IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
June 2024 Vol.:27, Issue:6

Combination Drug Treatment for Hypertension: The Essential Need of Current Time

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Mital Patel*[1], Piyush Patel[2]

[1]*Department of Pharmaceutics and Pharmaceutical Technology, L M College of Pharmacy, Ahmedabad - 380009, Gujarat, India.*

[2]*Chemical Engineering Department, L D College of Engineering, Ahmedabad -380015, Gujarat, India.*

Submitted: 22 May 2024
Accepted: 28 May 2024
Published: 30 June 2024

HUMAN JOURNALS
ijsrm.humanjournals.com

Keywords: Combination therapy, Hypertension treatment, fixed-dose combination

ABSTRACT

Elevated blood pressure remains the foremost cause of death globally. Hypertension is considered the top health-related factor in the world leading to mortality. Nowadays with the use of single-drug therapy, it is difficult to attain normal blood pressure though a higher dose of a single drug generally leads to some severe side effects. Specifically, for patients having co-morbidities. It has led to the formation of combination therapy as a solution for patients who have failed to reduce blood pressure with single-drug therapy or who have co-morbidities. The rationale behind this concept remains persistent as Fixed-dose combination therapy effectively lowers blood pressure because of two drugs, each specifically working by a different mechanism on a different site and blocking different effector pathways in a single dosing unit. With the added advantage the further added drug may work on a counter-regulatory system. This review article gives an outline regarding the current trend of combination drug treatment, how it can become beneficial to society, various advantages of fixed-dose combinations, preferred combinations, and various research that is carried out for the formulation and development of fixed-dose combinations.

1. Introduction to hypertension

Hypertension is the most common worldwide disease affecting humans (1). It is the most frequently diagnosed medical condition in the United States (2) and it is also the top health-related issue in India (3). It is related to leading risk factors for stroke, coronary artery disease, myocardial infarction, vascular disease, heart failure, renal failure, and death (2).

According to the "American Heart Association (AHA), approximately 86 million adults (34%) in the United States are affected by hypertension." (1). In India Hypertension contribute to mortality and the problem of disease. annually it leads to an estimated 1.6 million deaths. It is considered the non-communicable disease that is most common in India. The cause behind this could be the collective percentage of elderly people, a sedentary lifestyle, obesity, high level of salt intake, and alcohol and tobacco consumption. Another major lack is with lack of awareness of the disease and a low level of screening of the patient (3) (4).

Based on the Seventh Report recommendations of the "Joint National Committee on Detection, Prevention, Evaluation in addition to Treatment for High Blood Pressure (JNC 7)", the BP classification for adults aged 18 years or older has been given as follows (1).

Table 1: Classification of Blood Pressure

Classification of BP	**Systolic**	**Diastolic**
Normal BP	< 120 mm Hg	< 80 mm Hg
Prehypertension Stage	120 mm Hg to 139 mm Hg	80 mm Hg to 89 mm Hg
Stage 1 of High BP	140 mm Hg to 159 mm Hg	90 mm Hg to 99 mm Hg
Stage 2 of High BP	≥ 160 mm Hg	≥ 100 mm Hg

2. Treatment of hypertension

Lifestyle modification plays a vital role in the management of hypertension. Not only medication but along with that the physician should also consult the patients for lifestyle modification and diet control. Which leads to better and speedy control over the management of hypertension.

2.1 Nonpharmacologic therapy for hypertension

"International Society of Hypertension 2020" in a "Global Hypertension Practice Guidelines" well suggested the modification of lifestyle (5), which covers the following aspects as part of Nonpharmacologic therapy for hypertension.

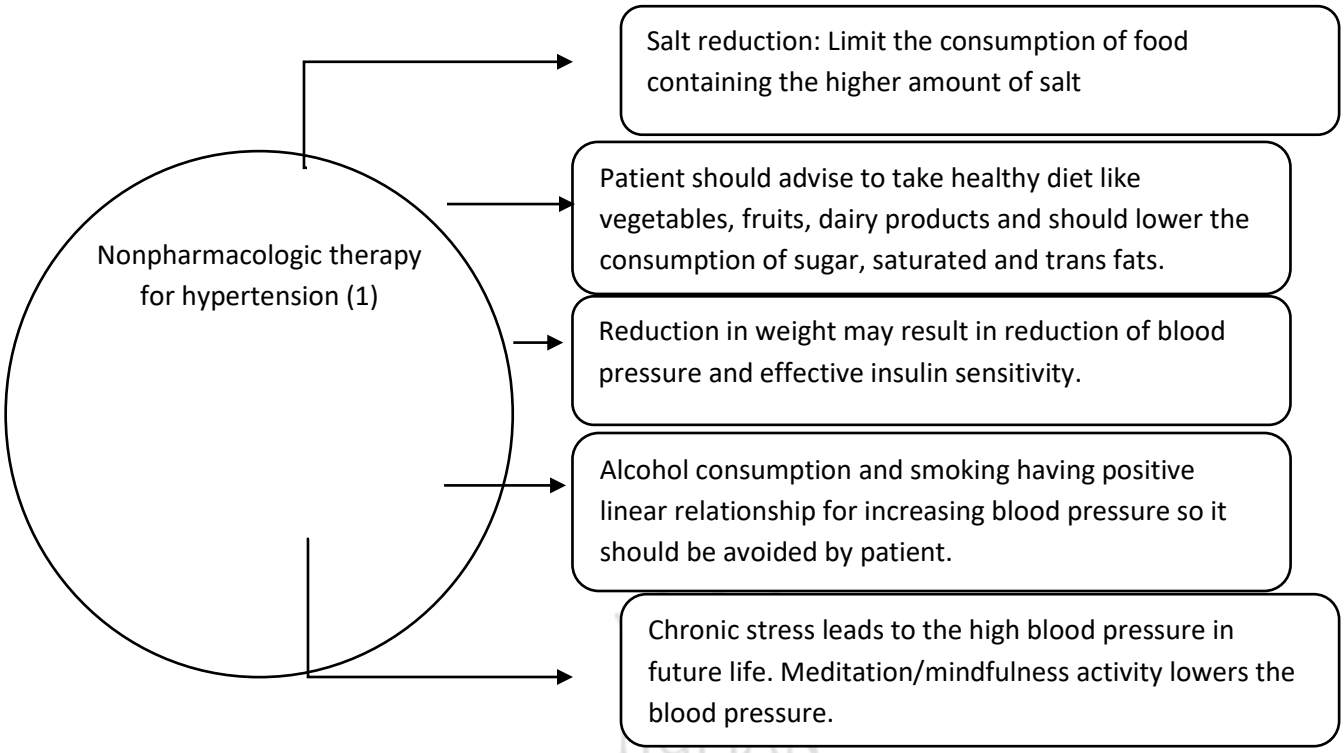

Figure 1: Nonpharmacologic therapy for hypertension

2.2 Pharmacologic Therapy for Hypertension

If the target blood pressure is difficult to achieve with the modification in the lifestyle of the patient having a pre-hypertensive stage and patient having stage 1 and stage 2 hypertension it becomes necessary to go with a pharmacologic therapy to achieve the blood pressure within the limit.

There are many therapeutic agents are available that are used for the treatment of hypertension. "The Joint National Committee (JNC 7)" recommended the seventh report for the prevention, recognition as well evaluation of High Blood Pressure for stage 1 hypertension with a thiazide-type diuretic. Alternative therapies include drugs such as calcium channel blockers (CCBs), angiotensin-receptor blockers (ARBs), beta-blockers, angiotensin-converting enzyme inhibitors

(ACEIs), and diuretics. All the mentioned drugs are quite similar in effectiveness with each other depending upon patient-to-patient variability (1).

There are many complex physiological systems are there for controlling hypertension amongst which a central role is played by the renin-angiotensin system. All of the available antihypertensive drugs have mechanisms related to that work on this system. other than this beta blocker works through a separate mechanism like reducing cardiac output and heart rate in the central nervous system. (6).

The below table-2 summarizes the different medications available for the management of hypertension (1)(7).

Table 2: Different medications available for the management of hypertension

Class	Mechanism	Drug	Side effects
Thiazide Diuretics	It primarily inhibits sodium chloride reabsorption in the distal tubules. They also increase potassium and bicarbonate excretion while decreasing calcium and uric acid retention.	Hydrochlorothiazide, Chlorthalidone, Metolazone, Indapamide	Headache, Fainting, Dizziness, Frequent urination, Upset stomach
Potassium-Sparing Diuretics	It reduces potassium secretion by interfering with sodium reabsorption at the region of distal tubules (mainly in the collecting duct region of the nephron).	Triamterene, Amiloride	
Loop Diuretics	It inhibits sodium chloride reabsorption by acting on the ascending limb of the loop of Henle. Because loop diuretics are highly protein-bound, they	Furosemide, Torsemide, Bumetanide.	

	enter the urine primarily through tubular secretion in the proximal tubule rather than glomerular filtration.		
ACEIs	ACEIs appear to work primarily by inhibiting the renin-angiotensin-aldosterone system. By inhibiting ACE, ACEIs prevent the conversion of angiotensin I to angiotensin II and block the major pathway of bradykinin deterioration.	Fosinopril, Captopril, Ramipril, Enalapril, Lisinopril, Quinapril	Headache, Cough, Feeling tired, Problems sleeping, Dizziness,
ARBs	This class of drug is generally preferred for those patients who are not able to tolerate ACE inhibitors. They completely prevent the binding of angiotensin-II to angiotensin-I leading to the reduction of sodium retention, aldosterone release, and vasoconstriction.	Losartan, Valsartan, Olmesartan, Eprosartan, Azilsartan	Dizziness, Sore throat, Heartburn, Cough, Headache, Sinus problems, Diarrhea, Back pain
Beta-Blockers, Beta-1 Selective	They only block beta-1 receptors alone. So, it is not specifically suggested for the treatment of hypertension as a first-line treatment.	Atenolol, Metoprolol, Propranolol, Bisoprolol, Timolol	Constipation or Diarrhea, Feeling tired, Upset stomach, Dizziness, Feeling lightheaded, Headache,
Beta-Blockers, Alpha Activity	This class of drug work by antagonism of alpha-1receptor with the addition of beta receptors	Labetalol, Carvedilol	
Beta-Blockers, Intrinsic Sympathomimetic	This class of drug is generally used with other anti-hypertensive agents as they	Acebutolol, Pindolol	

	possess inherent sympathomimetic activity.		
Vasodilators	They decrease blood pressure by relaxing the blood vessels.	Hydralazine, Minoxidil	Dizziness, Upset stomach, Growth in body hair
Calcium Channel Blockers	They are two types dihydropyridines and non-dihydropyridines. vasodilatation and a decrease in blood pressure in a vascular smooth muscle observed as a result of Dihydropyridines binding to L-type calcium channels.	Nifedipine, Clevidipine, Amlodipine, Felodipine, Diltiazem	Headache, feeling flushed (warm), Feeling drowsy, Upset stomach, Ankle swelling,
Aldosterone Antagonists, Selective	Reduction in sodium reabsorption and blood pressure is a result of these antagonists competing with aldosterone receptor sites.	Eplerenone, Spironolactone	Frequent urination, Dizziness, Fainting, Headache, Upset stomach
Alpha2-agonists, Central-acting	This agent reduces sympathetic nervous activity by stimulating presynaptic alpha2-adrenergic receptors in the brain stem,	Methyldopa, Clonidine, Guanfacine	Dry eyes, Dry mouth, Changes in vision, Dizziness, Mild skin rash, Decreased sexual ability,

			Headache, Feeling drowsy or tired
Inhibitors of renin	Renin inhibitors have an additive effect when used with diuretics. they act on the renin-angiotensin system which is important for the maintenance of electrolyte homeostasis and blood pressure.	Aliskiren	Cough, Diarrhea, Feeling light-headed, Abdominal pain, Acid reflux, Rash, Upset stomach,
Alpha-Blockers, Antihypertensives	They are responsible for the dilation of arterioles and veins by blocking postsynaptic alpha1 -adrenergic receptors which results in lowering blood pressure.	Prazosin, Terazosin, Doxazosin	Vision problems, Dizziness, Feeling tired, Feeling light-headed, Decreased sexual ability
Antihypertensives, Other Class	It is generally preferred for mild hypertension which is a peripherally acting adrenergic agent.	Reserpine	Bradycardia, Depression

3. Limitations of Single drug treatment

Since the 1980s, it has been recognized that single-drug therapy does not attain BP targets in most hypertensive patients, especially those who have stage 2 hypertension and those who have

comorbid conditions such as diabetes or renal insufficiency. Most patients require two antihypertensive medications from different classes to attain blood pressure control. (8).

The goals of antihypertensive therapy include optimal lessening of blood pressure (BP). for some patients with monotherapy, it is problematic to reach the target blood pressure (8). The following can be considered as the major limitations of the single drug treatment (9).

- If a single agent is used to attain target blood pressure then it is required in a higher dose.
- The higher dose of a single agent leads to severe side effects.
- It leads to the higher cost.
- It will lead to patient inconvenience and compliance, specifically for geriatric patients who need to take multiple medications.

For patients who are having mild hypertension or stage 1, hypertension single-drug treatment can be sufficient. But as the complexity of the disease increases like stage 2 hypertension or other comorbidities then the addition of further medication becomes necessary. It is better to use two different medications in a smaller amount than using a single agent in a higher dose to avoid its side effects (1). The development of a combination drug formulation is in higher demand for more effective control of high blood pressure. Many guidelines also in a way to support strategy to formulate the same (10). Combination drug formulation can become a solution for the problem that is faced by using a monotherapy to achieve target blood pressure(11).

4. Why combination drug therapy is essential at the current time?

In critical conditions hypertension, it can lead to deteriorating effects on different organs like the heart, kidney, and blood vessels. To prevent this condition combination drug therapy is essential as compared to monotherapy (12). When two or more different active pharmaceutical ingredients (which are having different modes of action) are combined in a single drug formulation then it is referred to as a fixed-dose combination. Which is more effective and more advantageous than single-drug therapy (13) There are various benefits to the new approach therapy of a combination

drug or a single pill fixed-dose formulation for the management of hypertension which can be recognized as below,

- Better effect

As there is more effectiveness and safety of using combination drug products it is preferred for long years to provide more effective management of the disease (13). If different classes of drugs are used to formulate combination drug formulations which are having different mechanisms of action and the capability to overcome each other's side effects then this type of formulation may responsible for providing synergistic effects(9). It is because the different classes of drug work by different mechanisms of action and can be responsible for blocking counter-regulatory mechanisms. Which leads to an improved and rapid antihypertensive effect rather than if we use a single drug in a higher dose (14).

- Fewer side effects

Anything which is in an excess amount is harmful. A similar thing can be compared with the consumption of a drug in a higher dose which can be responsible for the generation of side effects. by formulating a combination formulation, we can reduce the dose of individual drugs. As there is a low dose of individual components is there, the minimum chance of side effects is there with the improved antihypertensive effects. (15) by using lower doses there is lesser evidence of observed adverse effects (14).

- Convenience and compliance

The elderly patient generally needs multiple medications because of disease complexity and other co-morbid conditions. Multiple medications will lead to poor patient compliance as there is a higher chance of missing any dosage. But if there is a single pill with a different drug are there then there is less chance of missing any dosage. Which directly leads to improved patient convenience and compliance (16).

- Low cost

If it is focused on the industrial aspect of manufacturing and distribution the fixed-dose combination formulations are more cost-saving than the individual drug formulations(16) It can be concluded that the combination formulation is more economically saving concerning

improved control of blood pressure, and reduced cardiovascular complications obvious with cheaper drug formulations(14).

The additive effects of combining two drugs from different classes (angiotensin-converting enzyme inhibitors, thiazides, beta-blockers, and CCBs) are observed in a meta-analysis of approximately 11,000 patients from 42 trials. Five times greater additive effects were observed by combining different drugs as compared to doubling the dose of individual drugs. As an alternative to single-drug therapy, a combination of drug therapy is recommended by the recent guideline of European treatment in a patient specifically at high CV risk(15).

From large clinical trials, it is observed that approximately 60 % of the patient necessarily need two different antihypertensive drugs to achieve target blood pressure. This led to another motivating factor for the development of combination drug formulations for better control of blood pressure. (17). At the initial stage of combination drug therapy in a single pill, the formulation is preferred for a patient who wants to reduce their blood pressure. which is proposed by "The 2018 European Society of Cardiology/European Society of Hypertension and the 2020 International Society of Hypertension guidelines" (18). According to a clinical trial by Webster R et al, the use of a low dose of three different antihypertensive drugs has given better control on blood pressure as compared to single drug therapy(19).

5. Regulatory aspects on FDC products

According to the WHO guideline "new fixed-dose combinations are acceptable only when the dose of each ingredient meets the requirement of a defined population group, in a term of therapeutic effect, compliance and safety combination has proved advantage over the single compound." (WHO2003,2005). (14).

The code of federal registration 21 CFR 300.50 has defined the basic requirement for fixed-dose combination prescriptions for humans in the united states. The policy of the USFDA on fixed dose combination states that ''Two or more drugs may be combined in a single dosage form when each component contributes to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population. requiring such simultaneous therapy as defined in the labeling for the drug.''

(FDA2006,2015). A similar rule is also given by the European medicines agency for fixed-dose combination products (EMA2015) (13).

6. The preferred combination of choice

The selection of a drug for formulating a combination drug formulation should be based on the criteria that each used drug will act more effectively for control of blood pressure and the mechanism of action of the drug should be like that they are going to eliminate the adverse effect caused by each other (20). The following table summarizes the preferred combinations of choice for the better management of hypertension and some example of fixed-dose combination products which are there in the US market. (7)

Table 3: The preferred combination of choice for the treatment of hypertension

Combinations	Rationale	Example(7)	
		Generic name	Brand name
Angiotensin-Inhibiting Drugs and Diuretics	Angiotensin-converting enzyme inhibitors and diuretics can give synergistic effects. angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) can give the greatest antihypertensive effect with diuretic's increased excretion of salt and decreased volume of circulating plasma stimulating the renin-angiotensin system (RAS) to maintain minimally reduced blood pressure. Thiazide diuretics' beneficial effects in drugs increase the antihypertensive action of all	Benazepril and hydrochlorothiazide	Lotensin HCT
		Candesartan and hydrochlorothiazide	Atacand HCT
		Captopril and hydrochlorothiazide	Generic Medicine Only
		Enalapril and hydrochlorothiazide	Vaseretic
		Fosinopril and hydrochlorothiazide	Generic Medicine Only
		Hydrochlorothiazide and irbesartan	Avalide
		Hydrochlorothiazide and	Zestoretic

	major drugs, particularly those that block the RAS. When combined with an ACEI, they improve blood pressure control over the ACEI alone, and it has been recommended to correct diuretic-induced electrolyte disturbances. Thiazide diuretics and ACEI can form a nearly ideal group as they can produce a positive impact. The enhanced antihypertensive effect of ACEI was observed as a result of diuretic-induced intravascular volume depletion and increased sodium loss which activate the renin-angiotensin-aldosterone system. Patients who are resistant to angiotensin II antagonists / angiotensin-inhibiting drugs can be benefited by combining an ACEI or ARB with a diuretic. Combinations of ARBs and diuretics appear to protect against cerebrovascular, renovascular, and cardiovascular events (20). A potent effect of a fixed dose combination of ramipril/hydrochlorothiazide is observed in a study with uncontrolled hypertensive patients(9).	lisinopril	
		Hydrochlorothiazide and olmesartan	Benicar HCT
		Hydrochlorothiazide and quinapril	Accuretic and Quinaretic
		Hydrochlorothiazide and telmisartan	Micardis HCT
		Hydrochlorothiazide and losartan	Hyzaar
		Hydrochlorothiazide and moexipril	Generic Medicine Only
		Hydrochlorothiazide and valsartan	Diovan HCT
		Chlorthalidone and zilsartan	Edarbyclor
Angiotensin-Inhibiting	This combination is effective as the first line in the treatment of	Amlodipine besylate and valsartan	Exforge

Drugs and Calcium Channel Blockers	hypertension as a result of their complementary mechanism of action. At a lower dose, they reduce blood pressure by a distinct vasodilatory mechanism. For example, vasodilation caused by dihydropyridine-class CCB stimulates both the RAS and the sympathetic nervous system, resulting in reflex vasoconstriction and tachycardia. Both of these reactions decrease their efficacy; however, angiotensin-converting enzyme inhibitors reduce them, resulting in a more impactful blood pressure-lowering effect. The complementary vasodilatory effects of an ACEI/CCB combination made it more effective for lowering blood pressure when compared to monotherapy. Another advantage is that ACEI has been shown to reduce the extremity pedal edema seen with dihydropyridine CCB. Sustained-release verapamil in combination with trandolapril has also proven effective. (20). Many combinations of CCBs and ACEIs were also used to treat patients with comorbid conditions, in addition to improving their effects (9). RAS blockers and	Amlodipine besylate and benazepril	Lotrel
		Amlodipine besylate and olmesartan	Azor
		Amlodipine besylate and perindopril	Prestalia
		Amlodipine besylate and telmisartan	Twynsta
		Trandolapril and verapamil	Tarka

	Calcium channel blockers, as well as direct renin inhibitors, have pleiotropic properties that add value to additional endothelial benefits when used in combination. (21).		
Diuretic plus Beta-Blocking Agent	For the treatment of essential hypertension, diuretic/b-blocker combinations were found to be safe, effective, and well-tolerated as first-line therapy (20). The rationale behind this combination is that b-blockers lead to a reduction in increased plasma renin activity and tachycardia caused by diuretics, while the diuretic component of the mixture reduces sodium retention caused by b-blockers. b-Blocker/diuretic groupings have additive but not synergistic effects on antihypertensive effectiveness. The use of a fixed-dose b-blocker/diuretic combination has several theoretical benefits, including a drop in the risk of b-blocker-induced congestive heart failure, weakening of diuretic-induced hypokalaemia and the potentially related arrhythmias, and a possible cardioprotective effect (16). Nebivolol and hydrochlorothiazide fixed-dose combination was found	Atenolol and chlorthalidone	Tenoretic 50, Tenoretic 100
		Hydrochlorothiazide and metoprolol succinate	Dutoprol
		Hydrochlorothiazide and metoprolol tartrate	Lopressor HCT
		Bisoprolol and hydrochlorothiazide	Ziac
		Hydrochlorothiazide and metoprolol tartrate	Generic Medicine Only

	effective in controlling blood pressure levels during the study period while having no effect on glucose and lipid profiles in a recent trial (9).		
B-Blocker plus CCB	RAS and sympathetic stimulation caused by the CCB's vasodilatory effect is inhibited by the b-blocker on the other hand vasoconstriction caused by the b-blocker is reduced by CCB. This compensatory response proves more improvement in the control of blood pressure and avoids adverse effects (20). CCBs are classified into two groups based on their chemical structures: dihydropyridine and non-dihydropyridine. For the treatment of hypertension with the combination of b-blocker only dihydropyridine calcium antagonist should be used. The usage of this combination is prevented in patients with impaired systolic left ventricular function. (11). It has been reported that non-dihydropyridine CCBs such as diltiazem and verapamil cannot be combined with beta-blockers due to the occurrence of atrioventricular block and symptomatic bradycardia. b-blockers and dihydropyridine	Not available	Not available

	CCBs combination can be ideal as vasodilatory properties are reinforced by b-blocker which leads to synergistic antihypertensive effects(9).		
B-Blockers plus ACEI/ARB	B-blocker and ACE do not have noticeable blood pressure control over ACEI alone according to the early trial. Their antihypertensive mechanism may explain the result. Hypertensive patients with normal or high renin levels can be treated by ACEI, which generally interferes with b-blocker-induced renin inhibition. By comparing single-drug therapy and combinations of renin-angiotensin-aldosterone system blockers with beta-blockers there are a few additional antihypertensive effects observed (9).	----	----

7. Various Research in the development of combination drug therapy

The below table summarizes the different research that has been carried out for the development of FDCs formulations and development. Which reveals the wide scope of development of FDCs products.

Table 4: Various research in the development of combination drug therapy

Sr. No.	Description of work done/ Study
1	J.M.O. Pinto et al. 2021 prepared ternary Amorphous Solid Dispersions (ASD) of candesartan cilexetil and hydrochlorothiazide which are poorly water-soluble antihypertensive drugs as a fixed-dose grouping using hydroxy propyl methyl cellulose acetate succinate (HPMCAS) as a polymeric carrier. This can be considered a promising system for the combination drug formulation of both drugs which leads to an impact on biopharmaceutical properties and improvement of oral bioavailability of the drug (22).
2	Chikukwa et al. 2020, Formulated captopril and hydrochlorothiazide microparticles by an emulsion solvent evaporation approach with the use of polymer in different combinations. The outcome of a study is observed as an improvement in a dissolution of a drug. (23).
3	Maddiboyina et al. 2020 developed a gastro retentive drug delivery system for Hydrochlorothiazide and Losartan in a fixed-dose formulation for anti-hypertensive treatment. direct compression method was used to prepare bilayer tablets by using hydrophilic swellable polymer Hydroxy Propyl Methyl Cellulose K4M, ethyl cellulose as a buoyancy enhancer, and sodium bicarbonate as a gas spawning agent. (24).
4	Lodagekar et al. 2019 developed a co-amorphous system of nifedipine and valsartan with the use of quench cooling technique. Due to the presence of hydrogen bonds improved stability of a drug in an amorphous system was observed (25).
5	Bukhary et al. 2018 prepared a fast-dissolving oral fixed-dose combination of valsartan and amlodipine besylate. With the use of polyvinylpyrrolidone as the polymer matrix, Electrospun fibers were formulated and loaded with drugs (26).
6	Sadia et al. 2018 formulated flexible dose combinations in a single bilayer tablet with two anti-hypertensive drugs. doses of a drug were fabricated using a dual fused deposition modeling 3D printer. hydrochlorothiazide and Enalapril maleate-loaded filaments were produced by using hot-melt extrusion (27).

7	Singh et al. 2017 formulated a dendrimer-based hybrid formulation for providing a combination therapy of diuretic hydrochlorothiazide and ramipril the anti-hypertensive drug. phase-equilibration method was used to prepare drug-dendrimer complexes. The solubility of the drug was found dependent on pH and dendrimer concentration (12).
8	Tóth 2014, studied a triple-drug antihypertensive combination for control of blood pressure in patients having complexity with hypertension. The combination of perindopril/indapamide/amlodipine in a fixed dose formulation is supported by efficacy and safety results obtained by the study. It was possible to achieve target blood pressure in a patient with a high risk of hypertension(10).
9	Kreutz 2011 et al., in a randomized, double-blind trial showed the beneficial effect of olmesartan/amlodipine as compared with monotherapy for a reduction of blood pressure. This combination was well tolerated among the patient for the treatment of hypertension(15).
10	Kumaravelrajan et al. 2011, formulated Controlled porosity osmotic pump tablet (CPOP) for combination therapy of Metoprolol and Nifedipine in a controlled manner for up to 12 h. this developed formulation has given a better impression in the area of treatment of hypertension with multi-drug therapy by delivering both drugs in a controlled manner (28).

8. Future perspective

By looking at the various advantages of using combination drug formulations for the treatment of elevated blood pressure it is becoming more popular and also beneficial to society.

A combination drug formulation will lead to the various advantages of reducing the amount of dosage, reducing the severe side effect caused by higher strength of the individual dose, reducing the cost concerning the patient, and also concerning the manufacturing aspects of the pharmaceutical industry. also, it is going to become more concentrated in the future coming.

As there is an unmet medical need because of the disease's complexity there is a greater need for combination drug therapy with advancement in pharmacological and pathophysiological approaches. The major group of hypertensive patients because of their disease severity and

complexity necessarily need to use two or more than two antihypertensive drugs to achieve targeted blood pressure levels.

When monotherapy fails then combination drug therapy is recommended according to the current "European guidelines for the treatment of arterial hypertension" specifically in a condition of the patient that is at significant BP elevation, those who are at very high risk, or who are having a target that is lower BP. Theoretically, several combinations are possible, but the combination of an agent that are having a different mechanism of action, improved antihypertensive effect along with additive response should be preferred for formulation development. By considering all the evidence it is better to focus on the individual patient's need and which combination will be more effective for each patient as compared to the monotherapy.

The regulatory authorities have already focused on the therapeutic benefits behind the rationale of combination therapies and promoting the development of effective combination drug formulations for serious diseases (EMA2015; WHO2005). valid therapeutic principles and clinical outcomes should be the base for the rationale behind combination drug formulation development (FDA2015).

In reality for the development of combination drug formulation, there is a lot of space is there in the management of multiple alarming and refractory diseases in terms of efficacy, safety, and patient compliance. Elderly patients may be a powerful motivator for the more energetic development of FDC drug products as they require long-term concurrent therapies.

These current conditions and scenarios may provide further opportunities for the development of new oral FDC products of newly invented drug molecules for the improved management of elevated blood pressure and other complex diseases.

9. Conclusion

Due to the disease's complexity, when monotherapy fails to accomplish the target blood pressure, it becomes necessary and advantageous to use the fixed-dose combination as an effective as well as a safe regimen for starting therapy, particularly in patients who are having complications. For the development of the combination drug formulation for treating high blood pressure selection of the drug should be based on the suggestion from a large outcome trial and also on a

requirement that how much reduction in BP is desired. If the combination drug formulation is developed by taking into consideration of the complementary mechanism of action as well as diminishing adverse effects it will lead to providing more effective control over blood pressure along with low side effects, low dose, low cost, and improved patient convenience and compliance.

10. References

1. Hypertension Overview Practice Essentials [Internet]. Available from: https://emedicine.medscape.com/article/241381-printhttps://emedicine.medscape.com/article/241381-print1/83emedicine.medscape.com
2. Mukete BN, Ferdinand KC. Polypharmacy in Older Adults With Hypertension: A Comprehensive Review. J Clin Hypertens. 2016 Jan 1;18(1):10–8.
3. Hypertension Screening, Diagnosis, Assessment, and Management of Primary Hypertension in Adults in India Ministry of Health & Family Welfare Government of India 1Screening, Diagnosis, Assessment, and Management of Primary Hypertension-Full Document. 2016.
4. CLINICAL GUIDELINES FOR THE MANAGEMENT OF HYPERTENSION.
5. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020 Jun 1;75(6):1334–57.
6. Schmieder RE. The role of fixed-dose combination therapy with drugs that target the renin-angiotensin system in the hypertension paradigm. Vol. 32, Clinical and Experimental Hypertension. 2010. p. 35–42.
7. High Blood Pressure | FDA [Internet]. [cited 2022 Nov 4]. Available from: https://www.fda.gov/consumers/free-publications-women/high-blood-pressure
8. Gradman AH. Rationale for triple-combination therapy for management of high blood pressure. Vol. 12, Journal of Clinical Hypertension. 2010. p. 869–78.
9. Wan X, Ma P, Zhang X. A promising choice in hypertension treatment: Fixed-dose combinations. Vol. 9, Asian Journal of Pharmaceutical Sciences. Shenyang Pharmaceutical University; 2014. p. 1–7.
10. Tóth K. Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: Results of the PIANIST study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients). American Journal of Cardiovascular Drugs. 2014;14(2):137–45.
11. Tsioufis C, Thomopoulos C. Combination drug treatment in hypertension. Vol. 125, Pharmacological Research. Academic Press; 2017. p. 266–71.
12. Singh MK, Pooja D, Kulhari H, Jain SK, Sistla R, Chauhan AS. Poly (amidoamine) dendrimer-mediated hybrid formulation for combination therapy of ramipril and hydrochlorothiazide. European Journal of Pharmaceutical Sciences. 2017 Jan 1;96:84–92.
13. Moon C, Oh E. Rationale and strategies for formulation development of oral fixed dose combination drug products. Vol. 46, Journal of Pharmaceutical Investigation. Springer Netherlands; 2016. p. 615–31.
14. Escobar C, Barrios V. Combined therapy in the treatment of hypertension. Vol. 24, Fundamental and Clinical Pharmacology. 2010. p. 3–8.
15. Kreutz R. Olmesartan/amlodipine: A review of its use in the management of hypertension. Vol. 7, Vascular Health and Risk Management. DOVE Medical Press Ltd.; 2011. p. 183–92.
16. Siea DA. Fixed-Dose Combination Antihypertensive Drugs Do They Have a Role in Rational Therapy? Vol. 48, REVIEW ARTICLE Drugs. 1994.
17. Davis J, Oparil S. Novel Medical Treatments for Hypertension and Related Comorbidities. Vol. 20, Current Hypertension Reports. Current Medicine Group LLC 1; 2018.

18. Zhang ZY, Yu YL, Asayama K, Hansen TW, Maestre GE, Staessen JA. Starting Antihypertensive Drug Treatment With Combination Therapy: Controversies in Hypertension-Con Side of the Argument. Vol. 77, Hypertension. Lippincott Williams and Wilkins; 2021. p. 788–98.
19. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka a randomized clinical trial. JAMA - Journal of the American Medical Association. 2018 Aug 14;320(6):566–79.
20. Rosenthal T, Gavras I. Fixed-Drug Combinations as First-Line Treatment for Hypertension. Prog Cardiovasc Dis. 2006 May;48(6):416–25.
21. Mizuno Y, Jacob RF, Mason RP. Combined use of calcium channel blockers and inhibitors of the renin-angiotensin system for treating hypertension. Vol. 8, Therapy. 2011. p. 247–60.
22. Pinto JMO, Leão AF, Bazzo GC, Mendes C, Madureira LMP, Caramori GF, et al. Supersaturating drug delivery systems containing fixed-dose combination of two antihypertensive drugs: Formulation, in vitro evaluation and molecular metadynamics simulations. European Journal of Pharmaceutical Sciences. 2021 Aug 1;163.
23. Chikukwa MTR, Walker RB, Khamanga SMM. Formulation and characterisation of a combination captopril and hydrochlorothiazide microparticulate dosage form. Pharmaceutics. 2020 Aug 1;12(8):1–19.
24. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, et al. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. Heliyon. 2020 Nov 1;6(11).
25. Lodagekar A, Chavan RB, Mannava MKC, Yadav B, Chella N, Nangia AK, et al. Co amorphous valsartan nifedipine system: Preparation, characterization, in vitro and in vivo evaluation. European Journal of Pharmaceutical Sciences. 2019 Nov 1;139.
26. Bukhary H, Williams GR, Orlu M. Electrospun fixed dose formulations of amlodipine besylate and valsartan. Int J Pharm. 2018 Oct 5;549(1–2):446–55.
27. Sadia M, Isreb A, Abbadi I, Isreb M, Aziz D, Selo A, et al. From 'fixed dose combinations' to 'a dynamic dose combiner': 3D printed bi-layer antihypertensive tablets. European Journal of Pharmaceutical Sciences. 2018 Oct 15;123:484–94.
28. Kumaravelrajan R, Narayanan N, Suba V. Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination. Lipids Health Dis. 2011;10.