APPROVAL

The thesis paper, entitled "Design and Formulation of In Vitro release of **Combine**d Amlodipine (5mg) and Atenolol (50mg) Tablets and their **Compar**ative Study with other Similar Market Products", submitted by Zayed **Rafiq**, ID no: 2005-2-70-016, to the Department of Pharmacy, East West University Bangladesh has been accepted as a satisfactory for the partial fulfillment of requirement of the degree of Bachelor of Pharmacy (B.PHRM) (Hon's). The Paper is also approved in its content & style.

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ABSTRACT

The objective of this study is to develop a formulation for an immediate release Amlodipine (5mg) and Atenolol (50mg) tablet (a monolayer or mixed matrix tablet) and then utilize the correct manufacturing method to bring out the final sample. The combination therapy is useful for the effective treatment of cardiovascular diseases such as hypertension, Angina pectoris, Myocardial infarction. Multi-drug tablets of amlodipine besylate and atenolol were prepared as mono-layer (mixed matrix) tablets containing each drug in a separate layer by using various excipients and processing. After this is complete it is necessary to evaluate the performance of the obtained sample with its competitors that are currently available on the market. This has been done by deducing the % dissolution rate of the sample and then comparing this data with the % dissolution rates of its pharmaceutical competitors. We know that when launching a product onto the market, a lot of research is essential in order to determine whether it should or should not go into the market. This research work is similar to that, although not as extensive and thorough, and aims at determining whether the sample developed is comparable with its existing pharmaceutical competitors.

Keywords: combination therapy, amlodipine besylate, atenolol, Multi-drug tablets, % dissolution rate, monolayer tablet, hypertension, excipients

Contents

Chapter 1
Combination dosage therapy for hypertension

1.1 Why combination therapy for Hypertension

Hypertension even today is a triple paradox which is easy to diagnose but is often undetected. It is simple to treat often remains untreated. Despite availability of potent drugs, treatment is all too often is ineffective. Hypertension is a multifactorial entity; it is therefore not surprising that there is heterogeneity in responsiveness to treatment. Today, there is no simple way of predicting which patients will respond to which class of antihypertensive agents. In hypertension both beta-blockers and calcium antagonists are drugs with proved efficacy. Because only half the patients respond to a single drug, even at full dosage, a second hypotensive agent is frequently required to obtain adequate blood pressure control. The combination of a dihydropyridine calcium antagonist and a beta-blocker can be justified by their different mechanisms of action. A randomised double blind parallel group study versus placebo was performed, in order to assess the efficacy of atenolol combined with amlodipine in the treatment of stage I-II essential hypertension not controlled by atenolol alone. Twenty-four-hour arterial blood pressure monitoring showed that amlodipine added to atenolol produced a statistically significant reduction of blood pressure values compared with placebo in patients whose blood pressure was not controlled by atenolol alone. Blood pressure circadian rhythm was unchanged. The reduction of side-effects, obtained by adding a dihydropyridine derivate to a beta-blocker, confirms the effectiveness of this combination. Fixed-dose drug combination decreases the risk of patient non-compliance and should be considered in patients with chronic conditions like hypertension. Clinically, combination therapy in hypertension treatment involving two or more drugs from different classes can result in better drug efficacy and is recommended for the initial stage of hypertension treatment. The combination of atenolol and amlodipine significantly decreases blood pressure and systolic blood pressure variability. In spontaneously hypertensive rats, the synergistic effect between atenolol and amlodipine results in lowering and stabilizing of blood pressure. Both beta blockers and dihydropyridine calcium antagonist are widely used in the treatment of hypertension. Their combination is a logical choice and can also neutralize the side effects of each drug. Combination therapy is likely to be the

optimal way to control blood pressure and reduce blood pressure variability in the treatment of hypertension as well as in prevention of stroke in hypertension.

Hypertension is a major cardiovascular risk factor that contributes to MI (Myocardial infarction), CHF(Coronary Heart Failure), stroke and premature mortality.The last 3 decades have shown through clinical trials that aggressive pharmacological treatment of moderate and even mild Hypertension leads to better survival and less cardiovascular morbidity.

The JNC VI & WHO-ISH (1999) guidelines reinforce these findings

1.2 Fixed-dose Combination Therapy in Hypertension:

1.2.1 Introduction

In hypertension both beta-blockers and calcium antagonists are drugs with proved efficacy. Because only half the patients respond to a single drug, even at full dosage, a second hypotensive agent is frequently required to obtain adequate blood pressure control. The combination of a dihydropyridine calcium antagonist and a beta-blocker can be justified by their different mechanisms of action. A randomised double blind parallel group study versus placebo was performed, in order to assess the efficacy of atenolol combined with amlodipine in the treatment of stage I-II essential hypertension not controlled by atenolol alone. Twenty-four-hour arterial blood pressure monitoring showed that amlodipine added to atenolol produced a statistically significant reduction of blood pressure values compared with placebo in patients whose blood pressure was not controlled by atenolol alone. Blood pressure circadian rhythm was unchanged. The reduction of side-effects, obtained by adding a dihydropyridine derivate to a beta-blocker, confirms the effectiveness of this combination. Compliance to prescribed antihypertensive regimen is essential to achieve the target BP. Among many factors; the complexity and tolerability of the antihypertensive regimen are two major determinants of patient compliance. Multiple antihypertensive agents needed to achieve the target BP control in majority of the patients add to the complexity of such therapy. Fixed-dose combinations of antihypertensive

agents effectively lower BP and help simplify the therapeutic regimen and increase compliance. Several fixed-dose combinations of antihypertensive agents with different and often complementary mechanisms of actions are available in the market.

1.2.2 Better BP control

In the US, the control of BP to 140/90 mmHg increased from 29% in 1999 to 37% in 2003. However, it remains unacceptably low given the evidence that achieving optimal BP control is the single most important intervention in the management of hypertension. Furthermore the target achieved (140/90 mmHg) is rather conservative especially for patients with diabetes and proteinuric CKD. Combining antihypertensive agents with complementary mechanisms of action is more effective in lowering BP and may counteract some of the adverse effects seen with the individual drugs. Furthermore, combination therapy can achieve a better BP control without having to maximize the dose of a single agent thus reducing the dose-dependent side effects.

1.2.3 Patient adherence

Patient adherence to prescribed therapy and advice is a strong predictor of achieving BP control. The number of medications prescribed and the complexity of the treatment regimen are two important determinants of patient adherence. This has been shown inpatients with a variety of different diseases. Adherence improves with fewer medications or pills prescribed.

Reducing the number of pills by using combination of drugs reduces non-adherence compared with the same drugs given separately even with the same frequency.

Summing up

1. Better adherence to therapy and simplification of the therapeutic regimen.
2. Better BP control than monotherapy.
3. Avoidance of dose dependent adverse effects seen with higher doses of single agents.
4. Attenuation of the adverse effects of some agents when used alone.
5. Complementary/synergistic vasculoprotective effects

1.2.4 Combination therapy for hypertension – Recommended by JNC-VI guidelines and 1999 WHO-ISH guidelines

With any single drug, not more than 25–50% of hypertensives achieve adequate blood pressure control

For patients not responding adequately to low doses of monotherapy, increase the dose of drug. This, however, may lead to increased side effects.

Substitute with another drug from a different class or add a second drug from a different class **(Combination therapy)**

If inadequate response obtained add second drug from different class **(Combination therapy)**

According to American Heart Association:

"Starting with combination therapy may be the best way to get hypertensive patients' blood pressure down to goal levels."

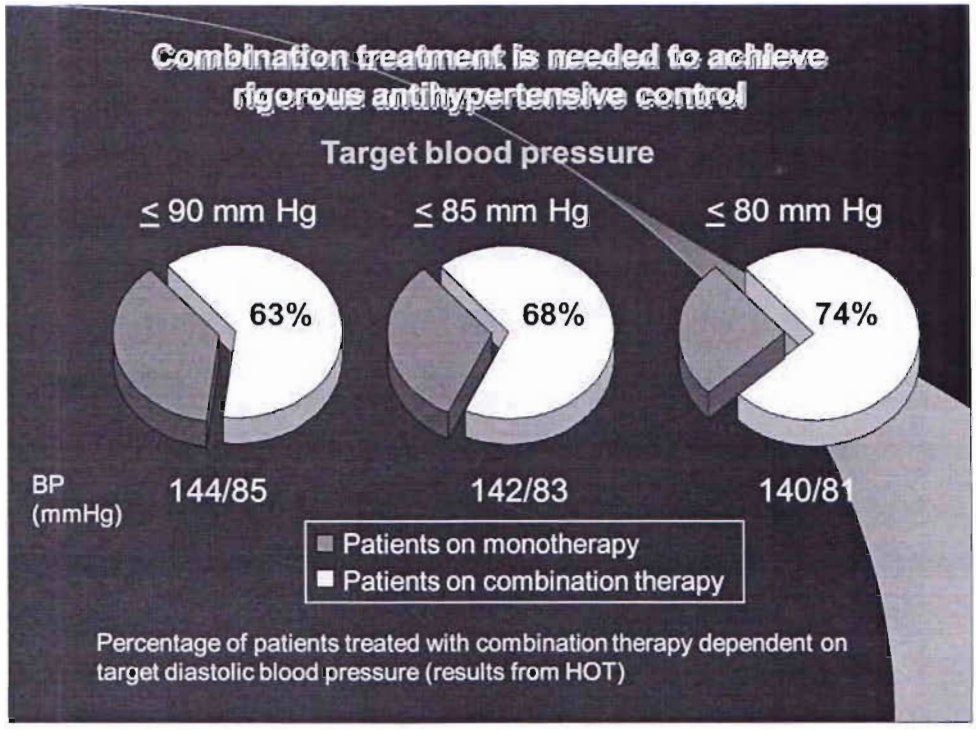


Chart 1: Comparison between monotherapy and combination therapy

1.3 Advantages of fixed-dose combination therapy

- Low (therapeutic) dose of 2 drugs
  - more effective than higher dose of single drug
  - usually well tolerated
  - adverse effects can be reduced
- Simplified treatment regimen: better adherence and potential for improved outcomes
- Economic benefits
  - Fewer copayments
  - health care costs reduced
  - fewer office visits
- Many combinations of agents with complementary Mechanism of action available, e.g.

- RAS blocker/diuretic
- RAS blocker/CCB

- Patient response to fixed dose combinations predictable
  - FDCs well studied and efficacy and tolerability data available in package inserts and publications
  - Similar data not always available for "ad hoc" free combinations

1.4 Disadvantages of fixed-dose combination therapy

- BP may be controlled with 1 drug in some patients
  - However, majority of patients require 2 drugs
- Combination 'too potent' causing hypotension
  - Benefit risk profile for each combination should be assessed in appropriate patient population
  - Individualize therapy
- Additive risk for dose independent adverse effects
  - However, mono components likely to be taken as part of a multi drug regimen
  - Balance against risk of dose dependent side effects with high dose monotherapy and risk of inadequate BP control (stroke, heart failure and MI)
- If adverse effects
  - must discontinue both drugs:
    - However components have well characterized safety profiles so causal components usually identified easily
  - more office visits
  - more lab tests

1.5 Theoretical requirements for a rational fixed-dose antihypertensive combination

- Each component should contribute to the final effect.
- Results should be superior to those achieved with a single agent.
- Dosage form(s) should be adequate relative to bioavailability
    - absence of unwanted interactions
    - selection of doses of each component
- A major proportion of the target population should respond.
- Physicians should be easily familiarised with individual components.

1.6 Fixed-dose combinations as recommended by JNC-VI (1997) guidelines and 1999 WHO-ISH guidelines

- Calcium channel blocker and b-blocker
  (e.g. Amlodipine and Atenolol)
- Calcium channel blocker and ACE-inhibitor (e.g. Amlodipine and Lisinopril)
- ACE-inhibitor and Diuretic (e.g. Lisinopril and Hydrochlorothiazide
- β-blocker and Diuretic (e.g. Atenolol and Hydrochlorothiazide)

Some brand name examples are:

Amlopres L (Amlodipine 5 mg and Lisinopril 5 mg)

Amlopres-Z (Losartan and Amlodipine)

Amplopres-AT (Amlodipine and Atenolol Tablets)

1.7 Suggested guidelines for the use of fixed-dose combinations

Coexisting condition:	**First choice:**
Ischaemic heart disease	Amlodipine + Atenolol
Diabetes	Amlodipine + Lisinopril Amlodipine + Losartan
Hyperlipidemia	Amlodipine + Lisinopril Amlodipine + Losartan
Congestive heart failure	Lisinopril + HCTZ Losartan + HCTZ
Tachycardia	Amlodipine + Atenolol
Bradycardia	Amlodipine + Lisinopril Amlodipine + Losartan
Asthma/COPD	Amlodipine + Losartan Amlodipine + Lisinopril
Elderly hypertensives	Amlodipine + Losartan Amlodipine + Lisinopril Lisinopril/Losartan + HCTZ
Peripheral vascular disease	Amlodipine + Lisinopril Amlodipine + Losartan Losartan + HCTZ Lisinopril + HCTZ

Gout	Amlodipine + Lisinopril Amlodipine + Losartan Amlodipine + Atenolol
Anxiety	Amlodipine + Atenolol
Depression	Amlodipine + Lisinopril Amlodipine + Losartan Lisinopril + HCTZ Losartan + HCTZ
Renal insufficiency (not due to renal artery stenosis)	Amlodipine + Lisinopril Amlodipine + Losartan

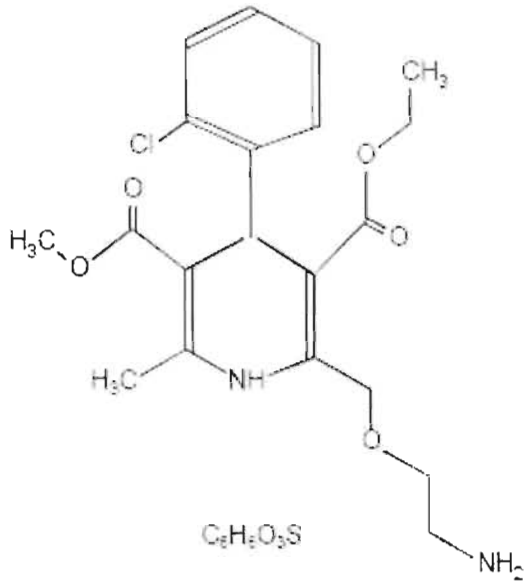
Chapter 2

Amlodipine Besylate

2.1 Introduction:

Amlodipine besylate is the besylate salt of Amlodipine, a long-acting calcium channel blocker.

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±) - 2 - [(2 - aminoethoxy) methyl] - 4 - (2 - chlorophenyl) - 1,4 - dihydro - 6 - methyl - 3,5 - pyridinedicarboxylate, monobenzenesulphonate. Its molecular formula is C20H25CIN2O5•C6H6O3S and its structural formula is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of Amlodipine for oral administration. In addition to the active ingredient, Amlodipine besylate, each tablet contains the following inactive ingredients: dibasic calcium phosphate dihydrous, magnesium stearate, microcrystalline cellulose.

2.2 Clinical Pharmacology

Mechanism of Action:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by Amlodipine. Within the physiologic pH range, Amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which Amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, Amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This

inhibition of coronary spasm is responsible for the effectiveness of Amlodipine in vasospastic (Prinzmetal's or variant) angina.

2.3 Pharmacokinetics and Metabolism:

After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of Amlodipine is not altered by the presence of food.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

2.4 Pharmacodynamics

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of Amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of Amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with Amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of Amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with Amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, Amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving Amlodipine and concomitant beta-blockers. In clinical studies in which Amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters

were observed. In clinical trials with angina patients alone, Amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

2.5 Clinical Studies

Effects in Hypertension

Adult Patients: The antihypertensive efficacy of Amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours post dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to Amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Effects in Chronic Stable Angina: The effectiveness of 5 to 10 mg/day of Amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving

1038 patients (684 Amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for Amlodipine 10 mg, and averaged 7.9% (38 sec) for Amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of Amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Effects in Vasospastic Angina: In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, Amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 Amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

2.6 Indications and Usage

1. Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Coronary Artery Disease (CAD)

Chronic Stable Angina: Amlodipine is indicated for the symptomatic treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina): Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

2.7 Contraindications

Amlodipine is contraindicated in patients with known sensitivity to Amlodipine.

2.8 Warnings

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

2.9 Precautions

General: Since the vasodilation induced by Amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution as with any other peripheral vasodilator, should be exercised when administering Amlodipine, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. Beta-Blocker Withdrawal: Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Since Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine to patients with severe hepatic impairment.

Drug Interactions: In vitro data indicate that Amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

2.10 Effect of other agents on Amlodipine

CIMETIDINE: Coadministration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.

GRAPEFRUIT JUICE: Coadministration of 240 mL of grapefruit juice with a single oral dose of Amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of Amlodipine.

MAALOX (antacid): Coadministration of the antacid Maalox with a single dose of Amlodipine had no significant effect on the pharmacokinetics of Amlodipine.

SILDENAFIL: A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Amlodipine. When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

2.11 Effect of Amlodipine on other agents

ATORVASTATIN: Coadministration of multiple 10 mg doses of Amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Coadministration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Amlodipine had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Coadministration of Amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Pediatric Use: The effect of Amlodipine on blood pressure in patients less than 6 years of age is not known.

Geriatric Use: Clinical studies of Amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of Amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required.

2.12 Adverse Reactions

In general, treatment with Amlodipine is well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with Amlodipine were of mild or moderate severity.

- Edema
- Dizziness
- Flushing
- Palpitation
- Headache
- Fatigue
- Nausea
- Abdominal Pain
- Somnolence

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, myalgia.

Psychiatric: sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea, epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus, rash erythematous, rash maculopapular.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occur rarely:

- cardiac failure
- pulse irregularity
- skin discoloration
- urticaria
- skin dryness
- alopecia

- dermatitis
- muscle weakness
- twitching
- migraine
- cold and clammy skin
- apathy
- agitation
- amnesia
- gastritis
- increased appetite
- loose stools
- coughing
- taste perversion
- abnormal visions

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event gynecomastia.has been reported infrequently where a causal relationship is uncertain

In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of Amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

2.13 Overdosage

Single oral doses of Amlodipine maleate equivalent to 40 mg Amlodipine/kg and 100 mg Amlodipine/kg in mice and rats, respectively, caused deaths. Single oral Amlodipine maleate doses equivalent to 4 or more mg Amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of Amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg Amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output.

Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As Amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

2.14 Dosage and administration

Adults: The usual initial antihypertensive oral dose of Amlodipine is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5 to 10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

The recommended dose range for patients with coronary artery disease is 5 to 10 mg once daily. In clinical studies the majority of patients required 10 mg

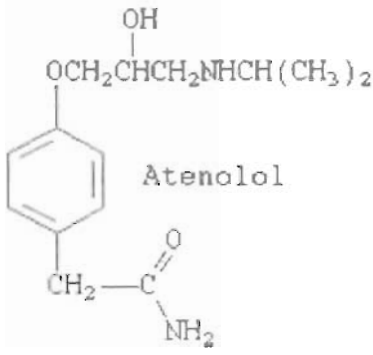
Children: The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Coadministration with Other Antihypertensive and/or Antianginal Drugs: Amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

Chapter 3
Atenolol

3.1 Structure and Characteristics:

Chemical name: (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide



Molecular formula: $C_{14}H_{22}N_2O_3$

Relative Molecular Mass = 266.3

Atenolol is a white or almost white powder.

It is odourless or almost odourless

3.2 Physical Properties of Atenolol

Melting Point=152-155°C

Dissociation Constant (pK_a) =9.6 at 24°C

Partition Coefficent (Log P (octanol))= 0.23

Solubility:-

Water= Sparingly Soluble

Ethanol/Methanol= Soluble

Ether =Practically Insoluble

3.3 Introduction

Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers , a class of drugs used primarily in cardiovascular diseases. Introduced in 1976, atenolol was developed as a replacement for propranolol in the treatment of hypertension. The chemical works by slowing down the heart and reducing its workload. Unlike propranolol, atenolol does not pass through the blood-brain barrier thus avoiding various central nervous system side effects. Atenolol is a beta-adrenergic blocking agent that blocks the effects of adrenergic drugs, for example, adrenaline or epinephrine, on nerves of the sympathetic nervous system. One of the important functions of beta-adrenergic stimulation is to stimulate the heart to beat more rapidly. By blocking the stimulation of these nerves, atenolol reduces the heart rate and is useful in treating abnormally rapid heart rhythms. Atenolol also reduces the force of contraction of heart muscle and lowers blood pressure. By reducing the heart rate, the force of muscle contraction, and the blood pressure against which the heart must pump, atenolol reduces the work of heart muscle and the need of the muscle for oxygen. Since angina occurs when oxygen demand of the heart muscle exceeds the supply, atenolol is helpful in treating angina. Atenolol was approved by the FDA in August 1981. Atenolol is prescribed for patients with high blood pressure (hypertension). It is also used to treat chest pain (angina pectoris) related to coronary artery disease. Atenolol also is useful in slowing and regulating certain types of abnormally rapid heart rates (tachycardias). It is also prescribed for acute myocardial infarction (heart attack). Other uses for atenolol include the prevention of migraine headaches and the treatment of certain types of tremors (familial or hereditary essential tremors).

3.4 Indications

Atenolol (trade name Tenormin) can be used to treat cardiovascular diseases and conditions such as hypertension, coronary heart disease, arrhythmias, angina (chest pain) and to treat and reduce the risk of heart complications following myocardial infarction (heart attack). It is also used to treat the symptoms of Graves Disease, until antithyroid medication can take effect.

Due to its hydrophilic properties, the drug is less suitable in migraine prophylaxis compared to propranolol, because for this indication, atenolol would have to reach the brain in high concentrations, which is not the case.

Atenolol is a so-called β_1-selective (or 'cardioselective') drug. That means that it exerts greater blocking activity on myocardial β_1-receptors than on β_2 ones in the lung. The β_2 receptors are responsible for keeping the bronchial system open. If these receptors are blocked, bronchospasm with serious lack of oxygen in the body can result. However, due to its cardioselective properties, the risk of bronchospastic reactions if using atenolol is reduced compared to nonselective drugs as propranolol. Nonetheless, this reaction may also be encountered with atenolol, particularly with high doses. Extreme caution should be exerted if atenolol is given to asthma patients, who are particularly at risk; the dose should be as low as possible. If an asthma attack occurs, the inhalation of a β_2-mimetic antiasthmatic, such as hexoprenaline or salbutamol, will usually suppress the symptoms.

Provisional data suggests that antihypertensive therapy with atenolol provides weaker protective action against cardiovascular complications (e.g. myocardial infarction and stroke) compared to other antihypertensive drugs. In some cases, diuretics are superior. However, controlled studies are lacking.

Unlike most other commonly-used β-blockers, atenolol is excreted almost exclusively by the kidneys. This makes it attractive for use in individuals with end-stage liver disease.

3.5 Pharmacokinetic data

- t_{cmax} = 2 to 4 hours after oral dosing (time elapsed before maximal concentration in the blood plasma is reached)
- The mean elimination halflife is 6 hours. However, the action of the usual oral dose of 25 to 100 mg lasts over a period of 24 hours.
- Atenolol is a hydrophilic drug. The concentration found in brain tissue is approximately 15% of the plasma concentration only. The drug crosses the placenta barrier freely. In the milk of breastfeeding

mothers, approximately 3 times the plasma concentrations are measured.

- Atenolol is almost exclusively eliminated renally and is well removable by dialysis. A compromised liver function does not lead to higher peak-activity and/or a longer halflife with possible accumulation.

3.6 Contraindications

- bradycardia (pulse less than 50 bpm)
- cardiogenic shock
- asthma (may cause broncho-constriction), although unlikely as atenolol is cardioselective
- symptomatic hypotension (blood pressure of less than 100/60 mm Hg with dizziness, vertigo etc.)
- angina of the Prinzmetal type (vasospastic angina)
- metabolic acidosis (a severe condition with a more acid blood than normal)
- severe disorders in peripheral arterial circulation
- AV-Blockage of second and third degree (a particular form of arrhythmia)
- acutely decompensated congestive heart failure (symptoms may be fluid retention with peripheral edema and/or abdominal fluid retention (ascites), and/or lung edema)
- sick sinus syndrome (a particular form of arrhythmia, very rarely encountered)
- hypersensitivity and/or allergy to atenolol
- phaeochromocytoma (a rare type of tumor of the adrenal glands)

Patients with preexisting bronchial asthma should exercise caution

Caution: only if clearly needed during pregnancy, as atenolol may retard fetal growth and possibly cause other abnormalities.

3.7 Side effects

Atenolol causes significantly fewer central nervous system side effects (depressions, nightmares) and fewer bronchospastic reactions, both due to its particular pharmacologic profile.

It was the main β-blocker identified as carrying a higher risk of provoking type 2 diabetes, leading to its downgrading in the United Kingdom in June 2006 to fourth-line agent in the management of hypertension.

In addition, β-blockers blunt the usual sympathetic nervous system response to hypoglycemia (i.e. sweating, agitation, tachycardia). These drugs therefore have an ability to mask a dangerously low blood sugar, which further decreases their safety and utility in diabetic patients.

Side effects include:

- indigestion, constipation
- dry mouth
- dizziness or faintness (especially cases of orthostatic hypotension
- cold extremities
- hair loss
- problems with sexual function
- runny/blocked nose
- depression
- confusion
- difficulty sleeping, nightmares
- fatigue, weakness or lack of energy

More serious side effects:

- hallucinations
- low blood pressure (hypotension)
- skin reactions, eg. rash, hives, flaking of skin, worsening of psoriasis
- sensation of 'pins and needles' hands or feet

- irritated eyes, visual disturbances
- difficulty hearing
- difficulty speaking
- unsteadiness when walking
- zombie like feeling - you are trapped in slow motion and unable to function normally

3.8 Dosage

In patients with normal renal function, the daily dose is 25 to 50 mg for the management of hypertension depending on the indication and severity of the disease. In most patients, the physician will start with a low initial dose and make increments in weekly intervals as tolerated. Dosage can vary from as little as 25 mg to 200mg a day. In cases of doses over 100mg, the dosage is usually divided and taken twice daily.

For the management of angina, 100mg daily may be given.

In patients with impaired renal function the daily dose should be reduced according to the clinical response of the individual patient. If a patient with end-stage renal failure is scheduled on regular dialysis, usually 50 mg are given after each dialysis procedure. In these patients, a severe hypotension may occur afterwards.

3.9 Combination treatment of hypertension

If atenolol alone fails to control arterial hypertension, the drug can be combined with a diuretic (e.g. with chlortalidone in co-tenidone) and/or a vasodilator (hydralazine, or in severe cases minoxidil). Central alpha-agonists (e.g. clonidine), ACE Inhibitors or Angiotensin II receptor antagonists such as losartan can also be given additionally. Also can be administered with amlodipine, a long-acting calcium channel blocker.

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3.10 Overdose

Symptoms of overdose are due to excessive pharmacodynamic actions on β_1 and also β_2-receptors. These include

- bradycardia,
- severe hypotension with shock,
- acute heart failure,
- hypoglycemia and
- bronchospastic reactions.

Treatment is largely symptomatic. Hospitalization and intensive monitoring is indicated. In early cases emesis can be induced. Activated charcoal is useful to absorb the drug.

Chapter 4
Hypertension

4.1 Introduction

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as **high blood pressure** or shortened to **HT**, **HTN** or **HPN**. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either **essential** (primary) or **secondary**. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. It is common. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated. Beginning at a systolic pressure (which is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting) of 115 mmHg and diastolic pressure (which is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood) of 75 mmHg (commonly written as 115/75 mmHg), cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmHg.

4.2 Classification

A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly. These readings are based on the average of seated blood pressure readings that were properly measured during 2 or more office visits. In individuals older

than 50 years, hypertension is considered to be present when a person's blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures over 130/80 mmHg along with Type 1 or Type 2 diabetes, or kidney disease require further treatment

Resistant hypertension is defined as the failure to reduce blood pressure to the appropriate level after taking a three-drug regimen (include thiazide diuretic).

Excessive elevation in blood pressure during exercise is called exercise hypertension. The upper normal systolic values during exercise reach levels between 200 and 230 mm Hg. Exercise hypertension may be regarded as a precursor to established hypertension at rest.

4.3 Signs and symptoms

Mild to moderate essential hypertension is usually asymptomatic.

Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur.

Some signs and symptoms are especially important in suggesting a secondary medical cause of chronic hypertension, such as centripetal obesity, "buffalo hump," and/or wide purple abdominal striae and maybe a recent onset of diabetes suggest glucocorticoid excess either due to Cushing's syndrome or other causes.

Hypertension due to other secondary endocrine diseases such as hyperthyroidism, hypothyroidism, or growth hormone excess show symptoms specific to these disease such as in hyperthyrodism there may be weight loss, tremor, tachycardia or atrial arrhythmia, palmar erythema and sweating.

Signs and symptoms associated with growth hormone excess such as coarsening of facial features, prognathism, macroglossia, hypertrichosis, hyperpigmentation, and hyperhidrosis may occur in these patients.

Other endocrine causes such as hyperaldosteronism may cause less specific symptoms such as numbness, polyuria, polydipsia, hypernatraemia, and metabolic alkalosis.

A systolic bruit heard over the abdomen or in the flanks suggests renal artery stenosis.

Also radio femoral delay or diminished pulses in lower versus upper extremities suggests coarctation of the aorta.

Hypertension in patients with pheochromocytomas is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting.

Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur.

In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia.

Chronic hypertension often leads to left ventricular hypertrophy, which can present with exertional and paroxysmal nocturnal dyspnea.

Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries.

Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema, which is reversible.

Signs and symptoms associated with pre-eclampsia and eclampsia, can be proteinuria, edema, and hallmark of eclampsia which is convulsions, Other cerebral signs may precede the convulsion such as nausea, vomiting, headaches, and blindness.

Accelerated hypertension is associated with

- headache,
- somnolence,
- confusion,
- visual disturbances, and
- nausea and
- vomiting (hypertensive encephalopathy).
- Retinas are affected with narrowing of arterial diameter to less than 50% of venous diameter
- Some signs and symptoms are especially important in infants and neonates such as failure to thrive, seizure, irritability or lethargy, and respiratory distress.
- in children hypertension may cause headache, fatigue, blurred vision, epistaxis.

4.4 Causes

4.4.1 Essential hypertension

Hypertension is one of the most common complex disorders. Essential hypertension is the form of hypertension that by definition, has no identifiable cause. It is the more common type and affects 90-95% of hypertensive patients, and even though there are no direct causes, there are many risk factors such as lifestyle, obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency. It is also related to aging and to some inherited mutations. Family history increases the risk of developing hypertension. Renin elevation is another risk factor, Renin is an enzyme secreted by the juxtaglomerular apparatus of the kidney and linked with aldosterone in a negative feedback loop. Also sympathetic overactivity is implicated. Insulin resistance which is a component of syndrome X, or the metabolic syndrome is also thought to cause hypertension. Recently low birth weight has been questioned as a risk factor for adult essential hypertension.

4.4.2 Secondary hypertension

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently than essential type by treating the underlying cause.

Many secondary causes can cause hypertension; some are common and well recognized secondary causes such as Cushing's syndrome, which is a condition where both adrenal glands can overproduce the hormone cortisol.

Hypertension results from the interplay of several pathophysiological mechanisms regulating plasma volume, peripheral vascular resistance and cardiac output, all of which may be increased. More than 80% of patients with Cushing's syndrome have hypertension.

Another important cause is the congenital abnormality coarctation of the aorta.

4.4.3 Adrenal

A variety of adrenal cortical abnormalities can cause hypertension, In primary aldosteronism there is a clear relationship between the aldosterone-induced sodium retention and the hypertension.

Another related disorder that causes hypertension is apparent mineralocorticoid excess syndrome which is an autosomal recessive disorder results from mutations in gene encoding 11β-hydroxysteroid dehydrogenase which normal patient inactivates circulating cortisol to the less-active metabolite cortisone. Cortisol at high concentrations can cross-react and activate the mineralocorticoid receptor, leading to aldosterone-like effects in the kidney, causing hypertension. This effect can also be produced by prolonged ingestion of liquorice(which can be of potent strength in liquorice candy), can result in inhibition of the 11β-hydroxysteroid dehydrogenase enzyme and cause secondary apparent mineralocorticoid excess syndrome.

Frequently, if liquorice is the cause of the high blood pressure, a low blood level of potassium will also be present.Yet another related disorder causing

hypertension is glucocorticoid remediable aldosteronism, which is an autosomal dominant disorder in which the increase in aldosterone secretion produced by ACTH is no longer transient, causing of primary hyperaldosteronism, the Gene mutated will result in an aldosterone synthase that is ACTH-sensitive, which is normally not.GRA appears to be the most common monogenic form of human hypertension. We can compare these effects to those seen in Conn's disease, an adrenocortical tumor which causes excess release of aldosterone, that leads to hypertension.

Another adrenal related cause is Cushing's syndrome which is a disorder caused by high levels of cortisol. Cortisol is a hormone secreted by the cortex of the adrenal glands. Cushing's syndrome can be caused by taking glucocorticoid drugs, or by tumors that produce cortisol or adrenocorticotropic hormone (ACTH). More than 80% of patients with Cushing's syndrome develop hypertension, which is accompanied by distinct symptoms of the syndrome, such as central obesity, buffalo hump, moon face, sweating, hirsutism and anxiety.

4.4.4 Kidney

Other well known causes include diseases of the kidney. This includes diseases such as polycystic kidney disease which is a cystic genetic disorder of the kidneys, PKD is characterized by the presence of multiple cysts (hence, "polycystic") in both kidneys, can also damage the liver, pancreas, and rarely, the heart and brain. It can be autosomal dominant or autosomal recessive, with the autosomal dominant form being more common and characterized by progressive cyst development and bilaterally enlarged kidneys with multiple cysts, with concurrent development of hypertension, renal insufficiency and renal pain. Or chronic glomerulonephritis which is a disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. Hypertension can also be produced by diseases of the renal arteries supplying the kidney. This is known as renovascular hypertension; it is thought that decreased perfusion of renal tissue due to stenosis of a main or branch renal artery activates the renin-angiotensin system. also some renal tumors can

cause hypertension. The differential diagnosis of a renal tumor in a young patient with hypertension includes Juxtaglomerular cell tumor, Wilms' tumor, and renal cell carcinoma, all of which may produce renin.

Neuroendocrine tumors are also a well known cause of secondary hypertension. Pheochromocytoma (most often located in the adrenal medulla) increases secretion of catecholamines such as epinephrine and norepinephrine, causing excessive stimulation of adrenergic receptors, which results in peripheral vasoconstriction and cardiac stimulation. This diagnosis is confirmed by demonstrating increased urinary excretion of epinephrine and norepinephrine and/or their metabolites (vanillylmandelic acid).

4.4.5 Medication side effects

Certain medications, especially NSAIDs (Motrin/Ibuprofen) and steroids can cause hypertension. High blood pressure that is associated with the sudden withdrawal of various antihypertensive medications is called Rebound Hypertension. The increases in blood pressure may result in blood pressures greater than when the medication was initiated. Depending on the severity of the increase in blood pressure, rebound hypertension may result in a hypertensive emergency. Rebound hypertension is avoided by gradually reducing the dose (also known as "dose tapering"), thereby giving the body enough time to adjust to reduction in dose. Medications commonly associated with rebound hypertension include centrally-acting antihypertensive agents, such as clonidine and beta-blockers.

4.4.6 Pregnancy

Few women of childbearing age have high blood pressure, up to 11% develop pregnancy. While generally benign, it may herald three complications of pregnancy: pre-eclampsia, HELLP syndrome and eclampsia. Follow-up and control with medication is therefore often necessary.

4.4.7 Sleep disturbances

Another common and under-recognized cause of hypertension is sleep apnea, which is often best treated with nocturnal nasal continuous positive airway pressure (CPAP), but other approaches include the Mandibular advancement splint (MAS), UPPP, tonsillectomy, adenoidectomy, septoplasty, or weight loss. Another cause is an exceptionally rare neurological disease called Binswanger's disease, causing dementia; it is a rare form of multi-infarct dementia, and is one of the neurological syndromes associated with hypertension.

4.5 Diagnosis

Initial assessment of the hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension. Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. Although popularly considered a symptom of elevated arterial pressure, headache generally occurs only in patients with severe hypertension. Characteristically, a "hypertensive headache" occurs in the morning and is localized to the occipital region. Other nonspecific symptoms that may be related to elevated blood pressure include dizziness, palpitations, easy fatiguability, and impotence.

4.6 Measuring blood pressure

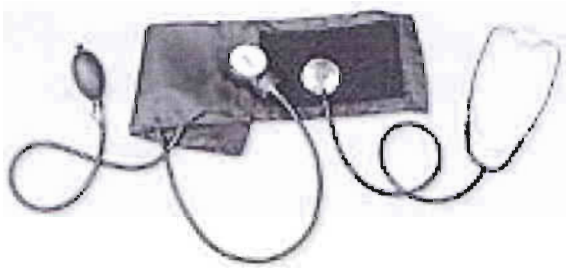

Fig: Conventional (mechanical) sphygmomanometer with aneroid manometer and stethoscope, used to measure blood pressure

Diagnosis of hypertension is generally on the basis of a persistently high blood pressure. Usually this requires three separate measurements at least one week apart. Exceptionally, if the elevation is extreme, or end-organ damage is present then the diagnosis may be applied and treatment commenced immediately.

Obtaining reliable blood pressure measurements relies on following several rules and understanding the many factors that influence blood pressure reading, for instance, measurements in control of hypertension should be at least 1 hour after caffeine, 30 minutes after smoking or strenuous exercise and without any stress. Cuff size is also important. The bladder should encircle and cover two-thirds of the length of the (upper) arm. The patient should be sitting upright in a chair with both feet flat on the floor for a minimum of five minutes prior to taking a reading. The patient should not be on any adrenergic stimulants, such as those found in many cold medications.

When taking manual measurements, the person taking the measurement should be careful to inflate the cuff suitably above anticipated systolic pressure. The person should inflate the cuff to 200 mmHg and then slowly release the air while palpating the radial pulse. After one minute, the cuff should be reinflated to 30 mmHg higher than the pressure at which the radial pulse was no longer palpable. A stethoscope should be placed lightly over the

brachial artery. The cuff should be at the level of the heart and the cuff should be deflated at a rate of 2 to 3 mmHg/s. Systolic pressure is the pressure reading at the onset of the sounds described by Korotkoff (Phase one). Diastolic pressure is then recorded as the pressure at which the sounds disappear (K5) or sometimes the K4 point, where the sound is abruptly muffled. Two measurements should be made at least 5 minutes apart, and, if there is a discrepancy of more than 5 mmHg, a third reading should be done. The readings should then be averaged. An initial measurement should include both arms. In elderly patients who particularly when treated may show orthostatic hypotension, measuring lying sitting and standing BP may be useful. The BP should at some time have been measured in each arm, and the higher pressure arm preferred for subsequent measurements.

BP varies with time of day, as may the effectiveness of treatment, and archetypes used to record the data should include the time taken. Analysis of this is rare at present.

Automated machines are commonly used and reduce the variability in manually collected readings. Routine measurements done in medical offices of patients with known hypertension may incorrectly diagnose 20% of patients with uncontrolled hypertension.

Home blood pressure monitoring can provide a measurement of a person's blood pressure at different times throughout the day and in different environments, such as at home and at work. Home monitoring may assist in the diagnosis of high or low blood pressure. It may also be used to monitor the effects of medication or lifestyle changes taken to lower or regulate blood pressure levels.

Home monitoring of blood pressure can also assist in the diagnosis of white coat hypertension. The American Heart Association states, "You may have what's called 'white coat hypertension'; that means your blood pressure goes up when you're at the doctor's office. Monitoring at home will help you measure your true blood pressure and can provide your doctor with a log of

blood pressure measurements over time. This is helpful in diagnosing and preventing potential health problems."

Some home blood pressure monitoring devices also make use of blood pressure charting software. These charting methods provide printouts for the patient's physician and reminders to take a blood pressure reading. However, a simple and cheap way is simply to manually record values with pen and paper, which can then be inspected by a doctor.

Systolic hypertension is defined as an elevated systolic blood pressure. If systolic blood pressure is elevated with a normal diastolic blood pressure, it is called isolated systolic hypertension. Systolic hypertension may be due to reduced compliance of the aorta with increasing age.

4.7 Prevention

The degree to which hypertension can be prevented depends on a number of features including: current blood pressure level, changes in end/target organs (retina, kidney, heart - among others), risk factors for cardiovascular diseases and the age at presentation. Unless the presenting patient has very severe hypertension, there should be a relatively prolonged assessment period within which repeated measurements of blood pressure should be taken. Following this, lifestyle advice and non-pharmacological options should be offered to the patient, before any initiation of drug therapy.

The process of managing hypertension according the guidelines of the British Hypertension Society suggest that non-pharmacological options should be explored in all patients who are hypertensive or pre-hypertensive. These measures include:

- Weight reduction and regular aerobic exercise (e.g., walking) are recommended as the first steps in treating mild to moderate hypertension. Regular exercise improves blood flow and helps to reduce resting heart rate and blood pressure. Several studies indicate that low intensity exercise may be more effective in lowering blood

pressure than higher intensity exercise. These steps are highly effective in reducing blood pressure, although drug therapy is still necessary for many patients with moderate or severe hypertension to bring their blood pressure down to a safe level.

- Reducing dietary sugar intake.
- Reducing sodium (salt) in the diet may be effective: It decreases blood pressure in about 33% of people. Many people use a salt substitute to reduce their salt intake.
- Additional dietary changes beneficial to reducing blood pressure include the DASH diet (**d**ietary **a**pproaches to **s**top **h**ypertension) which is rich in fruits and vegetables and low-fat or fat-free dairy foods. This diet has been shown to be effective based on research sponsored by the Institute. In addition, an increase in daily calcium intake has the benefit of increasing dietary potassium, which theoretically can offset the effect of sodium and act on the kidney to decrease blood pressure. This has also been shown to be highly effective in reducing blood pressure.
- Discontinuing tobacco use and alcohol consumption has been shown to lower blood pressure. The exact mechanisms are not fully understood, but blood pressure (especially systolic) always transiently increases following alcohol or nicotine consumption. Besides, abstention from cigarette smoking is important for people with hypertension because it reduces the risk of many dangerous outcomes of hypertension, such as stroke and heart attack. Coffee drinking (caffeine ingestion) also increases blood pressure transiently but does *not* produce chronic hypertension.
- Reducing stress, for example with relaxation therapy, such as meditation and other mind body relaxation techniques, by reducing environmental stress such as high sound levels and over-illumination can be an additional method of ameliorating hypertension. Jacobson's Progressive Muscle Relaxation and biofeedback are also used, particularly, device-guided paced breathing, although meta-analysis

suggests it is not effective unless combined with other relaxation techniques.

4.8 Treatment

4.8.1 Lifestyle modifications

Unless hypertension is severe, lifestyle changes such as those discussed in the preceding section are strongly recommended before initiation of drug therapy. Adoption of the DASH diet is one example of lifestyle change repeatedly shown to effectively lower mildly-elevated blood pressure. If hypertension is high enough to justify immediate use of medications, lifestyle changes are initiated concomitantly.

A series of UK guidelines advocate treatment initiation thresholds and desirable targets to be reached as set out in the following table. Of particular note is that for patients with blood pressures between 140-159/80-99 and without additional factors, that only lifestyle actions and regular blood pressure and risk-factor review is proposed.

4.8.2 Biofeedback

Biofeedback devices can be used alone or in conjunction with lifestyle changes or medications to monitor and possibly reduce hypertension. One example is Resperate, a portable, battery-operated personal therapeutic medical device, sold over the counter (OTC) in the United States.

4.8.3 Medications

There are many classes of medications for treating hypertension, together called antihypertensives, which — by varying means — act by lowering blood pressure. Evidence suggests that reduction of the blood pressure by 5–6 mmHg can decrease the risk of stroke by 40%, of coronary heart disease by 15–20%, and reduces the likelihood of dementia, heart failure, and mortality from vascular disease.

The aim of treatment should be blood pressure control to <140/90 mmHg for most patients, and lower in certain contexts such as diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). Each added drug may reduce the systolic blood pressure by 5–10 mmHg, so often multiple drugs are often necessary to achieve blood pressure control.

Commonly used drugs include the typical groups of:

- ACE inhibitors such as captopril, enalapril, fosinopril (Monopril), lisinopril (Zestril), quinapril, ramipril (Altace)
- Angiotensin II receptor antagonists may be used where ACE inhibitors are not tolerated: eg, telmisartan (Micardis, Pritor), irbesartan (Avapro), losartan (Cozaar), valsartan (Diovan), candesartan (Amias), olmesartan (Benicar, Olmetec)
- Calcium channel blockers such as nifedipine (Adalat), amlodipine (Norvasc), diltiazem, verapamil
- Diuretics: bendroflumethiazide, chlorthalidone, hydrochlorothiazide (also called HCTZ).
- Atenolol (Tenormin), selective β_1 receptor antagonist.

Other additionally used groups include:

- Additional diuretics such a furosemide or low-dosages of spironolactone
- Alpha blockers such as prazosin, or terazosin. Doxazosin has been shown to increase risk of heart failure, and to be less effective than a simple diuretic.
- Beta blockers such as atenolol, labetalol, metoprolol (Lopressor, Toprol-XL), propranolol. Whilst once first line agents, now less directly used for this in the United Kingdom due to the risk of diabetes.
- Direct renin inhibitors such as aliskiren (Tekturna).

Finally several agents may be given simultaneously:

- Combination products. The advantage of fixed combinations resides in the fact that they increase compliance with treatment by reducing the number of pills taken by the patients. A fixed combination of the ACE inhibitor perindopril and the calcium channel blocker amlodipine, recently been proved to be very effective even in patients with additional impaired glucose tolerance and in patients with the metabolic syndrome.

4.8.4 Choice of initial medication

Unless the blood pressure is severely elevated, consensus guidelines call for medically-supervised lifestyle changes and observation before recommending initiation of drug therapy. All drug treatments have side effects, and while the evidence of benefit at higher blood pressures is overwhelming, drug trials to lower moderately-elevated blood pressure have failed to reduce overall death rates.

If lifestyle changes are ineffective or the presenting blood pressure is critical, then drug therapy is initiated, often requiring more than one agent to effectively lower hypertension. Which type of many medications should be used initially for hypertension has been the subject of several large studies and various national guidelines.

The largest study, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), concluded that thiazide-type diuretics are better and cheaper than other major classes of drugs at preventing cardiovascular disease, and should be preferred as the starting drug. ALLHAT used the thiazide diuretic chlorthalidone. (ALLHAT showed that doxazosin, an alpha-adrenergic receptor blocker, had a higher incidence of heart failure events, and the doxazosin arm of the study was stopped.)

A subsequent smaller study (ANBP2) did not show the slight advantages in thiazide diuretic outcomes observed in the ALLHAT study, and actually

showed slightly better outcomes for ACE-inhibitors in older white male patients.

Thiazide diuretics are effective, recommended as the best first-line drug for hypertension by many experts, and are much more affordable than other therapies, yet they are not prescribed as often as some newer drugs. Hydrochlorothiazide is perhaps the safest and most inexpensive agent commonly used in this class and is very frequently combined with other agents in a single pill. Doses in excess of 25 milligrams per day of this agent incur an unacceptable risk of low potassium or Hypokalemia. Patients with an exaggerated hypokalemic response to a low dose of a thiazide diuretic should be suspected to have Hyperaldosteronism, a common cause of secondary hypertension.

Other drugs have a role in treating hypertension. Adverse effects of thiazide diuretics include hypercholesterolemia, and impaired glucose tolerance with increased risk of developing Diabetes mellitus type 2. The thiazide diuretics also deplete circulating potassium unless combined with a potassium-sparing diuretic or supplemental potassium. Some authors have challenged thiazides as first line treatment. However as the Merck Manual of Geriatrics notes, "thiazide-type diuretics are especially safe and effective in the elderly."

Current UK guidelines suggest starting patients over the age of 55 years and all those of African/Afrocaribbean ethnicity firstly on calcium channel blockers or thiazide diuretics, whilst younger patients of other ethnic groups should be started on ACE-inhibitors. Subsequently if dual therapy is required to use ACE-inhibitor in combination with either a calcium channel blocker or a (thiazide) diuretic. Triple therapy is then of all three groups and should the need arise then to add in a fourth agent, to consider either a further diuretic (e.g. spironolactone or furosemide), an alpha-blocker or a beta-blocker.Prior to the demotion of beta-blockers as first line agents, the UK sequence of combination therapy used the first letter of the drug classes and was known as the "ABCD rule".

4.9 How is end-organ damage assessed in the patient with high blood pressure?

Damage of organs fed by the circulatory system due to uncontrolled hypertension is called end-organ damage. As already mentioned, chronic high blood pressure can lead to an enlarged heart, kidney failure, brain or neurological damage, and changes in the retina at the back of the eyes. Examination of the eyes in patients with severe hypertension may reveal damage; narrowing of the small arteries, small hemorrhages (leaking of blood) in the retina, and swelling of the eye nerve. From the amount of damage, the doctor can gauge the severity of the hypertension.

People with high blood pressure have an increased stiffness, or resistance, in the peripheral arteries throughout the tissues of the body. This increased resistance causes the heart muscle to work harder to pump the blood through these blood vessels. The increased workload can put a strain on the heart, which can lead to heart abnormalities that are usually first seen as enlarged heart muscle. Enlargement of the heart can be evaluated by chest x-ray, electrocardiogram, and most accurately by echocardiography (an ultrasound examination of the heart). Echocardiography is especially useful in determining the thickness (enlargement) of the left side (the main pumping side) of the heart. Heart enlargement may be a forerunner of heart failure, coronary (heart) artery disease, and abnormal heart rate or rhythms (cardiac arrhythmias). Proper treatment of the high blood pressure and its complications can reverse some of these heart abnormalities.

Blood and urine tests may be helpful in detecting kidney abnormalities in people with high blood pressure. (Remember that kidney damage can be the cause or the result of hypertension.) Measuring the serum creatinine in a blood test can assess how well the kidneys are functioning. An elevated level of serum creatinine indicates damage to the kidney. In addition, the presence of protein in the urine (proteinuria) may reflect chronic kidney damage from hypertension, even if the kidney function (as represented by the blood creatinine level) is normal. Protein in the urine alone signals the risk of

deterioration in kidney function if the blood pressure is not controlled. Even small amounts of protein (microalbuminuria) may be a signal of impending kidney failure and other vascular complications from uncontrolled hypertension. African American patients with poorly controlled hypertension are at a higher risk than Caucasians for most end-organ damage and particularly kidney damage.

Uncontrolled hypertension can cause strokes, which can lead to brain or neurological damage. The strokes are usually due to a hemorrhage (leaking blood) or a blood clot (thrombosis) of the blood vessels that supply blood to the brain. The patient's symptoms and signs (findings on physical examination) are evaluated to assess the neurological damage. A stroke can cause weakness, tingling, or paralysis of the arms or legs and difficulties with speech or vision. Multiple small strokes can lead to dementia (impaired intellectual capacity). The best prevention for this complication of hypertension or, for that matter, for any of the complications, is control of the blood pressure. Recent studies have also suggested the angiotensin receptor blocking drugs may offer an additional protective effect against strokes above and beyond control of blood pressure.

4.10 High Blood Pressure (Hypertension) summarised

- High blood pressure (hypertension) is designated as either essential (primary) hypertension or secondary hypertension and is defined as a consistently elevated blood pressure exceeding 140/90 mm Hg.

- In essential hypertension (95% of people with hypertension), no specific cause is found, while secondary hypertension (5% of people with hypertension) is caused by an abnormality somewhere in the body, such as in the kidney, adrenal gland, or aortic artery.

- Essential hypertension may run in some families and occurs more often in the African American population, although the genes for essential hypertension have not yet been identified.

- High salt intake, obesity, lack of regular exercise, excessive alcohol or coffee intake, and smoking may all adversely affect the outlook for the health of an individual with hypertension.

- High blood pressure is called "the silent killer" because it often causes no symptoms for many years, even decades, until it finally damages certain critical organs.

- Poorly controlled hypertension ultimately can cause damage to blood vessels in the eye, thickening of the heart muscle and heart attacks, hardening of the arteries (arteriosclerosis), kidney failure, and strokes.

- Heightened public awareness and screening of the population are necessary to detect hypertension early enough so it can be treated before critical organs are damaged.

- Lifestyle adjustments in diet and exercise and compliance with medication regimes are important factors in determining the outcome for people with hypertension.

- Several classes of anti-hypertensive medications are available, including ACE inhibitors, ARB drugs, beta-blockers, diuretics, calcium channel blockers, alpha-blockers, and peripheral vasodilators.

- Most anti-hypertensive medications can be used alone or in combination: some are used only in combination; some are preferred over others in certain specific medical situations; and some are not to be used (contraindicated) in other situations.

- The goal of therapy for hypertension is to bring the blood pressure down to 140/85 in the general population and to even lower levels in diabetics, African Americans, and people with certain chronic kidney diseases.

- Screening, diagnosing, treating, and controlling hypertension early in its course can significantly reduce the risk of developing strokes, heart attacks, or kidney failure.

Chapter 6
Literature of the study

6.1 Solid dosage forms of atenolol and amlodipine in monolayer tablets as combination dosage therapy and their dissolution studies in vitro

6.1.1 Introduction

This present study is directed to solid dosage formulations containing a combination of atenolol and amlodipine. In hypertension both beta-blockers and calcium antagonists are drugs with proved efficacy. Because only half the patients respond to a single drug, even at full dosage, a second hypotensive agent is frequently required to obtain adequate blood pressure control. The combination of a dihydropyridine calcium antagonist and a beta-blocker can be justified by their different mechanisms of action. Multi-drug tablets of amlodipine besylate and atenolol were prepared as mono-layer (mixed matrix) using similar excipients and processing.

Fixed-dose drug combination decreases the risk of patient non-compliance and should be considered in patients with chronic conditions like hypertension. Clinically, combination therapy in hypertension treatment involving two or more drugs from different classes can result in better drug efficacy and is recommended for the initial stage of hypertension treatment. The combination of atenolol and amlodipine significantly decreases blood pressure and systolic blood pressure variability. In spontaneously hypertensive rats, the synergistic effect between atenolol and amlodipine results in lowering and stabilizing of blood pressure. Both beta blockers and dihydropyridine calcium antagonist are widely used in the treatment of hypertension. Their combination is a logical choice and can also neutralize the side effects of each drug. Combination therapy is likely to be the optimal way to control blood pressure and reduce blood pressure variability in the treatment of hypertension as well as in prevention of stroke in hypertension

6.1.2. Related Background Art

The development of fixed-combination solid dosage formulations of certain active ingredients is challenging. As used herein, "fixed-combination" refers to a combination of two drugs or active ingredients presented in a single dosage unit such as a tablet or a capsule; further as used herein, "free-combination" refers to a combination of two drugs or active ingredients dosed simultaneously but as two dosage units. When formulating fixed-combination solid dosage formulations, the objective is to provide a patient-convenient combination dosage form of active ingredients that is bioequivalent to the corresponding free-combination of the same active ingredients. Development of fixed-combination dosage formulations that are bioequivalent to the free-combination is challenging due to the multiplicity of challenges arising from pharmacokinetic and pharmaceutical properties of the drugs sought to be combined.

A fixed-combination solid dosage formulation of atenolol and amlodipine that is bioequivalent to the corresponding free-combination would be desirable.

6.1.3 Summary of the study

In a first aspect, the present study is directed to a solid dosage form comprising a combination of atenolol and amlodipine, and pharmaceutically acceptable additives suitable for the preparation of solid dosage forms of atenolol. In preferred embodiments of this invention, amlodipine free base is provided in the form of amlodipine besylate, and the pharmaceutically acceptable additives are selected from diluents, disintegrants, glidants, lubricants, colorants and combinations thereof.

In certain preferred embodiments of this study, the solid dosage form is a monolayer tablet. The amount of atenolol employed in such monolayer tablets is preferably 50 mg. The amount of amlodipine employed in such monolayer preferably 5 mg. Although during the formulation we see that the amount of amlodipine is around 7mg. This is because the amlodipine is in the form of amlodipine besylate, which is the besylate salt of Amlodipine, and the extra

weight accounts for the besylate part of the compound. The weight of amlodipine is 5mg; this is fixed.

Also by methods of another formulation and design, the solid dosage form can a bilayer tablet having the atenolol in one layer and the amlodipine in another layer. The amount of atenolol employed in such monolayer tablets is preferably 50 mg. The amount of amlodipine employed in such monolayer preferably 5 mg. However, this technology is very rarely used in Bangladesh.

The designing method is directed to a method of making a solid dosage form of atenolol comprising the steps of (a) blending atenolol, amlodipine and pharmaceutically acceptable additives to form a blended material; (b) sieving the blended material to form a sieved material; (c) blending the sieved material to form a blended/sieved material; (d) compacting the blended/sieved material to form a compacted material; (e) milling the compacted material to form a milled material; (f) blending the milled material to form blended/milled material; and (g) compressing the blended/milled material to form a monolayer solid dosage form.

Another aspect of the study is directed to a method of treating hypertension, congestive heart failure, angina, myocardial infarction, arteriosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, stroke, left ventricular hypertrophy, cognitive dysfunction, headache, or chronic heart failure comprising administering a solid dosage form of atenolol and amlodipine to a subject in need of such treatment. The solid dosage form is orally administered to the subject.

6.1.4 Details of the study

Atenolol, (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide can be purchased from commercial sources. Atenolol may be used for purposes of this invention in its free form.

Atenolol is employed in an amount of 50mg. The amount of Atenolol noted above refers to the amount of free Atenolol present in a given solid dosage form.

Amlodipine (3-ethyl-5-methyl-2(2-aminoethoxymethyl)-4-(2-chlrorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate) can be purchased from commercial sources. Amlodipine may be used for purposes of this formulation in a form where amlodipine free base is supplied to the solid dosage forms through the use of amlodipine besylate, a besylate salt of amlodipine

Amlodipine besylate is employed in an amount of 7.316mg. This amount of amlodipine refers to the amount of free amlodipine plus the amount of besylate salt present along with the amlodipine. The amount of free amlodipine is 5mg. The extra weight accounts for the weight of the besylate salt.

Pharmaceutically acceptable additives suitable for use in the present formulation include diluents or fillers, disintegrants, glidants, lubricants, binders. Preferred pharmaceutically acceptable additives include diluents and disintegrants.

Suitable diluents include microcrystalline cellulose (Avicel PH 101), dibasic calcium phosphate (dihydrous). Also maize starch used has some diluent properties. Dibasic calcium phosphate (dihydrous) is also employed as a dissolution enhancer and it also has the capability to increase the bulk density of amlodipine. It also has diluents properties.

Suitable disintegrant used here is dried maize starch.

Suitable glidants include, without limitation, colloidal silicon dioxide (e.g., Aerosil 200) and purified talc.

Suitable lubricant used is magnesium stearate.

Suitable binders used are microcrystalline cellulose (Avicel PH 101) as well as maize starch (dried).

The solid dosage forms are monolayer tablet dosage forms of suitable hardness (e.g., an average hardness ranging from about 70 N to about 92 N.

The second embodiment of the present invention is directed to a method of making a solid dosage form of atenolol comprising the steps of (a) blending atenolol, amlodipine and pharmaceutically acceptable additives to form a blended material; (b) sieving the blended material to form a sieved material; (c) blending the sieved material to form a blended/sieved material; (d) compacting the blended/sieved material to form a compacted material; (e) milling the compacted material to form a milled material; (f) blending the milled material to form blended/milled material; and (g) compressing the blended/milled material to form a monolayer solid dosage form.

After that, the proposed formulation tablets were compared with two other market products, Amdocal Plus 50(Amlodipine BP 5mg and Atenolol BP 50 mg) and Fixocard 50 (Amlodipine BP 5mg and Atenolol BP 50 mg). The comparison was done in terms of their rates of dissolution in vitro.

The drug dissolution release test is a requirement for solid dosage form pharmaceutical products. It is an increasingly important technique within the pharmaceutical industry because it provides valuable information on batch conformity, potentially the bioavailability of the active component of the formulation, the control of process variables, and the effects of formulation changes upon the drug release. The technique is therefore routinely used for quality control purposes as well as formulation development. Traditionally, in a drug dissolution test, samples are withdrawn from the vessels, either manually or automatically at selected times, filtered, diluted, and analyzed by UV or HPLC. Thus a dissolution release test could require a day to complete for a UV analytical method and even longer when analyzed by HPLC making dissolution analysis a time-consuming and labor-intensive procedure. In this study, we used the UV spectroscopic method for analysis.

Chapter 7

Preformulation factors and processing steps

7.1 Introductions

The goal of drug formulation and delivery is to administer a drug at a therapeutic concentration to a particular site of action for a specified period of time. The design of the final formulated product for drug delivery depends upon several factors. First, the drug must be administered using a narrow set of parameters that are defined by the therapeutic action of the drug. These parameters include the site of action (either targeted to a specific region of the body or systemic), the concentration of the drug at the time of administration, the amount of time the drug must remain at a therapeutic concentration, and the initial release rate of the drug for oral/controlled release systems. Second, the drug must remain physically and chemically stable in the formulation for at least 2 years. Third, the choice of delivery method must reflect the preferred administration route for the drug, such as oral, parenteral, or transdermal.

Hence a complete knowledge of the relevant therapeutic and physicochemical properties of the drug is required to determine the proper formulation and delivery method of a drug. They are closely interdependent on each other.

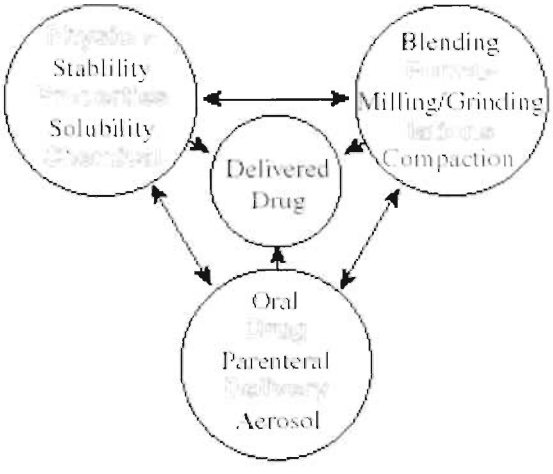

Figure: Schematic diagram showing the interdependence of physicochemical properties, formulation, and drug delivery.

7.2 Physicochemical properties:

The most important goal in the delivery of a drug is to bring the drug concentration to a specific level and maintain it at that level for a specified

period of time. Stability and solubility are two key physicochemical properties that must be considered when designing a successful drug formulation. Many challenges must be overcome to formulate a product that has sufficient chemical and physical stability to not degrade during the shelf life of the product, yet has sufficient solubility (and dissolution rate) to reach the required therapeutic level.

The physicochemical properties of the drug both in solution and in the solid state play a critical role in drug formulation. The solid-state form of the drug is often preferred, because it is often more chemically stable, easier to process, and more convenient to administer than liquid formulations. However, if the drug is in the solid state, it must dissolve before it can be therapeutically active, and once it is in solution, it must be both sufficiently soluble and chemically stable. For these reasons, it is critical to determine the physicochemical properties of the drug both in solution and in the solid state.

There are several parameters that affect the solubility and chemical stability of a drug in solution. The pH of the solution can dramatically affect both the solubility and chemical stability of the drug. Buffer concentration/composition and ionic strength can also have an effect, especially on chemical stability. The hydrophobic/ hydrophilic nature of the drug influences solubility.

7.3 Characterization of a drug

A typical characterization of a drug will start with a study of the chemical stability of the drug as a function of pH. The structure of the degradation product is characterized to determine the mechanism of the degradation reaction. In the solid state, the form of the drug will affect both its solubility and its physicochemical stability.

7.3.1 Solubility:

A drug must be maintained at a specific concentration to be therapeutically active. In many cases the drug's solubility is lower than the required

concentration, in which case the drug is no longer effective. There is a trend in new drug molecules toward larger molecular weights, which often leads to lower solubility. The ability to formulate a soluble form of a drug is becoming both more important and more challenging. This has resulted in extensive research on methods to increase drug solubility.

Solubility is affected by many factors. One of the most important factors is pH. Other factors that affect the solubility of the drug include

- ✓ Temperature,
- ✓ Hydrophobicity of the drug,
- ✓ Solid form of the drug, and
- ✓ The presence of complexing agents in solution.

For drugs with low solubility, special efforts must be made to bring the concentration into the therapeutically active range. There are some of the common methods to increase solubility naming: salt versus free form, inclusion compounds, prodrugs, solid form selection, and dissolution rate. It should be noted that efforts to increase solubility also have an influence (often negative) on the stability of a compound. For this reason, the most soluble form is often not the first choice when formulating the drug.

7.3.2 Stability

Formulation scientists must consider two types of stability: chemical and physical. Physical stability is the change in the physical form of the drug—for example, an amorphous form changing into a crystalline form.

- ↓ Physical Stability: Physical stability can refer to molecular level changes, such as polymorphic changes, or macroscopic changes, such as dissolution rate or tablet hardness. At the molecular level, form changes include amorphous to crystalline, changes in crystalline form (polymorphism), and changes in solvation state (solvatomorphism). In general, a metastable solid form may convert to a more thermodynamically stable form, and it is usually desirable to market the most stable form if possible to avoid such

transformations. The presence of seed crystals of the more stable form may initiate or accelerate the conversion from the metastable form to the more stable form. In addition, the presence of solvents, especially water, may cause formation of a solvate with significantly different physicochemical properties. Desolvation is also a possible reaction. For drug formulations, the choice of salt forms (hydrates, solvates, polymorphs) plays a role in identifying the most suitable form for the pharmaceutical product. Polymorphism in drug formulations makes the characterization of polymorphic forms very important.

- Chemical Stability Chemical degradation of the drug includes reactions such as hydrolysis, dehydration, oxidation, photochemical degradation, or reaction with excipients. The constant presence of water and oxygen in our environment means that exposure to moisture or oxygen can affect the chemical stability of a compound. Chemical stability is very important, not only because a sufficient amount of the drug is needed at the time of administration for therapeutic purposes, but also because chemical degradation products may adversely affect the properties of the formulated product and may even be toxic.

7.4 Formulations

Formulation is the stage of product manufacture in which the drug is combined with various excipients to prepare a dosage form for delivery of the drug to the patient. Excipients are (Gibson, 2002) ''substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form.'' These include binders to form a tablet, aggregates to keep the tablet together, disintegrants to aid dissolution once the drug is administered, and coloring agents. Excipients help keep the drug in the desired form until administration, aid in delivering the drug, control the release rate of the drug, or make the product more appealing in some way to the patient.

Formulation is dictated by the physicochemical properties of the drug and excipients. Each drug delivery method has specific formulation issues. The solid dosage form is the most convenient and most preferred means of

administering drugs. The vast majority of solid dosage forms are tablets, which are produced by compression or molding. Powders are the most common form of both the drug and the excipients prior to processing. The process of creating tablets from bulk materials has a number of steps, which are discussed below.

7.4.1 Processing Steps followed

The steps are directed to a method of making a solid dosage form of atenolol comprising the steps of (a) blending atenolol , amlodipine and pharmaceutically acceptable additives to form a blended material; (b) sieving the blended material to form a sieved material; (c) blending the sieved material to form a blended/sieved material; (d) compacting the blended/sieved material to form a compacted material; (e) milling the compacted material to form a milled material; (f) blending the milled material to form blended/milled material; and (g) compressing the blended/milled material to form a monolayer solid dosage form.

Atenolol, amlodipine and pharmaceutically acceptable additives are blended to form a blended material. Blending can be accomplished using any suitable means such as a diffusion blender or diffusion mixer. In the second step, the blended material is sieved to form a sieved material. Sieving can be accomplished using any suitable means. In the third step of the method of the second embodiment, the sieved material is blended to form a blended/sieved material. Again blending can be accomplished using any suitable means.

The blended/sieved material is compacted to form a compacted material. Compacting can be accomplished using any suitable means. Typically compacting is accomplished using a roller compactor with a compaction force ranging from about 20 kN to about 60 kN, preferably about 30 kN to about 40 KN. Compaction may also be carried out by slugging the blended powders into large tablets that are then size-reduced.

The compacted material is milled to form a milled material. Milling can be accomplished using any suitable means. The milled material is blended to

form blended/milled material. Here again blending can be accomplished using any suitable means. In the final step of the method of the second embodiment, the blended/milled material is compressed to form a monolayer solid dosage form. Compression can be accomplished using any suitable means. Typically compression is accomplished using a rotary tablet press. Compression force for such a rotary tablet press typically ranges from about 2 kN to about 30 kN.

7.4.2 Influence of Physicochemical Properties on Drugs in Formulations

Most of the processing steps depend at least indirectly upon the physicochemical properties of the drug. The solid form of the drug and the conditions from which the drug is crystallized often determines particle size, shape, and morphology. Aspirin, for example, can have multiple crystal morphologies, depending upon the conditions of recrystallization. (Byrn, Pfeiffer & Stowell, 1999) Processing can also result in changes in the form of the drug. Drug–excipient interactions can affect both solubility and stability. These interactions impact the physical properties of the drug by altering the chemical nature of the drug by reactions such as desolvation, or the Maillard reaction (also known as the ''browning reaction'' based on the color of the products).

Physicochemical changes in the form of the drug at the formulation and processing stages are almost always undesirable. Such changes can be very costly if found only toward the end of product development. Thus, it is often desirable to perform preformulation studies to determine the optimum form for delivery. (Stella & Yoshioka, 2000)

Chapter 8
Materials and methods

8.1 Formulation and design of the Amlodipine-Atenolol combination dosage tablet (our proposed and prepared sample), designated specifically for this study as Tablet X.

8.1.1 Formulation 1:

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Maize Starch (both as dried and paste form)
- Magnesium stearate

List of ingredients

Name of the material	Function
Atenolol, Amlodipine besylate	API (Active Pharmaceutical Ingredients)
Avicel 101(microcrystalline cellulose)	Diluent and Binder
colloidal silicon dioxide (Aerosil 200)	Glidant
Purified Talc	Glidant
Dihydrous dibasic Calcium phosphate	Diluent as well as a dissolution enhancer. It also increases the Bulk density of amlodipine
Maize Starch(paste)	Binder
Maize Starch(dried)	Diluent and Disintegrant
Magnesium stearate	Lubricant

Formula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.252 %	7.316 mg
2	Atenolol, Potency:	22.444 %	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	5.860 %	13.185 mg
4	Dibasic Calcium Phosphate Dihy.	50.222 %	113.000 mg
5	Maize Starch (Paste)	2.667 %	6.000 mg
6	Maize Starch (Dried)	6.222 %	14.000 mg
7	Colloidal Silicondioxide (Aerosil 200)	1.333 %	3.000 mg
8	Purified Talc	1.778 %	4.000 mg
9	Magnesium Stearate	2.222 %	5.000 mg
		100.00 %	225.000 mg

Step 1

We sieved weighed quantity of following materials through 20 mesh and took into glass beaker the following:

- Atenolol 50.500 gm
- Dibasic Calcium Phosphate Dihy. 113.000 gm
- Avicel PH 101 13.185 gm

We mixed manually for 5 minutes with the help of glass rod.

The LOD at 105^{O}C was calculated at 1.80%

Step 2:

We took 100 ml water in a beaker, added 6.000 gm Maize starch and stirred to make slurry, heated the slurry to make clear paste, cooled down the paste at $\leq$ 50^{O}C.

Step 3

We added the paste of Step 2 to Step 1 and kneaded manually with glass rod until good granules were formed. We dried the kneaded mass in tray dryer at 60^{O}C for 20 minutes, after 20 minutes passed the semidried mass through 20

mesh, finally drying the semidried granules for 15minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into polythene bag

The LOD was calculated at 105^{O}C to be 1.11%

Step 4

We sieved the weighed quantity of following materials through 30 mesh and took into glass beaker

- Amlodipine Besylate 7.316 gm
- Maize Starch (Dried) 14.000 gm
- Colloidal Silicon dioxide 3.000 gm

We mixed manually for 5 minutes with glass rod. Then we added granules of Step 30.00 gm and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mixed manually for 10 minutes in Polyethene bag.

Step 5

We sieved weighed quantity following materials through 30 mesh screen and diluted with weighed quantity of blended materials.

- Magnesium Stearate 5.000 gm
- Purified Talc 4.000 gm
- Blend of Step 3 20.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag
The Room Condition at that time was a Temperature 24.3^{O}C and a Relative Humidity of 49.3 %

Step 6

We compressed the blend granules of Step 1 into tablet using 7.50 X 9.00 mm semi biconcave oval shaped tools by mini compression machine at 3.0 to 5.0 ton

Step 7

Compression force and checked the following physical parameters:

Appearance : White to off-white colored, biconvex oval shaped both side plain tablet

Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)

Uniformity of weight : 208 mg to 242 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)

Friability : Not more than 0.8% w/w

DT in water at $37^{O}C$: Not more than 15 minutes

The Room Condition at that time was a Temperature 24.1 ^{O}C and a Relative Humidity of 48.3%

Step 8

After satisfactory result, the compression machine was run

8.1.2 Formulation 2

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Maize Starch (both as dried and paste form)
- Magnesium stearate

List of ingredients

Name of the material	Function
Atenolol, Amlodipine besylate	API (Active Pharmaceutical Ingredients)
Avicel 101(microcrystalline cellulose)	Diluent and Binder
colloidal silicon dioxide (Aerosil 200)	Glidant
Purified Talc	Glidant
Dihydrous dibasic Calcium phosphate	Diluent as well as a dissolution enhancer. It also increases the Bulk density of amlodipine
Maize Starch(paste)	Binder
Maize Starch(dried)	Diluent and Disintegrant
Magnesium stearate	Lubricant

Formula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.252 %	7.316 mg
2	Atenolol, Potency:	22.444 %	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	10.860 %	24.435 mg
4	Dibasic Calcium Phosphate Dihy.	40.222 %	90.500 mg
5	Maize Starch (Paste)	1.777 %	4.000 mg
6	Maize Starch (Dried)	8.000 %	18.000 mg
7	Colloidal Silicondioxide (Aerosil 200)	1.333 %	3.000 mg
8	Purified Talc	1.778 %	4.000 mg
9	Magnesium Stearate	2.222 %	5.000 mg
		100.00 %	225.000 mg

Step 1

We sieved weighed quantity of following materials through 20 mesh and took into glass beaker the following:

- Atenolol 50.500 gm
- Dibasic Calcium Phosphate Dihy. 90.500 gm
- Avicel PH 101 24.435 gm

We mixed manually for 5 minutes with the help of glass rod.

The LOD at 105^{o}C was calculated at 1.80%

Step 2:

We took 100 ml water in a beaker, added 4.000 gm Maize starch and stirred to make slurry, heated the slurry to make clear paste, cooled down the paste at $\leq$ 50^{o}C.

Step 3

We added the paste of Step 2 to Step 1 and kneaded manually with glass rod until good granules were formed. We dried the kneaded mass in tray dryer at 60^{o}C for 20 minutes, after 20 minutes passed the semidried mass through 20

mesh, finally drying the semidried granules for 15minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into polythene bag

The LOD was calculated at 105^{O}C to be 1.11%

Step 4

We sieved the weighed quantity of following materials through 30 mesh and took into glass beaker

- Amlodipine Besylate 7.316 gm
- Maize Starch (Dried) 18.000 gm
- Colloidal Silicon dioxide 3.000 gm

We mixed manually for 5 minutes with glass rod. Then we added granules of Step 3 and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mixed manually for 10 minutes in Polyethene bag.

Step 5

We sieved weighed quantity following materials through 30 mesh screen and diluted with weighed quantity of blended materials.

- Magnesium Stearate 5.000 gm
- Purified Talc 4.000 gm
- Blend of Step 3 20.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag
The Room Condition at that time was a Temperature 24.3^{O}C and a Relative Humidity of 49.3 %

Step 6

We compressed the blend granules of Step 1 into tablet using 7.50 X 9.00 mm semi biconcave oval shaped tools by mini compression machine at 3.0 to 5.0 ton

Step 7

Compression force and checked the following physical parameters:

Appearance: White to off-white colored, biconvex oval shaped both side plain tablet

Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)

Uniformity of weight: 208 mg to 242 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)

Friability : Not more than 0.8% w/w

DT in water at $37^{O}C$: Not more than 15 minutes

The Room Condition at that time was a Temperature 24.1 ^{O}C and a Relative Humidity of 48.3%

Step 8

After satisfactory result, the compression machine was run

8.1.3 Formulation 3

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Maize Starch (both as dried and paste form)
- Magnesium stearate

List of ingredients

Name of the material	Function
Atenolol, Amlodipine besylate	API (Active Pharmaceutical Ingredients)
Avicel 101(microcrystalline cellulose)	Diluent and Binder
colloidal silicon dioxide (Aerosil 200)	Glidant
Purified Talc	Glidant
Dihydrous dibasic Calcium phosphate	Diluent as well as a dissolution enhancer. It also increases the Bulk density of amlodipine
Maize Starch(paste)	Binder
Maize Starch(dried)	Diluent and Disintegrant
Magnesium stearate	Lubricant

Formula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.252 %	7.316 mg
2	Atenolol, Potency:	22.444 %	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	15.860 %	35.685 mg
4	Dibasic Calcium Phosphate Dihy.	35.222 %	79.250 mg
5	Maize Starch (Paste)	0.888 %	2.000 mg
6	Maize Starch (Dried)	45.000 %	20.000 mg
7	Colloidal Silicondioxide (Aerosil 200)	1.333 %	3.000 mg
8	Purified Talc	1.778 %	4.000 mg
9	Magnesium Stearate	2.222 %	5.000 mg
		100.00 %	225.000 mg

Step 1

We sieved weighed quantity of following materials through 20 mesh and took into glass beaker the following:

- Atenolol 50.500 gm
- Dibasic Calcium Phosphate Dihy. 79.250 gm
- Avicel PH 101 35.685 gm

We mixed manually for 5 minutes with the help of glass rod.

The LOD at 105^{o}C was calculated at 1.80%

Step 2:

We took 100 ml water in a beaker, added 2.000 gm Maize starch and stirred to make slurry, heated the slurry to make clear paste, cooled down the paste at $\leq$ 50^{o}C.

Step 3

We added the paste of Step 2 to Step 1 and kneaded manually with glass rod until good granules were formed. We dried the kneaded mass in tray dryer at 60^{o}C for 20 minutes, after 20 minutes passed the semidried mass through 20

mesh, finally drying the semidried granules for 15minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into polythene bag

The LOD was calculated at 105^{O}C to be 1.11%

Step 4

We sieved the weighed quantity of following materials through 30 mesh and took into glass beaker

- Amlodipine Besylate 7.316 gm
- Maize Starch (Dried) 20.000 gm
- Colloidal Silicon dioxide 3.000 gm

We mixed manually for 5 minutes with glass rod. Then we added granules of Step 30.00 gm and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mixed manually for 10 minutes in Polyethene bag.

Step 5

We sieved weighed quantity following materials through 30 mesh screen and diluted with weighed quantity of blended materials.

- Magnesium Stearate 5.000 gm
- Purified Talc 4.000 gm
- Blend of Step 3 20.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag
The Room Condition at that time was a Temperature 24.3^{O}C and a Relative Humidity of 49.3 %

Step 6

We compressed the blend granules of Step 1 into tablet using 7.50 X 9.00 mm semi biconcave oval shaped tools by mini compression machine at 3.0 to 5.0 ton

Step 7

Compression force and checked the following physical parameters:

Appearance: White to off-white colored, biconvex oval shaped both side plain tablet

Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)

Uniformity of weight: 208 mg to 242 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)

Friability : Not more than 0.8% w/w

DT in water at $37^{O}C$: Not more than 15 minutes

The Room Condition at that time was a Temperature 24.1 ^{O}C and a Relative Humidity of 48.3%

Step 8

After satisfactory result, the compression machine was run

8.1.4 Formulation 4

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Maize Starch (both as dried and paste form)
- Magnesium stearate

List of ingredients

Name of the material	Function
Atenolol, Amlodipine besylate	API (Active Pharmaceutical Ingredients)
Avicel 101(microcrystalline cellulose)	Diluent and Binder
colloidal silicon dioxide (Aerosil 200)	Glidant
Purified Talc	Glidant
Dihydrous dibasic Calcium phosphate	Diluent as well as a dissolution enhancer. It also increases the Bulk density of amlodipine
Maize Starch(paste)	Binder
Maize Starch(dried)	Diluent and Disintegrant
Magnesium stearate	Lubricant

Formula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.252 %	7.316 mg
2	Atenolol, Potency:	22.444 %	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	20.860 %	46.935 mg
4	Dibasic Calcium Phosphate Dihy.	30.222 %	68.000 mg
5	Maize Starch (Paste)	5.333 %	12.000 mg
6	Maize Starch (Dried)	4.444 %	10.000 mg
7	Colloidal Silicondioxide (Aerosil 200)	1.333 %	3.000 mg
8	Purified Talc	1.778 %	4.000 mg
9	Magnesium Stearate	2.222 %	5.000 mg
		100.00 %	225.000 mg

Step 1

We sieved weighed quantity of following materials through 20 mesh and took into glass beaker the following:

- Atenolol 50.500 gm
- Dibasic Calcium Phosphate Dihy. 68.000 gm
- Avicel PH 101 46.935 gm

We mixed manually for 5 minutes with the help of glass rod.

The LOD at 105^{O}C was calculated at 1.80%

Step 2:

We took 100 ml water in a beaker, added 12.000 gm Maize starch and stirred to make slurry, heated the slurry to make clear paste, cooled down the paste at $\leq 50^{O}$C.

Step 3

We added the paste of Step 2 to Step 1 and kneaded manually with glass rod until good granules were formed. We dried the kneaded mass in tray dryer at 60^{O}C for 20 minutes, after 20 minutes passed the semidried mass through 20 mesh, finally drying the semidried granules for 15minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into polythene bag

The LOD was calculated at 105^{O}C to be 1.11%

Step 4

We sieved the weighed quantity of following materials through 30 mesh and took into glass beaker

- Amlodipine Besylate 7.316 gm
- Maize Starch (Dried) 10.000 gm
- Colloidal Silicon dioxide 3.000 gm

We mixed manually for 5 minutes with glass rod. Then we added granules of Step 30.00 gm and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mixed manually for 10 minutes in Polyethene bag.

Step 5

We sieved weighed quantity following materials through 30 mesh screen and diluted with weighed quantity of blended materials.

- Magnesium Stearate 5.000 gm
- Purified Talc 4.000 gm
- Blend of Step 3 20.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag
The Room Condition at that time was a Temperature 24.3^{O}C and a Relative Humidity of 49.3 %

Step 6

We compressed the blend granules of Step 1 into tablet using 7.50 X 9.00 mm semi biconcave oval shaped tools by mini compression machine at 3.0 to 5.0 ton

Step 7

Compression force and checked the following physical parameters:

Appearance: White to off-white colored, biconvex oval shaped both side plain tablet

Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)

Uniformity of weight: 208 mg to 242 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)

Friability : Not more than 0.8% w/w

DT in water at $37^{O}C$: Not more than 15 minutes

The Room Condition at that time was a Temperature 24.1 ^{O}C and a Relative Humidity of 48.3%

Step 8

After satisfactory result, the compression machine was run

8.1.5 Formulation 5

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Maize Starch (both as dried and paste form)
- Magnesium stearate

List of ingredients

Name of the material	Function
Atenolol, Amlodipine besylate	API (Active Pharmaceutical Ingredients)
Avicel 101(microcrystalline cellulose)	Diluent and Binder
colloidal silicon dioxide (Aerosil 200)	Glidant
Purified Talc	Glidant
Dihydrous dibasic Calcium phosphate	Diluent as well as a dissolution enhancer. It also increases the Bulk density of amlodipine
Maize Starch(paste)	Binder
Maize Starch(dried)	Diluent and Disintegrant
Magnesium stearate	Lubricant

Formula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.252 %	7.316 mg
2	Atenolol, Potency:	22.444 %	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	16.860 %	37.934 mg
4	Dibasic Calcium Phosphate Dihy.	43.222 %	97.250 mg
5	Maize Starch (Paste)	3.556 %	8.000 mg
6	Maize Starch (Dried)	5.333 %	12.000 mg
7	Colloidal Silicondioxide (Aerosil 200)	1.333 %	3.000 mg
8	Purified Talc	1.778 %	4.000 mg
9	Magnesium Stearate	2.222 %	5.000 mg
		100.00 %	225.000 mg

Step 1

We sieved weighed quantity of following materials through 20 mesh and took into glass beaker the following:

- Atenolol 50.500 gm
- Dibasic Calcium Phosphate Dihy. 97.250 gm
- Avicel PH 101 37.934 gm

We mixed manually for 5 minutes with the help of glass rod.

The LOD at 105^{O}C was calculated at 1.80%

Step 2:

We took 100 ml water in a beaker, added 8.000 gm Maize starch and stirred to make slurry, heated the slurry to make clear paste, cooled down the paste at ≤ 50^{O}C.

Step 3

We added the paste of Step 2 to Step 1 and kneaded manually with glass rod until good granules were formed. We dried the kneaded mass in tray dryer at 60^{O}C for 20 minutes, after 20 minutes passed the semidried mass through 20

mesh, finally drying the semidried granules for 15minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into polythene bag

The LOD was calculated at 105^{O}C to be 1.11%

Step 4

We sieved the weighed quantity of following materials through 30 mesh and took into glass beaker

- Amlodipine Besylate 7.316 gm
- Maize Starch (Dried) 12.000 gm
- Colloidal Silicon dioxide 3.000 gm

We mixed manually for 5 minutes with glass rod. Then we added granules of Step 30.00 gm and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mixed manually for 10 minutes in Polyethene bag.

Step 5

We sieved weighed quantity following materials through 30 mesh screen and diluted with weighed quantity of blended materials.

- Magnesium Stearate 5.000 gm
- Purified Talc 4.000 gm
- Blend of Step 3 20.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag
The Room Condition at that time was a Temperature 24.3^{O}C and a Relative Humidity of 49.3 %

Step 6

We compressed the blend granules of Step 1 into tablet using 7.50 X 9.00 mm semi biconcave oval shaped tools by mini compression machine at 3.0 to 5.0 ton

Step 7

Compression force and checked the following physical parameters:

Appearance: White to off-white colored, biconvex oval shaped both side plain tablet

Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)

Uniformity of weight: 208 mg to 242 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)

Friability : Not more than 0.8% w/w

DT in water at $37^{O}C$: Not more than 15 minutes

The Room Condition at that time was a Temperature 24.1 ^{O}C and a Relative Humidity of 48.3%

Step 8

After satisfactory result, the compression machine was run

8.2 In Vitro Dissolution Study of Tablet X (a comparison with similar pharmaceutical products currently available in the Bangladesh Market)

Materials:

- Our sample(Sample X) tablets (Amlodipine BP 5 mg+ Atenolol BP 50 mg)
- Fixocard 50 Tablets (Amlodipine BP 5 mg+ Atenolol BP 50 mg), manufactured by Incepta Pharmaceuticals Ltd.
- Amdocal Plus 50 Tablets (Amlodipine BP 5 mg+ Atenolol BP 50 mg), manufactured by Beximco Pharmaceuticals Ltd.
- Sodium acetate Buffer
- Dissolution Tester, Model UDT-804
- S2100UV UV/Vis Spectrophotometer
- Filter paper
- All other rudimentary laboratory equipments
- pH probe

Dissolution test method:

First, the dissolution medium was made by the following process: 5800ml 0r 5.6 litres of water were taken and 60 gm of sodium acetate salt was dissolved in it. The pH was measured with a pH probe and it was found to be 8.4 as the sodium acetate is an alkaline substance. Then we slowly added 1N aqueous solution of acetic acid to the sodium acetate solution until the pH dropped to 4.6. This was done with the help of the pH probe. Thus we got the sodium acetate buffer which is the dissolution medium. We then distributed this into 6 vessels, each containing 900 ml of dissolution medium. The test was conducted on a UDT-804 Dissolution Tester of the paddle stirrer type The tests were performed for a total of 6 tablets, 2 of Amdocal Plus 50, 2 of Fixocard 50 and 2 of tablet X. The samples were taken in 10, 20, 30, 40, 50, and 60 min after the test start. The samples for analyses were diluted by the

dissolution medium and filtered through a paper filter (white band grade); the first portion of filtrate was rejected. Then reference standard solution was prepared using Atenolol API of potency 99.06% and Amlodipine Besylate API of potency 99.52%.

Quantitative analysis:

The samples of drug solutions were analyzed by UV spectrophotometry. The spectrophotometric measurements were performed on an S2100UV UV/Vis Spectrophotometer at 272 nm (for atenolol) and 365 nm (for amlodipine). The spectra were recorded with reference to the corresponding solvent. Reference sample solutions with concentrations 17.8mg/100ml (for amlodipine) and 30mg/50ml (for atenolol) (for UV analyses) were freshly prepared for each test and filtered through a paper filter (white band grade, the same as that used for the test solutions).

Chapter 9
Results and Discussion

Results of Formulations

The first formulation showed picking in the tablets. The second one showed a chipped and somewhat abraded appearance in the tablets. The third showed sticking characteristics to the die and punch. The fourth showed a poor flow property of the granules. The fifth was however successful to give a suitable immediate release dosage form. The tablets from this formulation were taken as the ideal formulation and these tablets were taken to be subjected to further analysis.

Modifications were made on amounts of microcrystalline cellulose Avicel PH 101, Dibasc calcium phosphate, Maize Starch Paste and Maize Starch Dried. Avicel PH 101 and Dibasic Calcium Phosphate both are super disintegrants. Maize starch paste acts as binder, loose binding characteristics; for faster disintegration as well as faster dissolution.

The results of the successful formulation are described in detail below:

Physical Properties (Blended Granules)

Parameters	**Observation**		
Appearance	**Granular**	Coarse	Powder
Bulk Density	Poor	Medium	**Good**
Flow ability	Poor	Medium	**Good**
Sticking (Punch Tip)	Yes	**No**	
Sticking (Die wall)	Yes	**No**	
Capping/Lamination	Yes	**No**	

Physical Properties (Core Tablet)

Test Parameters	Specifications	Results
Appearance	White to off-white colored, biconvex oval shaped both side plain tablet	Complies
Average weight	218 mg to 232 mg (± 3% of the calculated weight, BP)	223.83mg
Uniformity of weight	208 mg to 242 mg (± 7.5% of the average weight, BP)	217-229mg
LOD at 105^{O}C	Not more than 3.5%, BP	1.69%
Hardness	Not less than 40 N, BP	70-92N
Thickness	3.80 mm to 4.20 mm (4.00 mm ± 5%, BP)	3.83-4.01mm
Friability	Not more than 0.8% w/w, BP	0.00%
DT in water at 37^{O}C	Not more than 15 minutes, BP	3-4min

Conclusion:

Most suitable formulation. Tablet was perfectly compliant. No problems were seen.

Dissolution Test Results

We measured the % dissolution rates for atenolol and amlodipine for the drugs: Our sample (tablet X), Amdocal Plus 50 and Fixocard 50.

The wavelengths used for the UV spectroscopic measurements were 272nm for Atenolol and 365nm for amlodipine besylate.

The absorbance readings were as follows:

After 10 mins:

Tablet X:		
	Atenolol	Amlodipine
Sample 1	0.3051	0.1052
Sample 2	0.2944	0.1116

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.3198	0.1186
Sample 2	0.3167	0.1142

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3120	0.1068
Sample 2	0.3003	0.0836

After 20 mins

Tablet X		
	Atenolol	Amlodipine
Sample 1	0.3150	0.1089
Sample 2	0.2898	0.1123

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.3169	0.1099
Sample 2	0.3099	0.1079

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3098	0.1102
Sample 2	0.3018	0.0986

After 30 mins

Tablet X		
	Atenolol	Amlodipine
Sample 1	0.2852	0.0981
Sample 2	0.2873	0.1127

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.2965	0.1199
Sample 2	0.2932	0.1047

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3106	0.1136
Sample 2	0.3060	0.1098

After 40 mins:

Tablet X		
	Atenolol	Amlodipine
Sample 1	0.2998	0.1130
Sample 2	0.2963	0.1172

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.2986	0.1172
Sample 2	0.2973	0.1189

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3186	0.1198
Sample 2	0.3139	0.1123

After 50 mins

Tablet X		
	Atenolol	Amlodipine
Sample 1	0.2951	0.1196
Sample 2	0.2979	0.1182

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.3129	0.1182
Sample 2	0.3133	0.1198

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3136	0.1183
Sample 2	0.3189	0.1189

After 60 mins

Tablet X		
	Atenolol	Amlodipine
Sample 1	0.3098	0.1198
Sample 2	0.3127	0.1196

Amdocal Plus 50		
	Atenolol	Amlodipine
Sample 1	0.3157	0.1198
Sample 2	0.3169	0.1189

Fixocard 50		
	Atenolol	Amlodipine
Sample 1	0.3156	0.1192
Sample 2	0.3174	0.1189

From these absorbances we calculated mathematically the % dissolution rates of atenolol and amlodipine for Tablet X, Amdocal Plus 50 and Fixocard 50.

The results are shown on the following pages:

Time	Tablet X	Amdocal Plus 50	Fixocard 50
10 min	105.80%	112.40%	108.20%
20 min	106.80%	110.70%	108.10%
30 min	101.20%	104.10%	108.90%
40 min	105%	105.30%	111.70%
50 min	104.80%	110.60%	111.70%
60 min	110%	111.70%	111.80%

Table: % dissolution rates of atenolol

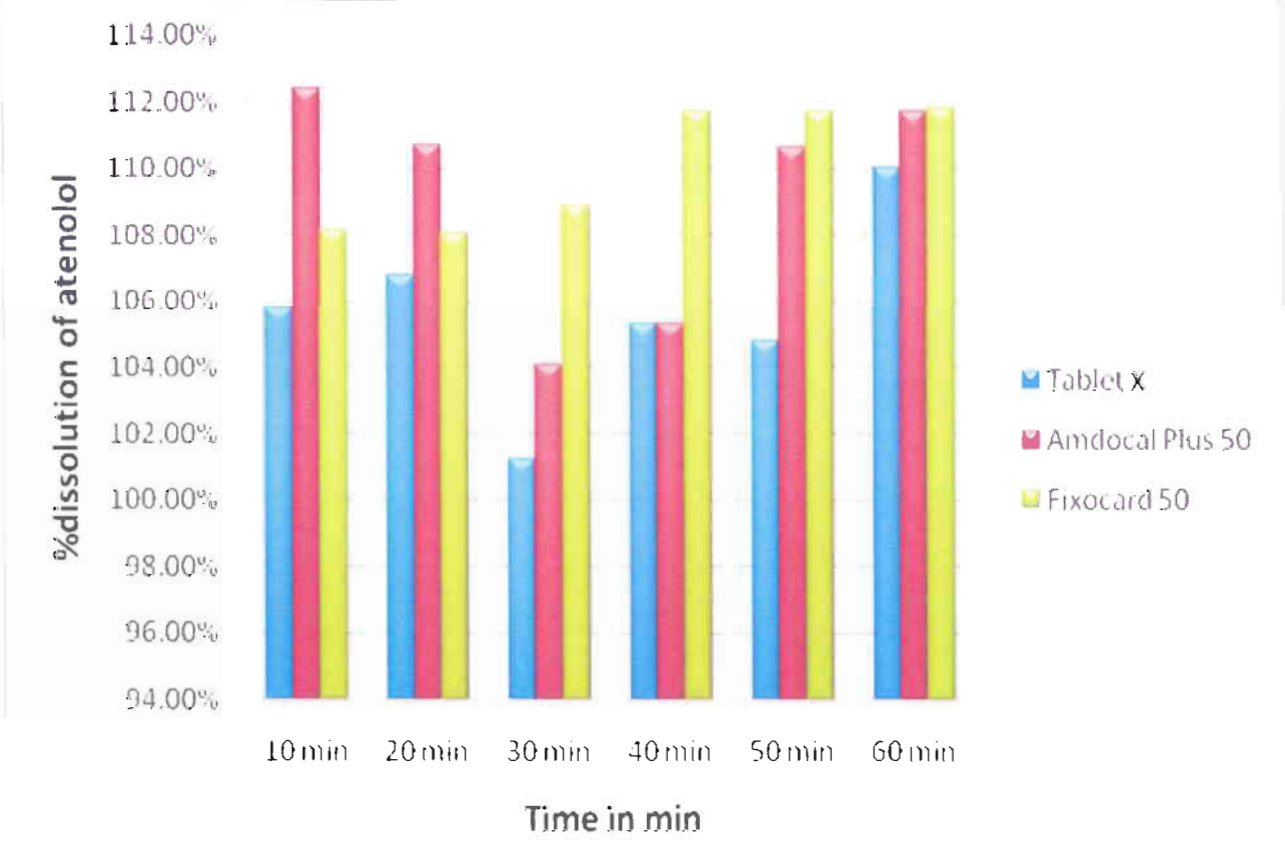

Fig: Graph showing the % dissolution rates of atenolol

Time	Tablet X	Amdocal Plus 50	Fixocard 50
10 min	101.80%	109.34%	89.40%
20 min	103.90%	102.30%	98.00%
30 min	99.10%	105.50%	104.90%
40 min	108%	110.90%	109.00%
50 min	111.80%	111.80%	111.40%
60 min	112%	112.10%	112.20%

Table: % dissolution rates of amlodipine

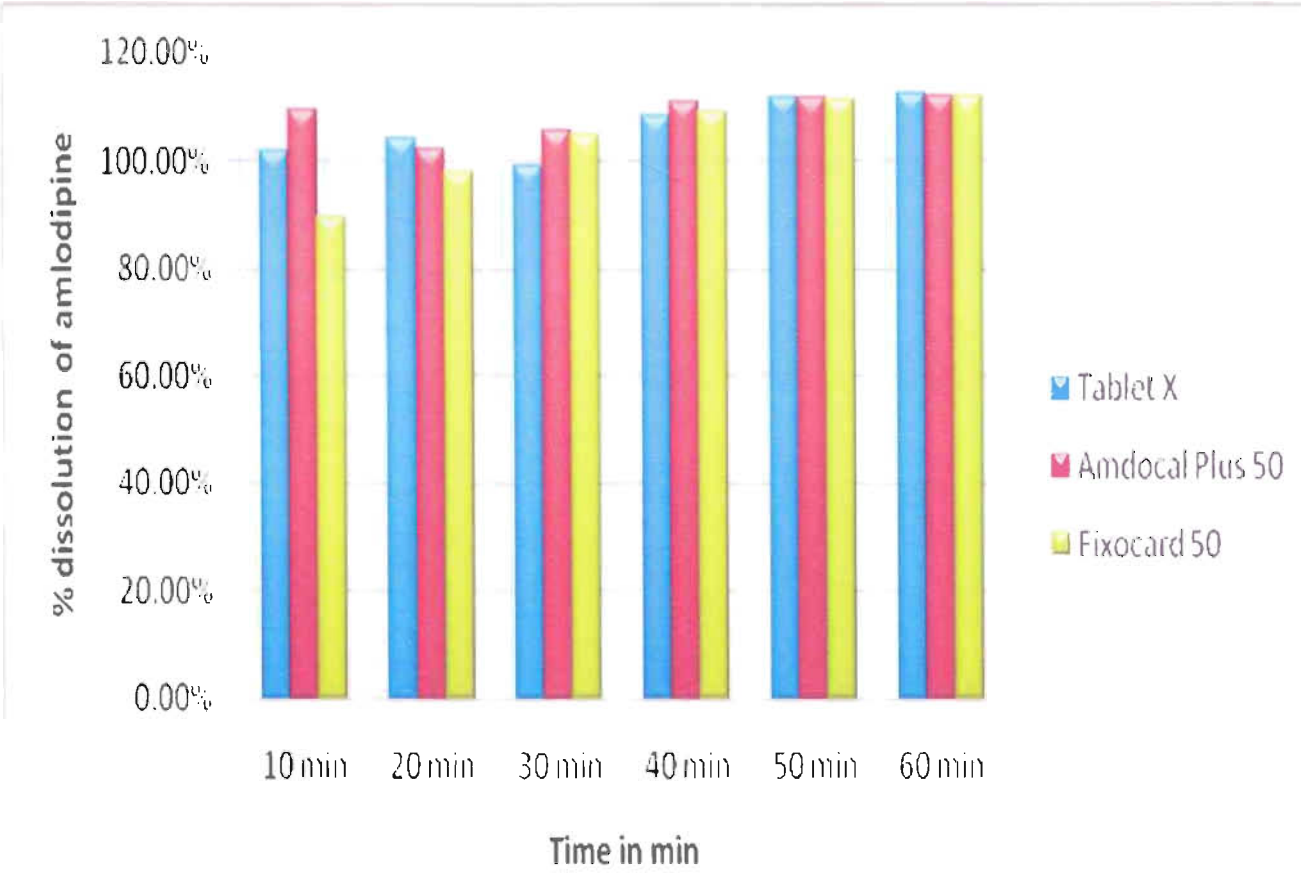

Fig: Graph showing the % dissolution rates of amlodipine

Discussion and conclusion:

According to rates of Dissolution we can see that by the end of 10 mins, almost 100% of the atenolol and amlodipine from all three drugs have dissoluted. All three drugs show similar patterns of dissolution. After 10 mins to the end of 60 mins, the dissolution rates are still around the 100% level, which means that after 10 mins, the rate remains constant for all three drugs and that dissolution is complete by 10 mins. This means that all three are ideal immediate release dosage forms since they are able to dissolute in a very short period of time. This in turn ensures better bioavailability which further ensure better efficacy. Neither of the drugs show significant difference in terms of their dissolution rates. They show negligible difference and high similarity, so it is quite difficult to say which drug is better than the other, in terms of dissolution. Nevertheless, all three drugs prove that they are perfect for immediate release dosage forms and their formulations are very good at making the drug very suitable as immediate release dosage forms due to their fast rates of dissolution. Our sample Tablet X also proves effective and suitable as an immediate release dosage form of multi drug tablet. Therefore, our formulation and methods of design of the drug have proved successful in enabling our sample to compete effectively with its Pharmaceutical competitors.

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