to be 112.54 mg/ml ± 0.92. The solubility and rate of dissolution of SDs in the solvent evaporation method increase with the drug: polymer ratio. Amlodipine besylate's solubility was thus greatly increased by the two approaches; nevertheless, the microemulsion technique had a superior solubility profile.[81] Solid dispersions (SD) have been used to increase solubility, with the solvent or co-precipitation method being the preferred technique. This involves co-dissolving the carrier and solute in a volatile alcohol-based solvent, followed by solvent removal (evaporation or freeze-drying) to generate an amorphous phase dispersed in a crystalline carrier. Gaidhani et al. (2021) reported that the SD produced by supercritical precipitation (SAS) method maintained consistent particle size for six hours due to enhance solubility, whereas those from the conventional solvent evaporation (CSE) showed an increased in particle size within an hour of dispersion in distilled water. Furthermore, the SAS-prepared SDs achieved a 90% dissolution rate within 2 hours, highlighting its potential application.[82]

Co-solvency is another successful approach for increasing drug solubility, and is achieved using a mixture of water and compatible solvents that are miscible with water. Commonly used co-solvents include propylene glycol, ethanol, and PEG 300. Co-solvent formulations can be administered orally or parenterally. However, a dilution step with an aqueous media may be required before parenteral administration. Co-solvents can also be used in combination with other solubilization methods, and pH adjustment may also be applied. The most commonly used parenteral cosolvents are ethanol, glycerin, dimethyl sulfoxide, and polyethylene glycol, which are less toxic. Mbah et al. (2018) discovered that glycerol and propylene glycol increased the maximum plasma concentration (Cmax) compared to the control, indicating improved drug solubility. Cmax refers to the highest concentration of a drug measured in the blood, cerebrospinal fluids, or tissues post-dosing.[83]

Nanocrystal technology represents a promising strategy for enhancing solubility. Nanocrystals consist of particles that are 100% API, devoid of any carriers, and form an ultrafine dispersion (nanosuspension) in liquid media. Despite their name, nanocrystals can exist in both crystalline and amorphous states. Upon administration, formulation particles in the nanorange are released, providing numerous advantages, such as rapid dissolution, increased kinetic saturation solubility, and biological membrane adhesion. This technique is effective for delivering BCS class II and IV drugs, as exemplified by the conversion of nifedipine, a class II drug, into nanoparticles.[84] This method is relatively straightforward for reducing particle size, and its broad applicability depends on drug hardness and stabilizer utilization.[85] Initially, the drug size distribution and particle size were optimized. After water removal, nanoparticles were characterized for size, redispersion, and morphology. Furthermore, dissolution characteristics and saturation solubility were compared to un-milled commercial nifedipine to confirm the hypothesis that increasing the surface area improves drug performance. The crystalline structure was analyzed before and after particle size reduction using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to assess potential amorphous transformation during homogenization. The results showed no changed in the crystalline structure after size reduction, while the dissolution properties were significantly enhanced compared to the commercial formulation.[86] This finding is also relevant for the long-term stability of nifedipine formulations.

A recent study by Alhagiesa et al. (2021) also showed a significant improvement in the solubility of the CCB nimodipine, which is classified as a class II drug characterized by low solubility and high permeability. The results indicated a remarkable increase in saturation solubility, achieving up to 24-fold enhancement, with complete dissolution occurring within 90 minutes. In contrast, pure nimodipine only reached a 6% dissolution at the same time point. These results highlight the substantial influence of nanoparticle formulations on improving the solubility of CCBs.[87] The summary of the solubility enhancement of CCBs is presented in Table 3.

CONCLUSION

In summary, this review demonstrates that CCBs are effective for hypertension management and mitigating its common complications such as coronary artery disease, heart failure, and stroke. However, certain CCBs, such as verapamil, nifedipine, and diltiazem, exhibit pharmacokinetic properties that limit their efficacy, such as being highly lipophilic, poorly soluble, and having a large volume distribution, as well as being primarily cleared through metabolism and susceptible to first-pass metabolism, which can impact their bioavailability. Consequently, various strategies, including solid dispersions, cosolvency, and nanocrystals, have been explored to enhance the solubility of CCBs and improve their effectiveness. Overall, these methods have demonstrated promising results in increasing the solubility of CCBs, indicating their potential to improve therapeutic outcomes.

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