

# A Review on Antihypertensive Chewable Tablets for Geriatrics

Nikhil Batra<sup>1</sup>, Dr. Hariom Sharma<sup>2</sup>, Jaya Singh<sup>3</sup>

<sup>1</sup>M Pharm Student, <sup>2</sup>Principal, <sup>3</sup>Assistant professor

<sup>1,2,3</sup>Innovative college of pharmacy, Greater Noida, Uttar Pradesh, India

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## INTRODUCTION

Oral route of drug administration is commonest technique for administering drug for general action. Except in bound cases parental route is deployed e.g. insulin. The parental route of administration is very important in treating medical emergencies during which the topic is comatose or cannot swallow the tablets. even so, a minimum of ninetieth of all medication accustomed give general impact area unit administered by oral route. once a replacement drug is discovered, the primary question drug company raise is whether or not the drug is administered orally or not with correct general effects. medication that area unit administered orally, solid oral indefinite quantity forms represent the well-liked category of product. pill and capsules represent unit indefinite quantity forms during which usual dose of drug has been accurately placed. By comparison liquid forms like syrups, suspensions, emulsions, solutions and elixirs area unit typically selected to contain one medication in five -30ml, such indefinite quantity measurements area unit usually error by an element starting from twenty -50%, once the drug is self administered by patient [38, 39].

### Advantages:

- Unit indefinite quantity kind provides the dose preciseness and least content variability.
- Lesser price
- Light and compact indefinite quantity forms
- Easiest and economical for the trade

## ABSTRACT

Chewable tablets that are needed to be broken and chewed in between the teeth before intake. These tablets are given to the kids and create some problem in swallowing and to the adults who dislike swallowing. These tablets are supposed to disintegrate swimmingly within the mouth at a moderate rate either with or while not actual chew, characteristically chewable tablets have a sleek texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant style. Geriatric and medicine patients and move patients WHO might not have prepared access to water are most want of simple swallowing quantity forms like chewable tablets. The composition of chewable tablet consists of gum core, which can or may not be coated. The core consists of associate degree insoluble gum base like fillers, waxes, inhibitors, sweeteners, flavourer agents. . A flavourer agent is enclosed to create it a lot of eatable. numerous factors involved within the formulation of chewable tablets. the most important formulation factors are flow, lubrication, disintegration, organoleptic properties, hardness, compatibility and stability, that are common to regular (swallowed) and chewable tablet. This article discuss about chewable tablets, dysphasia, advantages and disadvantages of chewable tablet, hypertension and antihypertension.

**Keywords:** Chewable Tablets, hypertension

- Product identification is best
- Easily modifications into specialised tablets like enteric or delayed unharness
- Large scale production is simple
- Patient compliance
- Product identification is simple by the help of adorned or monogrammed punched face.

### Disadvantages:

- Some amorphous kinds of medication resist compression
- Some medication with poor wetting, dissolution properties makes it tough to formulate and manufacture as a pill
- Drugs that area unit sensitive to element or at risk of simple degradation in traditional surroundings

### Types of tablets

Tablets are classified into differing kinds in the main to deliver the drug into the circulation that's comparatively easy and cheap to manufacture. Tablets area unit classified additional as:

- Standard compressed tablets
- Multiple compressed tablets
- Modified unharness tablets
- Delayed action tablets
- Targeted action tablets
- Chewable tablets
- Dispersible tablets

**CHEWABLE TABLETS**

Chewable tablets are a unit meant to disintegrate swimmingly in mouth at traditional rate with mastication in mouth before swallowing and not supposed to be swallowed intact. The first purpose of pill is to deliver unit indefinite quantity sort of medication that may be to infants or to the elder patients, WHO could have issues in swallowing the pill. Chewable pill typically have sleek texture upon disintegration, with pleasant style and leave no bitter style behind.

**Advantages:[38]**

- Improved therapeutic impact and higher bioavailability by reduction in size and bypassing disintegration.
- Patient convenience i.e. No need for water for swallowing
- Rapid onset of action
- Better stability
- Patient compliance particularly in kids
- Absorption of drug is quicker

**Methods concerned in formulation of tablets [40]**

- Direct Compression
- Dry Granulation
- Wet granulation

**Direct compression**

Direct compression is employed once ingredients are often integrated and pill are often created exploitation pill press with none modification in ingredients. This system isn't often used as a result of several tablets have active pharmaceutical ingredient that may fail to point out the content uniformity for the direct compression [40].

**Advantages of direct compression:**

- Cost effective
- Low stability problems
- Good dissolution profile
- Simplified validation method

**Limitations of direct compression:**

- Low dilution potential
- Lubricant sensitivity
- Variation in practicality

**Dry Granulation**

Granulation may be a method of jutting particles along by making bonds in between them. In dry granulation technique, the powder is compressed while not the employment of warmth and alternative solvents. The 2 basic procedures are unit to create a compact material by compression so to mill the compact to get granules. 2 ways are unit primarily used for dry granulation. The foremost wide deployed technique is slugging, during which powder is recompressed and final pill area unit polished to get granules. The opposite technique is to pre-compress the powder with pressure rolls exploitation machine like chilsonator [40].

It primarily involves many process steps like deliberation or staple, screening, compounding and compression into final tablets.

**Advantages of dry granulation:**

- Less area power
- Cost effective
- Useful for warmth and wet sensitive material

**Disadvantages of dry granulation:**

- Requires specialised significant duty pill press
- Color uniformity can not be obtained
- Creates additional dirt, enhances the potential for contamination

**Wet granulation:**

It is most loosely used processed for granulation in pharmaceutical trade. Wet granulation method merely involves wet massing of powder mix with granulating liquid, wet size and drying. Granulation technique involves following steps:

- Mixing of medication and recipients
- Preparation of binder answer
- Mixing of binder answer with powder to create wet mass
- Drying of wet granules
- Mixing of screened granules with disintegrant, glidant and material [40].

**Advantages of wet granulation:**

- Ease of mechanical handling
- Improve flow properties of powder
- Improves uniformity of powder
- Reduces air demurrer
- Reduces probabilities of dirt and alternative contamination
- Allows the addition of liquid phase to powder
- Enhances the hydrophobic surfaces to hydrophilic

**Limitations of wet granulation:**

- Expensiveness of method because it needs plenty of labor, energy and area
- Loss of fabric
- Stability problems with thermo labile medication
- Involves complicated series of processes
- Incompatibility problems are often aggravated

**HYPERTENSION**

Hypertension is extremely standard quiet killer and affected more or less one billion adults worldwide. High blood pressure is sort of epidemic and one in every of the most important risk factors for many diseases associated with heart, renal, eyes, liver, etc that is principally related to metabolic syndromes together with endocrine secretion/actions. Pressure level but 120/80mm Hg for beat and blood pressure are thought-about to be traditional, whereas the patients with pressure level >140/90mmHg are thought-about to be hypertensive. Around 28-44% of world population has high blood pressure [1]. Consistent with the planet Health Organization high blood pressure is that the beat pressure level 140-160mmHg and blood pressure 90-95mmHg is taken into account to be the borderline case for hypertension [2]. High blood pressure is that the one in every of the most typical vessel disorder that affects more or less twenty p.c of the adult population worldwide. Consistent with many reports, prevalence of high blood pressure is chop-chop increasing in developing countries and regarded together of the leading reason for death and incapacity. Consistent with the reports, the prevalence of high blood pressure in Asian nation ranges from ten to thirty.9%. Out of that twenty fifth of urban and 100 percent of rural population are hypertensive. By 2020, vessel diseases are calculable to cause four.6 million death in Asian nation [3]. Hypertension could be a condition during which the pressure on the blood vessel wall is exerted whereas the blood is tense into the vascular system. The

circulation of the blood within the vascular system below the sure limit isn't harmful. once because of another abnormalities in vascular system happens like blockage of vessels, constriction by many mediators causes additional blocked within the passage of blood, resulting in increase in pressure level. It was conjointly seen that quite sixty fourth of the patients with high blood pressure are dyslipidemic and elevated TG levels are primarily found in hypertensive patients as compared to normotensive patients [4, 5]. additionally, high blood pressure could be an important risk factor about patients with elevated cholesterol and polygenic disease [6]. high blood pressure is termed as a silent killer because it is sometimes happens while not symptoms and takes terribly very long time before gets diagnosed. Thereby, inflicting major health issues as stroke and different vessel diseases [7].

Hypertension may be a disorder of unknown origin that affects the BP regulation mechanism. quite ninetyth of the hypertensive patients are full of hyperlipidemia and remaining five-hitter of patients are suffering from high blood pressure. it's a lot of usually determined in middle aged male subjects than in females. The prevalence of cardiovascular disease has been increasing, in year 2000 or so 972 million folks are full of cardiovascular disease and projected to extend by pure gold to one.48 billion folks by the year 2025 [14]. Individual with case history of cardiovascular disease is chance to develop hypertension. Primary cardiovascular disease is four-hundredth times a lot of frequent in black people than in White people. many environmental factors are accountable for development of cardiovascular disease like nerve-wracking life vogue, un-healthy diet, obesity, smoking, alcoholism, lack of exercise and usage of medicine like anti-inflammatory, etc.

**Table1. Classification of Hypertension**

Classification	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥160	≥100

#### RISK FACTORS AND CAUSES OF HYPERTENSION:

Causes of cardiovascular disease are clearly unknown until currently. many alternative attainable risk factors are accountable behind the reason behind cardiovascular disease.

#### Obesity:

many medicine studies have known fleshiness because the major risk issue for cardiovascular disease as larger the obesity, a lot of are the probabilities of risk of elevated pressure level. it's conjointly been seen that once weighty patients slenderize their pressure level decreases step by step.

#### Salt intake:

many evidences are collected that prime salt intake (i.e. 7-8g per day) will increase pressure level considerably. additionally, it's been found that low atomic number 11 intake has been coupled with lower pressure level. as an example, higher incidence of cardiovascular disease is determined in Japanese patients wherever atomic number 11 intake is 400mmol/day whereas in primitive societies with sodium intake 60mmol/day, just about no

cardiovascular disease was seen. it's been mentioned in many studies that cardiovascular disease is directly coupled with the excretion of atomic number 11 from excretory organ. Whereas, K antagonizes the biological result of atomic number 11 and therefore lowers the pressure level of gentle to moderate hypertensive patients. alternative cations like atomic number 20, cadmium, atomic number 12 are prompt that plays a task in reducing the elevated pressure level.

#### Saturated Fat:

many evidences have shown that saturated fat will increase the pressure level furthermore as bodily fluid cholesterol that thereby, increase the strain on the cells and enhances Triglycerides, LDL, very low density lipoprotein in blood stream inflicting thickening of blood vessels.

#### Alcohol use:

High alcohol intake is directly coupled with the multiplied risk of elevated pressure level. it's been found that alcohol consumption will increase the blood pressure quite blood pressure. however the elevated conditions retreat to traditional conditions once the abstinence of alcohol elicited elevations.

#### Physical activity:

physical activity like effort, walking, jogging, etc helps in reduction of weight and pressure level.

#### Environmental stress:

cardiovascular disease is disorder itself implies initiated by stress or tension. it's associate accepted proven fact that psychological factors, mental processes consciously or unconsciously produces cardiovascular disease.

#### Secondary hypertension:

it's primarily called nephritic or endocrine malady or tube-shaped structure disease or through its treatment. Endocrine malady which will initiate high blood pressure are acromegalia, Conn's syndrome, Cushing's syndrome, tumor, Pre-eclampsia, Adrenal steroids, Antidepressants, craving suppressants, Cocaine, Cyclosporine, glycoprotein, Nasal decongestants, NSAIDs, Oral contraceptives, Sympathomimetics are the first causes behind the cardiovascular disease [15, 16].

#### COMPLICATIONS ATTACHED CARDIOVASCULAR DISEASE

1. myocardial infarction
2. Stroke
3. {malignant cardiovascular disease|high blood pressure|hypertension}
4. hypertensive nephroangiosclerosis
5. Peripheral tube sickness

#### Myocardial pathology

Heart attack typically happens once flow of blood to a locality of heart is blocked for long amount of your time that a part of that muscle is broken or bear gangrene. Most of the guts attacks are caused by the grume that blocks the arteria (that brings the ventilated blood to heart). If the coronary blood flow is blocked, the guts is starved of gas and heart cells die. a tough substance known as plaque is buildup within the walls of arteria is that the primary reason for the guts attack. One could feel the pain the many a part of the body like arms, shoulder, neck, teeth, jaw, belly area, etc. alternative symptoms of heart failure are often anxiety, cough, fainting, dizziness, nausea, vomiting, sweating, palpitations, etc.

### Stroke

Stroke typically happens once the flow of blood to a locality of the brain stops. Stroke is usually known as a brain attack. If the blood flow is stopped for extended than few seconds, the brain cannot get blood and gas leading to harm in cells of brain. There are 2 varieties of stroke, cerebrovascular accident and haemorrhagic stroke. cerebrovascular accident happens once vas provides blood to the brain is blocked by the grume that is principally because of the deposition of plaque. Whereas, haemorrhagic stroke happens once a vas within the a part of the brain becomes weak and burst open, inflicting blood to leak into the brain.

### Malignant cardiovascular disease

It is a really high vital sign conditions that arises suddenly and quickly. The pulsation vital sign reading that is often around 80mmHg is commonly higher than 130mm Hg. The disorder typically affects concerning I Chronicles of individuals with high vital sign. it's additional typically seen in younger adults and also the folks with albuminoid tube disorder, urinary organ issues, etc. high risk for high blood pressure includes kidney disease, nephritic cardiovascular disease.

### Hypertensive nephroangiosclerosis

Hypertensive uropathy or hypertensive nephroangiosclerosis or hypertensive nephritic disease could be a condition concerning the harm to the urinary organ because of chronic elevated vital sign. It are often distinguished from reno-vascular hypertension that could be a kind of hypertension. within the kidneys, hyaline accumulates within the walls of little arteries and arterioles, manufacturing the thickening of their walls and narrowing of lumina hyaline sclerosis.

### Peripheral tube sickness

Peripheral tube sickness is cited as narrowing of blood vessels that restricts the blood flow. it's typically discovered within the legs, however generally seen within the arms additionally. Peripheral tube sickness includes a bunch of diseases within which blood vessels becomes restricted or blocked. In short, the patient has peripheral tube sickness from coronary artery disease within which development of plaque happens within walls of blood vessels. All the symptoms and consequences of peripheral tube sickness are associated with the restricted blood flow. it's a progressive

tube sickness that may result in gangrene of the affected space. There are many causes of peripheral tube sickness. one in every of the most important risks is smoking, alcoholism and alternative sickness that predisposes peripheral disease includes polygenic disorder, Burger's sickness, hypertension, and Reynaud's sickness. the first symptoms could embrace AN aching, tired sensation within the affected space which can disappear once taking rest. because the sickness becomes worse, the symptoms occur even throughout light-weight toil and eventually occur the least bit the time. The skin becomes dry ad scaly and also the leg ulcers are normally seen, correct healing cannot turn up [17-21].

The most common and vital vessel complication related to cardiovascular disease are infarction and stroke. a rise of 5mmHg blood pressure from usual vary shows around 35-40% raised risk of stroke. per Framingham heart study, subjects with vital sign between a hundred thirty to 139 and 85-89 mmHg are related to important rise in relative risk from disorder as compared to normotensive patients.

### PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE

Hypertension could be a hemodynamic disorder. the key hemodynamic findings related to higher levels of pressure are rise within the peripheral resistance. This observation LED to the event of medicament agents, by the virtue of their actions obstruction the sympathetic system, had a vasodilative part to their mode of action. many approaches may be adopted so as to focus on the cardiovascular disease are The Sympathetic system (SNS) was explored in the main for the treatment of cardiovascular disease. SNS is concerned within the physiological state regulation of big variety of functions like vital sign, force of contraction of heart, tone of contraction and ultimately the pressure [22, 23].

Diuretics in the main work by the means that of forced diacritic to extend the excretion of water from the excretory organ that's to blame for the upkeep of blood fluid volume. There are many kinds of diuretics like thiazides, loop and metal frugal, etc. [24, 25].

Rennin vasoconstrictor System (RAS) is a vital target for the nephritic and vessel protection. vasoconstrictor changing accelerator inhibitors (ACEIs), vasoconstrictor Receptor Blockers (ARBs), and chymosin inhibitors are used [26, 27].

**Table2. Oral antihypertensive agents**

S. No.	Class	Drugs
1.	ARBs	Losartan, Valsartan, Olmesartan, Telmisartan, Candesartan, Irbesartan, Eprosartan
2.	ACEIs	Captopril, Ramipril, Benzapril, Enalapril, Fosinopril, Lisinopril, Trandolapril, Perindopril, Quinapril, Moexipril,
3.	CCBs	Amlodipine, Felodipine, Nifedipine, Nifedipine, Nisoldipine Diltiazem, Verapamil
4.	$\beta_1$ - Blockers	Atenolol, Betaxolol, Bisprolol, Metoprolol, Nadolol, Propranolol, Timolol
5.	$\alpha_1$ - Blockers	Prazosin, Doxazosin, Terazosin
6.	Aldosterone antagonists	Eplerenone, Spironolactone
7.	Diuretics	Hydrochlorothiazide, Chlorothiazide, Chlorthalidone, Polythiazide, Indapamide, Metolazone, Bumetamide, Furosemide, Torsemide, Amiloride, Triamterene
8.	Direct vasodilators	Hydralazine, Minoxidil
9.	$\alpha$ and $\beta$ blockers	Carvedilol, Labetalol
10.	Central $\alpha_2$ agonists	Clonidine, Methyldopa, Reserpine, Guanfacine

Hypertension could be a risk issue and will keep company with alternative disorder or other conditions. The medicament medical care is ready to treat cardiovascular disease in patients with many hypertensive disorders. The systems, their targets and advantages in treating cardiovascular disease related to alternative disorder are mentioned below:

### SYMPATHETIC SYSTEM

Sympathetic system is concerned within the physiological state regulation of a numerous quite operate like vital sign, constriction tone, force of contraction of heart and ultimately the pressure. The sympathetic system is additional classified into  $\hat{1}\pm$  and  $\hat{1}^2$  system. The upset of system can results in numerous kinds of vessel disorder like cardiovascular disease, internal organ failure, shock, asthma, hypersensitivity reaction.  $\alpha_1$  receptor causes peripheral constriction and its antagonist are Minipress, doxazosin, and alpha-adrenergic blocking agent [28].  $\beta_1$ -blockers receptor blockade result into reduced rate of flow.  $\beta_1$ -blockers have a vital role within the management of cardiovascular disease with diabetic uropathy [29].

### DIURETICS

Diuretics are economical medicament agents. Treatment with diuretics like hydrochlorthiazide ends up in a dose dependent pressure reduction that saturates off with higher doses [30]. In long run studies diuretics have shown to cut back the incidence of shock, symptom coronary failure, coronary cardiovascular disease and total mortality from upset.

### CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are effective medicament agents that scale back the pressure by acting primarily through arteria vasodilatation. CCBs have additionally shown to enhance vessel risk profile against the elevated pressure and supply addition benefits in terms of nephritic and vascular protection, etc.[31].

### RENIN-ANGIOTENSIN SYSTEM (RAS)

RAS is a vital target for nephritic and vessel protection. It follows secretion cascade that regulates the blood volume and blood pressure to take care of adequate organ intromission. Chronic RAS activation ends up in vascular and internal organ hypertrophy, constriction and salt/water retention. The RAS cascade initiates with the discharge of chymosin into the circulation from Juxta-glomerular cells of the excretory organ. The active chymosin within the blood cleaves angiotensinogen (produced by the liver) to angiotonin (Ang I), that is additional regenerate into angiotensin (Ang II) by vasoconstrictor changing accelerator (ACE). Its impact are exerted by its binding to angiotensin kind one receptor (AT1) [32]. ARBs are a good category of medicament agents that have shown vital effects on the far side the pressure management. many trials of ARBs in patients with cardiovascular disease have shown management in elevated pressure levels with renoprotective effectualness and reduced upset morbidity and mortality as well as those with DM, coronary failure or left chamber hypertrophy (LVH) and infarction. This category of antihypertensive agents includes Losartan, Valsartan, Olmesartan, Telmisartan, Candesartan, Irbesartan, Eprosartan [33].

### REFERENCES

- [1] Wolf-Maier, K., et al., *Hypertension Prevalence and Blood Pressure Levels in 6 European Countries, Canada, and the United States*. JAMA, 2003. **289**(18): p. 2363-2369.
- [2] WHO, *Arterial hypertension : report of a WHO expert committee* [March 21to 13ng held in Geneva from meeti [1978. 1978.
- [3] Gupta, R., *Trends in hypertension epidemiology in India*. Journal of Human Hypertension, 2004. **18**(2): p. 73-78.
- [4] Kyvelou, S.M., et al., *Effects of antihypertensive treatment with angiotensin II receptor blockers on lipid profile: an open multi-drug comparison trial*. Hellenic J Cardiol, 2006. **47**(1): p. 21-8.
- [5] Devabhaktuni, M. and S. Bangalore, *Fixed combination of amlodipine and atorvastatin in cardiovascular risk management: patient perspectives*. Vascular health and risk management, 2009. **5**(1): p. 377-387.
- [6] Nickenig, G., *Should Angiotensin II Receptor Blockers and Statins Be Combined?* Circulation, 2004. **110**(8): p. 1013-1020.
- [7] John P. Cunha, D., FACOEP. *High Blood Pressure (Hypertension) Signs, Causes, Diet, and Treatment*. 2011 [cited 2019 June 05]; Available from: [https://www.medicinenet.com/high\\_blood\\_pressure\\_hypertension/article.htm](https://www.medicinenet.com/high_blood_pressure_hypertension/article.htm).
- [8] KAPLAN, N.M., *Hypertension: Prevalence, Risks, and Effect of Therapy*. Annals of Internal Medicine, 1983. **98**(5\_Part\_2): p. 705-709.
- [9] National High Blood Pressure Education, P., in *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. 2004, National Heart, Lung, and Blood Institute (US): Bethesda (MD).
- [10] Mancia, G., et al., *Blood-pressure control in the hypertensive population*. The Lancet, 1997. **349**(9050): p. 454-457.
- [11] Zareian, Z., *Hypertensive disorders of pregnancy*. International Journal of Gynecology & Obstetrics, 2004. **87**(2): p. 194-198.
- [12] McNiece, K.L., et al., *Prevalence of Hypertension and Pre-Hypertension among Adolescents*. The Journal of Pediatrics, 2007. **150**(6): p. 640-644.e1.
- [13] Mohan, V., et al., *Prevalence, awareness and control of hypertension in Chennai-the Chennai urban rural epidemiology study (CURES-52)*. Journal of Association of Physicians of India, 2007. **55**: p. 326-32.
- [14] Kearney, P.M., et al., *Global burden of hypertension: analysis of worldwide data*. Lancet, 2005. **365**(9455): p. 217-23.
- [15] Kaplan, N.M., *Microalbuminuria: A risk factor for vascular and renal complications of hypertension*. The American Journal of Medicine, 1992. **92**(4, Supplement 2): p. S9-S12.
- [16] Ayad, F., et al., *Association between cardiac autonomic neuropathy and hypertension and its potential influence on diabetic complications*. Diabetic Medicine, 2010. **27**(7): p. 804-811.

- [17] Strandgaard, S., *Hypertension and stroke*. Journal of hypertension. Supplement : official journal of the International Society of Hypertension, 1996. **14**(3): p. S23-7.
- [18] Alderman, M.H., et al., *Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension*. New England Journal of Medicine, 1991. **324**(16): p. 1098-1104.
- [19] Psaty, B.M., et al., *The risk of myocardial infarction associated with antihypertensive drug therapies*. Jama, 1995. **274**(8): p. 620-625.
- [20] Kitiyakara, C. and N. Guzman, *Malignant hypertension and hypertensive emergencies*. Journal of the American Society of Nephrology, 1998. **9**(1): p. 133-142.
- [21] Oparil, S., M.A. Zaman, and D.A. Calhoun, *Pathogenesis of hypertension*. Annals of internal medicine, 2003. **139**(9): p. 761-776.
- [22] Dibona, G.F., *The sympathetic nervous system and hypertension: recent developments*. Hypertension, 2004. **43**(2): p. 147-150.
- [23] Mark, A., *The sympathetic nervous system in hypertension: a potential long-term regulator of arterial pressure*. Journal of hypertension. Supplement: official journal of the International Society of Hypertension, 1996. **14**(5): p. S159-65.
- [24] Wikstrand, J., et al., *Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study*. Hypertension, 1991. **17**(4): p. 579-588.
- [25] Shah, S., S. Anjum, and W. Littler, *Use of diuretics in cardiovascular disease:(2) hypertension*. Postgraduate medical journal, 2004. **80**(943): p. 271-276.
- [26] Peach, M.J., *Renin-angiotensin system: biochemistry and mechanisms of action*. Physiological reviews, 1977. **57**(2): p. 313-370.
- [27] Navar, L.G., et al., *Intratubular renin-angiotensin system in hypertension*. Hypertension, 2011. **57**(3): p. 355-362.
- [28] Cohn, J.N., et al., *Effect of vasodilator therapy on mortality in chronic congestive heart failure*. New England Journal of Medicine, 1986. **314**(24): p. 1547-1552.
- [29] Bakris, G.L., *Role for  $\beta$ -blockers in the management of diabetic kidney disease*. American journal of hypertension, 2003. **16**(S2): p. 7S-12S.
- [30] Neutel, J.M., *Metabolic manifestations of low-dose diuretics*. The American journal of medicine, 1996. **101**(3): p. 71S-82S.
- [31] Alcocer, L., et al., *Use of Calcium Channel Blockers in Cardiovascular Risk Reduction*. American journal of cardiovascular drugs, 2010. **10**(3): p. 143-154.
- [32] PrisantMD, L.M., *Target-organ protection with combination renin-angiotensin-system blockade*. Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease, 2009. **32**(1): p. 4-12.
- [33] Maggioni, A.P., et al., *Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors*. Journal of the American College of Cardiology, 2002. **40**(8): p. 1414-1421.
- [34] Kakuta, H., et al., *Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers*. International journal of clinical pharmacology research, 2005. **25**(1): p. 41-46.
- [35] Derosa, G., et al., *Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study*. Hypertension Research, 2004. **27**(7): p. 457-464.
- [36] Sharpe, M., B. Jarvis, and K.L. Goa, *Telmisartan*. Drugs, 2001. **61**(10): p. 1501-1529.
- [37] Pubchem-Telmisartan, *Telmisartan*.
- [38] Lachman, H.A.L., Joseph L. Kaing, *The theory and practice of industrial pharmacy*. 3rd ed. 1986: Verghese Publishing, Indian edition.
- [39] Donald, I.W., *Hand book of pharmaceuticals controlled release technology*. 1st ed. 2005: Marcel Dekker
- [40] Parik.M, *Handbook of Pharmaceutical Granulation Technology (Drugs and the Pharmaceutical Sciences,ed. Dilip. Vol. 81. 2009.*

[1]