APPROVAL

The thesis paper, entitled "In Vitro Kinetic Studies of Combined Amlodipine (5mg) and Atenolol (50mg) Tablet Dosage Form : A Comparative Study with Similar Market Products Available in Bangladesh", submitted by Anusha Rahman, ID no: 2005-1-70-036, 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 establish an immediate release Amlodipine (5mg) and Atenolol (50mg) tablet (a multilayer tablet) based upon the physical properties of granules and prepared tablets. Multi-drug tablets of amlodipine besylate and atenolol were prepared as either mono-layer (mixed matrix) containing each drug in a separate layer by using similar excipients and processing. The combined dosage form is beneficial in the treatment of cardiovascular diseases such as hypertension, Angina pectoris, and Myocardial infarction. Before going to evaluate the % release of a drug, it is necessary to develop a suitable formulation first and then apply the correct tablet manufacturing process to obtain the required sample. In the designing of the tablet, the excipients and tablet manufacturing technique plays an important role. The sample is then compared with other market products currently available, in terms of their % dissolution rates. This study gives idea on how different excipients and manufacturing techniques can be used to formulate and hence develop a sample of a combined dosage form and compare its rates of dissolution with other market products. Accordingly we can get an idea of the performance of the developed tablet in relation with its competitors.

Keywords: Amlodipine (5mg) and Atenolol (50mg) tablet, excipients, % dissolution rates, manufacturing technique, combined dosage form.

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Chapter 1
Fixed dose combination therapy in the treatment of hypertension

1.1 Introduction

Raised blood pressure is a common and quantitatively important cardiovascular risk factor. Over 50% of over 65's in industrialised countries may be considered to have hypertension and 50% of people in this age group go on to die a cardiovascular death such as myocardial infarct or stroke. Studies have clearly demonstrated the benefit and safety of an aggressive strategy of blood pressure lowering with targets of below 140 mm Hg systolic and 90 mm Hg diastolic. Hypertension-induced stroke appears to be largely preventable and a significant reduction is seen in hypertension-attributable ischaemic heart disease when the above targets are achieved. Reaching and maintaining these targets in the majority of patients however presents a clinical challenge.

Currently several drug classes can be utilised in the treatment of hypertension: thiazide diuretics, beta β-blockers, calcium channel blockers (CCB's), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (AII) receptor blockers, alpha (α) blockers and centrally acting agents. Both the British Hypertension Society 1999 guidelines and the American 6th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (JNC VI) of 1997 recommend that, in the absence of contra-indications or compelling indications for other agents, thiazide diuretics and β-blockers are the drugs of choice. These drugs have proved to be both safe and efficacious in numerous randomised control trials. Practice has been to begin treatment with one of these agents as monotherapy at a low dose. If this does not control blood pressure adequately then the physician is faced with three options.

The first is upward drug dose titration. The patient is continued on their current monotherapy but the daily dosage is increased. While benefiting from maintaining the patient on a familiar drug and a probable reduction in prescription costs this strategy falls foul of the law of diminishing returns. In many cases increasing the dose leads to only modest increases in blood pressure response at the cost of more frequent or severe side effects. If a drug

fails to lower blood pressure at the usual dose then it is unlikely to be much more successful at higher doses thereafter.

An alternative strategy is a trial of sequential monotherapy until an effective agent is found. Unfortunately there is no simple reliable method to predict which agent will work for an individual patient. A sequence of therapies can be substituted until the one which lowered blood pressure adequately is found. While, eventually, this method may prove successful in some patients, a lengthy titration period ensues with a loss of patient confidence in the prescribing physician. In many patients the ideal monotherapy can never be identified.

The third option is to use more than one drug either as multiple individual drugs or a fixed dose combination therapy. In recent years the latter has not been favoured with many physicians particularly in the United Kingdom. It offends the purists who have labelled it 'polypharmacy'. Rational drug combinations in fixed dose formulations however are widely used in the treatment of other conditions such as Parkinson's disease (L-dopa plus an extracerebral dopa-decarboxylase inhibitor) or bacterial infection (trimethoprim and sulfamethoxazole as co-trimoxazole). The use of multiple drug classes is also widely accepted in the management of other chronic conditions such as angina. Fixed dose combinations are still viewed suspiciously in some quarters for the treatment of hypertension. There is a renewed interest in the use of low-dose combination therapy and increasing recognition that this approach may offer efficacy and tolerability with simplicity.

Randomised control led trials of the treatment of hypertension performed over the past 30 years have shown that many patients will require more than one drug to reach the recommended level of blood pressure control. Only one-third of patients in the Hypertension Optimal Treatment (HOT) study achieved their targets on one drug alone. The remainder needed up to five drugs. This trial confirms that more aggressive treatment targets are safe and effective in preventing cardiovascular events.

A judicious approach to prescribing would therefore suggest the use of low-dose combination products early in the treatment plan. The benefits of the combination selected and actual doses used over monotherapy must be proven. The two drugs in combination must be established to lower blood pressure by a greater amount than each alone. Lower doses in combination must be as effective as usual monotherapy doses but with fewer side effects.

1.2 Potential advantages of Fixed dose combination therapy in the treatment of hypertension:

- Hypertension is heterogeneous in its response to treatment and a combination of two drugs will increase the likelihood of response in a given individual
- There may be enhancement of each drugs antihypertensive effect which in ideal combinations may even be synergistic rather than simply additive
- As the two drugs exert their antihypertensive effects by differing modes of action there is a potential for a smoother onset and longer duration of action
- By keeping both drugs at low dose the incidence of side effects from each may be minimised
- In many cases the combination of the two drugs can offset each others side-effect profile to some degree, e.g. the hypokalaemia caused by thiazide diuretics can be prevented by concurrent use of an ACE inhibitor, and palpitations caused by some CCB's may be reduced by β-blocker therapy
- Different mechanisms may exert different beneficial effects beyond the benefits of blood pressure reduction on target organs. This concept is attractive but not yet fully substantiated by evidence. When a hypertensive patient develops cardiac, renal, or cerebral end-organ damage their prognosis worsens. Combination treatments may reduce the rate of progression. For example trials have shown that an ACE inhibitor plus a non-dihydropyridine CCB have a greater effect on reducing hypertension-induced left ventricular hypertrophy than

monotherapy. The ACE inhibitor lisinopril and the CCB verapamil also significantly reduce microalbuminuria, an indication of renal damage

- Combination therapies, particularly in low dose, can usually be taken once daily with improvement in patient compliance with treatment
- Dose adjustments and titration will be simpler, blood pressure targets will be attained more quickly, and require fewer clinic or physician visits will be required to achieve targets. This results in simpler and more effective strategies therapy for induction of antihypertensive therapy in primary care
- The overall cost of treatment can be reduced. Low-dose combination products may be less costly than the constituents prescribed separately and prescribing costs may be less in some countries for a single medication rather than for two separate drugs

1.3 Thiazide diuretics and β-blockers

The most common combination products comprise a thiazide diuretic plus a β-blocker, thus utilising the two drug classes with the established outcome benefits in the treatment of hypertension. The mechanism of action of diuretics is still controversial but there is increased retention of sodium by the hypertensive kidney when blood pressure is lowered by non-diuretic drugs, thus reducing antihypertensive efficacy. Thiazides minimise the sodium retention and so restore efficacy when used in combination. The exact mechanism by which β-blockers lower blood pressure is also not fully understood although they are known to decrease cardiac output, alter baroceptor reflex sensitivity and block peripheral adrenoceptors. Their efficacy when combined with a thiazide may however lie in the fact that β-blockers suppress renin and so angiotensin II production. This will thus attenuate the responses to intravascular volume depletion and total body sodium loss caused by thiazides so causing a greater fall in blood pressure. These two treatments have been shown in clinical trials to have an additive effect on lowering blood pressure while having a side-effect profile similar to placebo at low doses. Thiazides are now used in lower doses than before. Low

doses provide adequate efficacy with few metabolic side effects. Some of the early fixed dose combinations include what are now considered to be high doses of thiazides and should probably be avoided.

1.4 Thiazide diuretics and ACE inhibitors/A II blockers

Another powerful combination is a thiazide combined with an ACE inhibitor. The diuretic causes intravascular volume depletion and increased sodium loss as mentioned above. This causes reflex activation or the renin-angiotensin-aldosterone system (RAAS) thus potentiating the effects of an ACE inhibitor. Their effective combination at low-dose was demonstrated by Chrysant in a large double-blind placebo-controlled multicentre study using different fixed-dose combinations of lisinopril and hydrochlorothiazide.A combination of 12.5 mg hydrochlorothiazide plus 10 mg lisinopril was found to exert the best antihypertensive effect whilst having the lowest incidence of side effects. ACE inhibitors will also reduce the incidence of hypokalaemia in patients taking thiazides. Combining AII antagonists with thiazides relies on the same principles with the additional benefit of avoiding the side effects of ACE inhibitors such as cough and angioedema. There are fewer clinical trials of this combination than with ACE inhibitors but those published confirm the enhanced efficacy and good tolerability of AII antagonists in combination with thiazide diuretics.

1.5 β blockers and calcium channel blockers

Non-dihydropyridine CCB's, such as verapamil and diltiazem, should be avoided in combination with β-blockers due to the risk of symptomatic bradycardia and atrioventricular block. Dihydropyridine CCB's have however been shown to be effective with β-blockers and are another therapeutic option in low-dose combination. β-blockers suppress renin secretion which potentiates the vasodilatory properties of CCB's and this theoretical advantage is supported by data combining felodipine plus metoprolol. This combination appears to have an additive effect on blood pressure. Appropriate drugs and formulations should be selected for combination therapy. The pharmacokinetics and pharmacodynamics of the two should be compatible.

Combination of a dihydropyridine such as nifedipine with a rapid onset and short duration of effect with a slower onset, longer lasting beta-blocker like atenolol may not give optimal combined responses over the dose interval.

1.6 Thiazide diuretics and calcium channel blockers

This is a more controversial and usually less effective combination. A previous studyexamined a group of hypertensives (diastolic blood pressure >95 mm Hg) who took bendrofluazide for 1 month followed by the addition of nifedipine. A fall in blood pressure was observed after the first month of bendrofluazide but an even greater reduction was seen after nifedipine was added. In contrast when patients received nifedipine for the first month followed by the addition of bendrofluazide no additional reduction in blood pressure was seen. This finding was re-affirmed when another of similar design study substituted the long-acting CCB amlodipine for the shorter-acting nifedipine. The most obvious reason for these findings is that CCB's have natriuretic properties in their own right and so possibly attenuate the effect of a thiazide

1.7 Calcium channel blockers and ACE inhibitors

Calcium channel blockers are potent vasodilators. This may induce reflex activation of the sympathetic nervous system and or the RAAS. There is an increase in plasma renin activity and thus angiotensin II production. This will potentiate the action of ACE inhibitors and a greater reduction in blood pressure should occur. This theory is borne out in practice where the addition of ramipril to felodipine causes a greater blood pressure reduction than when placebo is added. Additionally combinations of CCB's and ACE inhibitors have been reported to have fewer side effects than each individual medication alone.

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1.9 β blockers and ACE inhibitors

In contrast to calcium channel blockers, β-blockers appear to offer little advantage on blood pressure when combined with ACE inhibitors. Previous studies have shown that adding a β-blocker to an ACE inhibitor does not cause a further blood pressure fall. This may be a result of the action of β-blockers to inhibit renin secretion, cause sodium retention and increase peripheral vasoconstriction. ACE inhibitors may be less effective in this low-renin state and thus little further blood pressure reduction is observed.

1.10 Summary

The majority of patients will require more than one drug to control their hypertension. The use of low-dose combination therapy is justifiable as a safe and effective approach to initiating therapy. It allows maximisation of each constituent drug's mode of action while minimising, or even offsetting, side effects. Blood pressure may be controlled more easily and with fewer clinic visits and a shorter titration period. Patient compliance should be optimised, the risk of switching and poor persistence on therapy avoided, and the financial burden of treating hypertension and its sequelae will be minimised. An increasing evidence base exists to justify the selection of optimal low doses in newer combinations. Rational combinations at appropriate dose offer safety and efficacy in the short term and with longer term treatment of hypertension.

According to American Heart Association:

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

1.11 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. In that case, 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)**

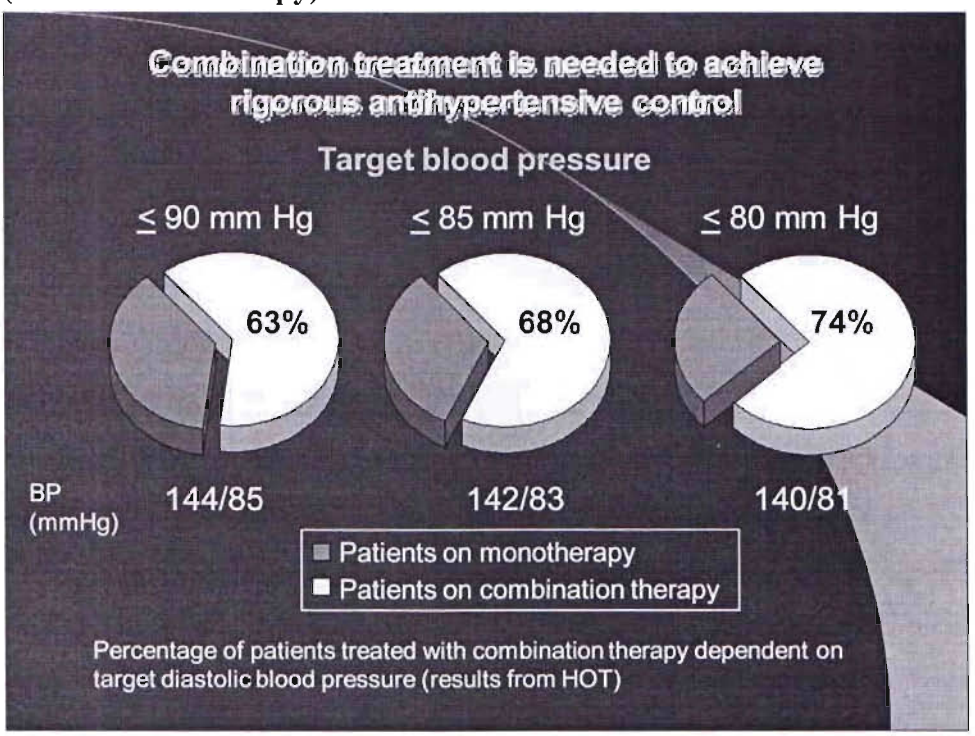


Chart 1: Comparison between monotherapy and combination therapy

1.12 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.

1.13 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)

1.14 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-Atenolol combined dosage therapy

2.1 Amlodipine plus Atenolol Tablets

An example is **Amplopres-AT** manufactured by Cipla Pharmaceuticals, India.

2.1.1 Composition:

Each uncoated tablet may contain Amlodipine besylate equivalent to Amlodipine 5 mg and Atenolol IP 50 mg

OR

Amlodipine besylate equivalent to Amlodipine 5 mg and Atenolol IP 25 mg.

Description:

Amlodipine plus Atenolol Tablets are fixed-dose combinations of amlodipine and atenolol.

2.1.2 Indications

The combination is indicated for the treatment of hypertension and chronic stable angina

2.1.3 Dosage and Administration

The recommended dosage is one tablet of (Amlodipine 5 mg and Atenolol IP 50 mg) or (Amlodipine 5 mg and Atenolol IP 25 mg) daily. If necessary, the dosage may be increased to two tablets daily. The dosage however should be individualized.

Some renally-impaired or elderly patients being treated for hypertension may be initiated on a lower starting dose of (Amlodipine 5 mg and Atenolol IP 25 mg) given as one tablet a day.

2.1.4 Contraindications

Hypersensitivity to either component, sinus bradycardia, second and higher degrees of heart block, cardiogenic shock, hypotension and overt cardiac failure.

2.1.5 Warnings and Precautions

2.1.5.1 Drug Interactions

Catecholamine depleting drugs: may have additive effect when given with beta-blocker, and hence patients taking both the drugs concomitantly should be observed for hypotension and/or marked bradycardia.

Clonidine: Beta-blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Prostaglandin synthase inhibiting drugs: Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

2.1.5.2 Hypotension

Excessive fall of blood pressure can occur in some patients especially the elderly.

2.1.5.3 Aggravation of Angina

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed 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.

2.1.5.4 Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. Placebo-controlled trials of amlodipine in patients with NYHA Class III or IV heart failure showed no overall adverse effect on survival or cardiac morbidity. In NYHA class II/III heart failure patients, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms or LVEF.

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, atenolol should be administered cautiously. Both digitalis and atenolol slow AV conduction.

2.1.5.5 In Patients without a History of Cardiac Failure

Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, (Amlodipine 5 mg and Atenolol IP 50 mg)should be withdrawn.

2.1.5.6 Bronchospasm

The combination should be used with caution in patients with airway obstruction who do not respond to, or cannot tolerate, other antihypertensive treatment.

2.1.5.7 Cessation of Therapy

Patients with coronary artery disease, who are being treated with (Amlodipine 5 mg and Atenolol IP 50 mg), should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta-blockers, when discontinuation of (Amlodipine 5 mg and Atenolol IP 50 mg)is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that (Amlodipine 5 mg and Atenolol IP 50 mg)be promptly reinstituted, at least temporarily. Because coronary artery disease is common

and may be unrecognized, it may be prudent not to discontinue (Amlodipine 5 mg and Atenolol IP 50 mg) therapy abruptly even in patients treated only for hypertension.

2.1.5.8 Anaesthesia and Major Surgery

It is not advisable to withdraw (Amlodipine 5 mg and Atenolol IP 50 mg)prior to surgery in the majority of patients. However, care should be taken when using anaesthetic agents such as those, which may depress the myocardium. Atenolol is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution.

2.1.5.9 Diabetes and Hypoglycaemia

(Amlodipine 5 mg and Atenolol IP 50 mg) should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses atenolol does not potentiate insulin-induced hypoglycaemia and, unlike nonselective beta-blockers, does not delay recovery of blood glucose to normal levels.

2.1.5.10 Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom (Amlodipine 5 mg and Atenolol IP 50 mg) therapy is to be withdrawn should be monitored closely.

2.1.5.11 Untreated Phaeochromocytoma

(Amlodipine 5 mg and Atenolol IP 50 mg) should not be given to patients with untreated phaeochromocytoma.

2.1.5.12 Renal Impairment

The combination can be used in patients with renal impairment. However, caution may be necessary if the creatinine clearance is less than 30 ml/min because of possible reduction in the excretion of unchanged atenolol. Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of atenolol

2.1.5.13 Hepatic Impairment

Caution may be necessary in the use of the combination in patients with severe liver damage because of the prolongation of the elimination half- life of amlodipine.

2.1.5.14 Pregnancy

The combination should be used during pregnancy only if the expected benefit outweighs the potential foetal risk.

2.1.5.15 Lactation

The combination should not be used by nursing mothers. If its use is considered necessary, breast feeding should be stopped.

2.1.5.16 Pediatric use

Safety and effectiveness of this combination has not been evaluated in pediatrics.

2.1.5.17 Undesirable Effects

The combination of amlodipine and atenolol is well tolerated. Side effects include headache, palpitations, flushing, oedema, depression, dizziness, dyspepsia, dyspnoea, muscle cramps, fatigue, cold extremities and bradycardia.

2.1.5.18 Overdosage

Though not documented, hypotension and less frequently congestive cardiac failure may occur in cases of overdosage. Unabsorbed drugs may be removed

by gastric lavage or administration of activated charcoal. Symptomatic treatment is suggested.

2.2 Amlodipine besylate

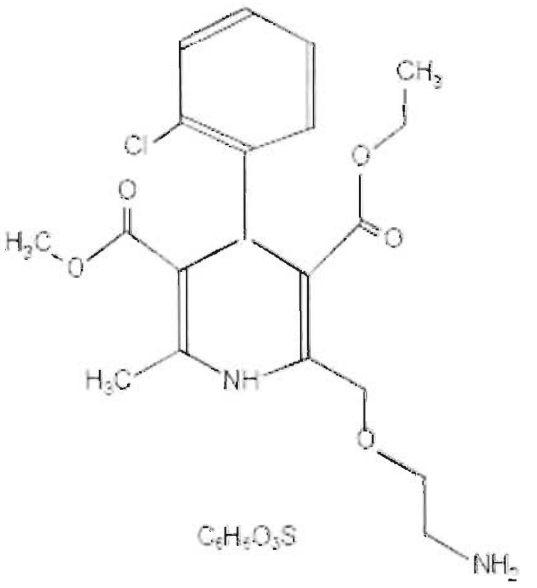
2.2.1 General Characteristics:

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

Chemically described as 3-Ethyl-5-methyl (±) - 2 - [(2 - aminoethoxy) methyl] - 4 - (2 - chlorophenyl) - 1,4 - dihydro - 6 - methyl - 3,5 - pyridinedicarboxylate, monobenzenesulphonate.

Molecular formula: C20H25CIN2O5•C6H6O3S

Structural formula:



- white crystalline powder
- molecular weight of 567.1.
- slightly soluble in water and sparingly soluble in ethanol.
- tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of Amlodipine for oral administration.

- Contains the following inactive ingredients: dibasic calcium phosphate dihydrous, magnesium stearate, microcrystalline cellulose.

2.2.2 Pharmacology and Pharmacodynamics

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. 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.

Amlodidpine 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.

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 co-administered with beta-blockers to man. Similar findings, however, have been observed in normals 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 com-bination 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.

2.2.3 Pharmacokinetics

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.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pediatric Patients: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

2.2.4 Indications and Contraindications

- Hypertension: Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
- 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.
- 4Vasospastic 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.
- Amlodipine is contraindicated in patients with known sensitivity to Amlodipine

2.2.5 Precautions

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.

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.

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.

2.2.6 Adverse Reactions

- Edema
- Dizziness
- Flushing
- Palpitation
- Headache
- Fatigue
- Nausea
- Abdominal Pain
- arrhythmia (including ventricular tachycardia and atrial fibrillation)
- bradycardia
- chest pain
- hypotension
- peripheral ischemia
- tachycardia
- postural dizziness and hypotension
- tremor
- vertigo
- anorexia
- constipation

- dyspepsia
- diarrhea
- flatulence
- pancreatitis
- vomiting
- allergic reaction,
- back pain
- hot flushes
- pain
- rigors
- weight gain
- weight decrease
- arthrosis
- muscle cramps
- sexual dysfunction (male and female)
- insomnia
- nervousness
- depression
- abnormal dreams
- anxiety
- depersonalization
- abnormal vision
- conjunctivitis
- diplopia
- eye pain
- tinnitus
- nocturia
- dry mouth
- increased sweating
- hyperglycemia
- thirst
- leukopenia

- 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

2.2.7 Dosage and Overdosage

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.

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.

Amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

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.

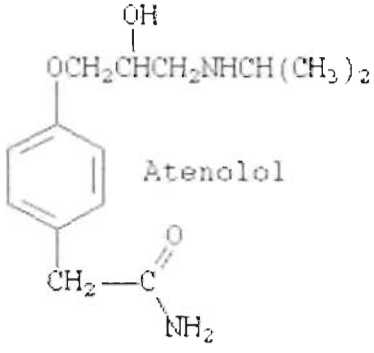
If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. 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 helpful

2.3 Atenolol

2.3.1 General Characteristics and Physical Properties

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



It has a Molecular formula of $C_{14}H_{22}N_2O_3$ with a Relative Molecular Mass of 266.3 Atenolol is a white or almost white powder which is odourless or almost odourless. It has a Melting Point of 152-155°C and the Dissociation Constant (pK_a) is 9.6 at 24°C. Partition Coefficent (Log P (octanol)) is 0.23 Sparingly Soluble in Water. Soluble in Ethanol and Methanol. Practically Insoluble in Ether

2.3.2 Pharmacology and Pharmacodynamics

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.

Atenolol is a beta $_1$ -selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits beta 2 -adrenoreceptors, chiefly located in the bronchial and vascular musculature.

In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of atenolol has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of atenolol, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma atenolol concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as

has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta $_1$ selectivity of atenolol has been shown by its reduced ability to reverse the beta $_2$ -mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of atenolol producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, atenolol produced a significantly smaller decrease of FEV $_1$ than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, atenolol increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. Atenolol is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of atenolol with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular

fiber length and end diastolic pressure, particularly in patients with heart failure.

In general, elderly patients present higher atenolol plasma levels with total clearance values about 50% lower than younger subjects. The half-life is markedly longer in the elderly compared to younger subjects. The reduction in atenolol clearance follows the general trend that the elimination of renally excreted drugs is decreased with increasing age.

2.3.3 Indications

- hypertension
- coronary heart disease
- arrhythmias
- angina (chest pain)
- treat and reduce the risk of heart complications following myocardial infarction (heart attack)
- used to treat the symptoms of Graves Disease, until antithyroid medication can take effect

2.3.4 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.

2.3.5 Side effects

Atenolol causes significantly fewer central nervous system side effects (depressions, nightmares) and fewer bronchospastic reactions. In addition, β-blockers numb 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

2.3.6 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.

2.3.7 Pharmacokinetics

In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. Atenolol also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral atenolol is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m ^{2}.

Chapter 3

High Blood Pressure (Hypertension)

3.1 What is high blood pressure?

High blood pressure (HBP) or hypertension means high pressure (tension) in the arteries. Arteries are vessels that carry blood from the pumping heart to all the tissues and organs of the body. High blood pressure does not mean excessive emotional tension, although emotional tension and stress can temporarily increase blood pressure. Normal blood pressure is below 120/80; blood pressure between 120/80 and 139/89 is called "pre-hypertension", and a blood pressure of 140/90 or above is considered high.

The top number, the systolic blood pressure, corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The bottom number, the diastolic pressure, represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed.

An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), eye damage, and stroke (brain damage). These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic (long duration) high blood pressure. For that reason, the diagnosis of high blood pressure is important so efforts can be made to normalize blood pressure and prevent complications.

It was previously thought that rises in diastolic blood pressure were a more important risk factor than systolic elevations, but it is now known that in people 50 years or older systolic hypertension represents a greater risk.

The American Heart Association estimates high blood pressure affects approximately one in three adults in the United States - 73 million people. High blood pressure is also estimated to affect about two million American teens and children, and the Journal of the American Medical Association reports that many are under-diagnosed. Hypertension is clearly a major public health problem.

3.2 How is the blood pressure measured?

The blood pressure usually is measured with a small, portable instrument called a blood pressure cuff (sphygmomanometer). (Sphygmo is Greek for pulse, and a manometer measures pressure.) The blood pressure cuff consists of an air pump, a pressure gauge, and a rubber cuff. The instrument measures the blood pressure in units called millimeters of mercury (mm Hg).

The cuff is placed around the upper arm and inflated with an air pump to a pressure that blocks the flow of blood in the main artery (brachial artery) that travels through the arm. The arm is then extended at the side of the body at the level of the heart, and the pressure of the cuff on the arm and artery is gradually released. As the pressure in the cuff decreases, a health practitioner listens with a stethoscope over the artery at the front of the elbow. The pressure at which the practitioner first hears a pulsation from the artery is the systolic pressure (the top number). As the cuff pressure decreases further, the pressure at which the pulsation finally stops is the diastolic pressure (the bottom number).

3.3 How is high blood pressure defined?

Blood pressure can be affected by several factors, so it is important to standardize the environment when blood pressure is measured. For at least one hour before blood pressure is taken, avoid eating, strenuous exercise (which can lower blood pressure), smoking, and caffeine intake. Other stresses may alter the blood pressure and need to be considered when blood pressure is measured.

Even though most insurance companies consider high blood pressure to be 140/90 and higher for the general population, these levels may not be appropriate cut-offs for all individuals. Many experts in the field of hypertension view blood pressure levels as a range, from lower levels to higher levels. Such a range implies there are no clear or precise cut-off values to separate normal blood pressure from high blood pressure. Individuals with so-called pre-hypertension (defined as a blood pressure between 120/80 and

139/89) may benefit from lowering of blood pressure by life style modification and possibly medication especially if there are other risk factors for end-organ damage such as diabetes or kidney disease (life style changes are discussed below).

For some people, blood pressure readings lower than 140/90 may be a more appropriate normal cut-off level. For example, in certain situations, such as in patients with long duration (chronic) kidney diseases that spill (lose) protein into the urine (proteinuria), the blood pressure is ideally kept at 130/80, or even lower. The purpose of reducing the blood pressure to this level in these patients is to slow the progression of kidney damage. Patients with diabetes (diabetes mellitus) may also benefit from blood pressure that is maintained at a level lower than 130/80. In addition, African Americans, who have an increased risk for developing the complications of hypertension, may decrease this risk by reducing their systolic blood pressure to less than 135 and the diastolic blood pressure to 80 mm Hg or less.

In line with the thinking that the risk of end-organ damage from high blood pressure represents a continuum, statistical analysis reveals that beginning at a blood pressure of 115/75 the risk of cardiovascular disease doubles with each increase in blood pressure of 20/10. This type of analysis has led to an ongoing "rethinking" in regard to who should be treated for hypertension, and what the goals of treatment should be.

3.3.1 Isolated systolic high blood pressure

Remember that the systolic blood pressure is the top number in the blood pressure reading and represents the pressure in the arteries as the heart contracts and pumps blood into the arteries. A systolic blood pressure that is persistently higher than 140 mm Hg is usually considered elevated, especially when associated with an elevated diastolic pressure (over 90).

Isolated systolic hypertension, however, is defined as a systolic pressure that is above 140 mm Hg with a diastolic pressure that still is below 90. This disorder primarily affects older people and is characterized by an increased (wide)

pulse pressure. The pulse pressure is the difference between the systolic and diastolic blood pressures. An elevation of the systolic pressure without an elevation of the diastolic pressure, as in isolated systolic hypertension, therefore, increases the pulse pressure. Stiffening of the arteries contributes to this widening of the pulse pressure.

Once considered to be harmless, a high pulse pressure is now considered an important precursor or indicator of health problems and potential end-organ damage. Isolated systolic hypertension is associated with a two to four times increased future risk of an enlarged heart, a heart attack (myocardial infarction), a stroke (brain damage), and death from heart disease or a stroke. Clinical studies in patients with isolated systolic hypertension have indicated that a reduction in systolic blood pressure by at least 20 mm to a level below 160 mm Hg reduces these increased risks.

3.3.2 White coat high blood pressure

A single elevated blood pressure reading in the doctor's office can be misleading because the elevation may be only temporary. It may be caused by a patient's anxiety related to the stress of the examination and fear that something will be wrong with his or her health. The initial visit to the physician's office is often the cause of an artificially high blood pressure that may disappear with repeated testing after rest and with follow-up visits and blood pressure checks. One out of four people that are thought to have mild hypertension actually may have normal blood pressure when they are outside the physician's office. An increase in blood pressure noted only in the doctor's office is called 'white coat hypertension.' The name suggests that the physician's white coat induces the patient's anxiety and a brief increase in blood pressure. A diagnosis of white coat hypertension might imply that it is not a clinically important or dangerous finding.

However, caution is warranted in assessing white coat hypertension. An elevated blood pressure brought on by the stress and anxiety of a visit to the doctor may not necessarily always be a harmless finding since other stresses in a patient's life may also cause elevations in the blood pressure that are not

ordinarily being measured. Monitoring blood pressure at home by blood pressure cuff or continuous monitoring equipment or at a pharmacy can help estimate the frequency and consistency of higher blood pressure readings. Additionally, conducting appropriate tests to search for any complications of hypertension can help evaluate the significance of variable blood pressure readings.

3.4 What are the causes of secondary high blood pressure?

As mentioned previously, 5% of people with hypertension have what is called secondary hypertension. This means that the hypertension in these individuals is secondary to (caused by) a specific disorder of a particular organ or blood vessel, such as the kidney, adrenal gland, or aortic artery.

3.4.1 Renal (kidney) hypertension

Diseases of the kidneys can cause secondary hypertension. This type of secondary hypertension is called renal hypertension because it is caused by a problem in the kidneys. One important cause of renal hypertension is narrowing (stenosis) of the artery that supplies blood to the kidneys (renal artery). In younger individuals, usually women, the narrowing is caused by a thickening of the muscular wall of the arteries going to the kidney (fibromuscular hyperplasia). In older individuals, the narrowing generally is due to hard, fat-containing (atherosclerotic) plaques that are blocking the renal artery.

How does narrowing of the renal artery cause hypertension? First, the narrowed renal artery impairs the circulation of blood to the affected kidney. This deprivation of blood then stimulates the kidney to produce the hormones, renin and angiotensin. These hormones, along with aldosterone from the adrenal gland, cause a constriction and increased stiffness (resistance) in the peripheral arteries throughout the body, which results in high blood pressure.

Renal hypertension is usually first suspected when high blood pressure is found in a young individual or a new onset of high blood pressure is discovered in an older person. Screening for renal artery narrowing then may include renal isotope (radioactive) imaging, ultrasonographic (sound wave) imaging, or magnetic resonance imaging (MRI) of the renal arteries. The purpose of these tests is to determine whether there is a restricted blood flow to the kidney and whether angioplasty (removal of the restriction in the renal arteries) is likely to be beneficial. However, if the ultrasonic assessment indicates a high resistive index within the kidney (high resistance to blood flow), angioplasty may not improve the blood pressure because chronic damage in the kidney from long-standing hypertension already exists. If any of these tests are abnormal or the doctor's suspicion of renal artery narrowing is high enough, renal angiography (an x-ray study in which dye is injected into the renal artery) is done. Angiography is the ultimate test to actually visualize the narrowed renal artery.

A narrowing of the renal artery may be treated by balloon angioplasty. In this procedure, the physician threads a long narrow tube (catheter) into the renal artery. Once the catheter is there, the renal artery is widened by inflating a balloon at the end of the catheter and placing a permanent stent (a device that stretches the narrowing) in the artery at the site of the narrowing. This procedure usually results in an improved blood flow to the kidneys and lower blood pressure. Moreover, the procedure also preserves the function of the kidney that was partially deprived of its normal blood supply. Only rarely is surgery needed these days to open up the narrowing of the renal artery.

Any of the other types of chronic kidney disease that reduces the function of the kidneys can also cause hypertension due to hormonal disturbances and/or retention of salt.

It is important to remember that not only can kidney disease cause hypertension, but hypertension can also cause kidney disease. Therefore, all patients with high blood pressure should be evaluated for the presence of kidney disease so they can be treated appropriately.

3.4.2 Adrenal gland tumors

Two rare types of tumors of the adrenal glands are less common, secondary causes of hypertension. The adrenal glands sit right on top of the kidneys. Both of these tumors produce excessive amounts of adrenal hormones that cause high blood pressure. These tumors can be diagnosed from blood tests, urine tests, and imaging studies of the adrenal glands. Surgery is often required to remove these tumors or the adrenal gland (adrenalectomy), which usually relieves the hypertension.

One of the types of adrenal tumors causes a condition that is called primary hyperaldosteronism because the tumor produces excessive amounts of the hormone aldosterone. In addition to the hypertension, this condition causes the loss of excessive amounts of potassium from the body into the urine, which results in a low level of potassium in the blood. Hyperaldosteronism is generally first suspected in a person with hypertension when low potassium is also found in the blood. (Also, certain rare genetic disorders affecting the hormones of the adrenal gland can cause secondary hypertension.)

The other type of adrenal tumor that can cause secondary hypertension is called a pheochromocytoma. This tumor produces excessive catecholamines, which include several adrenaline-related hormones. The diagnosis of a pheochromocytoma is suspected in individuals who have sudden and recurrent episodes of hypertension that are associated with flushing of the skin, rapid heart beating (palpitations), and sweating, in addition to the symptoms associated with high blood pressure.

3.4.3 Coarctation of the aorta

Coarctation of the aorta is a rare hereditary disorder that is one of the most common causes of hypertension in children. This condition is characterized by a narrowing of a segment of the aorta, the main large artery coming from the heart. The aorta delivers blood to the arteries that supply all of the body's organs, including the kidneys.

The narrowed segment (coarctation) of the aorta generally occurs above the renal arteries, which causes a reduced blood flow to the kidneys. This lack of blood to the kidneys prompts the renin-angiotensin-aldosterone hormonal system to elevate the blood pressure. Treatment of the coarctation is usually the surgical correction of the narrowed segment of the aorta. Sometimes, balloon angioplasty (as described above for renal artery stenosis) can be used to widen (dilate) the coarctation of the aorta.

3.4.4 The metabolic syndrome and obesity

Genetic factors play a role in the constellation of findings that make up the "metabolic syndrome." Individuals with the metabolic syndrome have insulin resistance and a tendency to have type 2 diabetes mellitus (non-insulin-dependent diabetes).

Obesity, especially associated with a marked increase in abdominal girth, leads to high blood sugar (hyperglycemia), elevated blood lipids (fats), vascular inflammation, endothelial dysfunction (abnormal reactivity of the blood vessels), and hypertension all leading to premature atherosclerotic vascular disease. The *American Obesity Association* states the risk of developing hypertension is five to six times greater in obese Americans, age 20 to 45, compared to non-obese individuals of the same age. The American Journal of Clinical Nutrition reported in 2005 that waist size was a better predictor of a person's blood pressure than body mass index (BMI). Men should strive for a waist size of 35 inches or under and women 33 inches or under. The epidemic of obesity in the United States contributes to hypertension in children, adolescents, and adults.

3.5 What are the symptoms of high blood pressure?

Uncomplicated high blood pressure usually occurs without any symptoms (silently) and so hypertension has been labeled "the silent killer." It is called this because the disease can progress to finally develop any one or more of the several potentially fatal complications of hypertension such as heart attacks or strokes. Uncomplicated hypertension may be present and remain unnoticed for

many years, or even decades. This happens when there are no symptoms, and those affected fail to undergo periodic blood pressure screening.

Some people with uncomplicated hypertension, however, may experience symptoms such as headache, dizziness, shortness of breath, and blurred vision. The presence of symptoms can be a good thing in that they can prompt people to consult a doctor for treatment and make them more compliant in taking their medications. Often, however, a person's first contact with a physician may be after significant damage to the end-organs has occurred. In many cases, a person visits or is brought to the doctor or an emergency room with a heart attack, stroke, kidney failure, or impaired vision (due to damage to the back part of the retina). Greater public awareness and frequent blood pressure screening may help to identify patients with undiagnosed high blood pressure before significant complications have developed.

About one out of every 100 (1%) people with hypertension is diagnosed with severe high blood pressure (accelerated or malignant hypertension) at their first visit to the doctor. In these patients, the diastolic blood pressure (the minimum pressure) exceeds 140 mm Hg! Affected persons often experience severe headache, nausea, visual symptoms, dizziness, and sometimes kidney failure. Malignant hypertension is a medical emergency and requires urgent treatment to prevent a stroke (brain damage).

Chapter 4

Literature of the study

4.1 Stable Pharmaceutical composition containing Amlodipine Besylate and Atenolol

The present study relates to a stable pharmaceutical composition containing a combination of medicaments such as a dihydropyridine class calcium channel blocker drug Amlodipine besylate and a benzeneacetamide class β- adrenergic blocker drug Atenolol having utility in certain cardiovascular diseases like Angina pectoris, Myocardial infarction, Hypertension. It is also related to selection of pharmaceutical excipients to prepare stable composition of Amlodipine besylate in combination with Atenolol.

The present study also relates to methods of preparing said stable pharmaceutical combination product.

4.2 Backgorund of the study

It is known that certain dihydropyridine derivatives such as Nifedipine, Felodipine, Nicardipine, Amlodipine and Nisolidipine have a calcium channel blocking action and are useful for the treatment of various cardiovascular disorders such as Angina pectoris, Myocardial infarction, Hypertension etc.

It is also known that β-adrenergic blocking agents such as Propranolol, Metaprolol, Atenolol, Timolol etc. are also useful for the treatment of such cardiovascular diseases.

However, the mechanism of action of dihydropyridine derivative class calcium channel blocking agents is entirely different from that of β-adrenoceptor blocking agents in treating cardiovascular ailments.

It has been reported that a combined administration of a calcium ion antagonist Verapamil and a β-blocker drug Propranolol can achieve maximal symp- tomatic improvement in clinical Angina pectoris.

Further it has been reported that Plasma renin activity of normo- tensive and hypertensive subjects is increased by calcium channel blocker- Nifedipine. Combined administration of Nifedipine and β-blocker drug Propranolol decreases plasma renin activity in both normotensive and hypertensive patients. The antihypertensive effect of Nifedipine is enhanced and prolonged by Propranolol.

The observed increase in heart rate and plasma renin activity with Nifedipine is inhibited by Propranolol. That is, β-blocker inhibits the calcium antagonist induced reflex increase of heart rate; and also completely inhibits the calcium ion antagonist induced increase of plasma renin activity. Since the side effects of either drug are almost abolished or inhibited by the combination administration of both the drugs, combined administration of such two kinds of drug can be recommended for the satisfactory management of Hypertension with minimal adverse drug reactions.

Combinations of various β-blockers with various calcium antagonists and/or with an ACE inhibitor are described in the literature, which can be used in the treatment of circulatory diseases a combination product of Amlodipine besylate and Atenolol makes a good combination for the treatment of Hypertension, angina pectoris and Myocardial infarction.

The purpose of this study is to identify the excipients which are compatible with both Amlodipine besylate and Atenolol in combination, to develop a stable composition and the process for manufacturing of such stable combination product of Amlodipine besylate and Atenolol.

4.3 Summary of the study

In accordance with the present study, a stable pharmaceutical composition is provided containing a calcium channel blocker drug-Amlodipine besylate in combination with a β-adrenergic blocker drug-Atenolol in the form of a solid dosage form for oral administration to the individuals suffering with certain cardiovascular ailments.

The combination product of Amlodipine besylate and Atenolol according to the study is preferably used as a solid formulation, for example, in the form of tablets.

The study further provides a stable pharmaceutical combination product of Amlodipine besylate with Atenolol in admixture with carefully screened excipients compatible with both the drugs when taken in combination and are necessary for the processing.

The present study further provides different processes for preparing a stable pharmaceutical combination product of Amlodipine besylate with Atenolol and selected excipients.

4.4 Detailed description of the study

The dose range of Amlodipine besylate in the combination product according to the present study is 5mg and dose range for Atenolol is 50mg. A preferred combination product according to the present study includes the besylate salt of Amlodipine and Atenolol in admixture with commonly known but carefully screened pharmaceutical excipients belonging to the categories: diluents, binders, disintegrating agents, lubricants and glidants.

Examples of excipients commonly known in the pharmaceutical art are: Diluents such as Lactose, anhydrous Lactose, spray dried Lactose, starch, Directly compressible starches, Hydrolyzed starches, Microcrystalline cellulose, other cellulose derivatives, Mannitol, Sorbitol, Sucrose and sucrose based materials, Dextrose, dibasic calcium phosphate dihydrate, Calcium sulfate dihydrate; Binders, such as cellulose derivatives, acacia, Gelatin, Tragacanth, Sorbitol, Glucose, Starch paste, Pregelatinised starch, Polyvinylpyrrolidone, Sodium alginate and alginate derivatives; Lubricants, such as Stearic acid, Stearic acid salts, Talc, Polyethylene glycols, and Waxes; and Glidants, such as Silica derivatives, Talc and corn starch.; Examples of Disintegration promoters which may be mentioned are: Starch, modified Starch, Cellulose and cellulose derivatives, crosslinked polyvinyl- pyrrolidone and Sodium alginate.

It is apparent to those versed in the art that for good physical and chemical stability of a pharmaceutical product, it is necessary that each of the excipients in the composition shall have good physical and chemical compatibility with the active substances in the product and with other excipients independently

Accordingly, the present study provides a stable pharmaceutical composition containing a dihydropyridine derivative and a benzeneacetamide derivative together with selected excipients which include, diluents microcrystalline cellulose (Avicel PH 101), Dried Maize Starch, dibasic calcium phosphate in its dihydrous form; disintegrants used are dried Maize Starch; Binders used are Maize Starch as paste, microcrystalline cellulose (Avicel PH 101); Lubricant used is Magnesium stearate; Glidants used are Talc and colloidal Silicon dioxide(Aerosil 200). 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 is apparent to those versed in the art that for good physical and chemical stability of a pharmaceutical product, the manufacturing process selected and used to prepare the product with the selected excipients shall not affect the drug substances present in the product physically or chemically during the process stage or during the shelf life period of the product. Apart from this character, it is generally desirable that the process selected should be simple, rugged and shall be possible with the equipment known to the art without much of processing difficulty.

According to an embodiment of the present study there is provided a process for preparing a stable pharmaceutical composition containing a dihydropyridine derivative and a benzeneacetamide derivative which comprises (i) Granulating the β-blocker drug-Atenolol together with carefully screened excipients using a moist granulation process, (ii) preparing the blend of such granules together with calcium channel blocker drug-Besylate salt of Amlodipine and compatible excipients, (iii) Such prepared blend can be compressed into tablets using standard compression tooling known in the art or can be filled into capsules or sachets for human oral administration.

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 5

Formulation and processing steps

5.1 Formulations and its general concepts:

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 determined 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 moulding. 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.

5.2 Processing Steps followed in the making of amlodipine-atenolol combined dosage form tablets:

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 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 which 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 using any suitable means

The blended/sieved material is compacted to form a compacted material and this 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.

The compacted material is milled to form a milled material which is accomplished using any suitable means.

The milled material is blended to form blended/milled material. Here again blending is accomplished using any suitable means.

In the final step of the method 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.

Chapter 6
Preformulation factors

6.1 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:

- 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
- 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.

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.

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

6.2 Physicochemical properties

The most important target 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.

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.

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.

6.3 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)

6.4 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.
- ✓

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. 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.

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.

6.5 Stability

Two types of stability are there which must be considered: chemical and physical.

- **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.

Chapter 7
Materials and methods

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

7.1.1 Formulation 1(Direct Compression Methods)

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Sodium Starch Glycolate
- 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
Sodium Starch Glycolate	Binder/Diluent
Magnesium stearate	Lubricant

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate	3.658	7.316 mg
2	Atenolol	25.25	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 102)	64.692	129.384 mg
4	Sodium Starch Glycolate	2.000	4.000 mg
5	Colloidal Silicondioxide (Aerosil 200)	3.000	6.000 mg
6	Magnesium Stearate	1.400	2.800 mg
		100.000	200.000 mg

Step 1

(A) We sieved weighed quantity of following materials through 20 mesh and take into glass beaker

- Atenolol 15.150 gm
- Avicel PH 102 38.815 gm

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

B) We sieved weighed quantity of following materials through 30 mesh and take into glass beaker

- Mixture of Step 1(A) approx. 10.00 gm
- Amlodipine Besylate 2.195 gm
- Sodium Starch Glycolate 1.200 gm
- Colloidal Silicondioxide 1.800 gm
- Mix manually for 5 minutes with the help of glass rod.

We mixed manually for 10 minutes in PE bag.

Step 2

We sieved weighed quantity of Magnesium Stearate through 30 mesh screen and dilute with weighted quantity of blended materials.

Magnesium Stearate 0.840 gm

Blend of Step 1 5.000 gm

We added to Step 1 and blend manually for 1 minute in PE bag

Step 3

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 4

Compression force and checked the following physical parameters:

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

Average Weight : 194.00 mg to 206.00 mg (± 3% of the calculated weight)

Uniformity of weight : 185 mg to 215 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.85mm ± 5%

Friability : Not more than 0.8% w/w

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

Step 5

After satisfactory result, the compression machine was run

7.1.2 Formulation 2 (Direct Compression Methods)

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Pregelatinized Starch
- 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
Pregelatinized Starch	Binder/ diluent
Magnesium stearate	Lubricant

mula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate,	3.658	7.316 mg
2	Atenolol,	25.25	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 102)	19.692	39.384 mg
4	Pregelatinized Starch	47.50	95.000 mg
5	Colloidal Silicondioxide (Aerosil 200)	2.000	4.000 mg
5	Purified Talc	1.250	2.500 mg
5	Magnesium Stearate	0.650	1.300 mg
		100.000	200.000 mg

Step 1

A) We sieved weighed quantity of following materials through 20 mesh and took into glass beaker

- Atenolol 10.100 gm
- Pregelatinized Starch 19.000 gm

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

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

- Mixture of Step 1(A) approx. 10.00 gm
- Amlodipine Besylate 1.463 gm
- Avicel PH 102 7.877 gm
- Colloidal Silicondioxide 0.800 gm

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

Then we transferred to Step 1(A) and mixed manually for 10 minutes in PE bag.

Step 2

We sieved weighed quantity of Magnesium Stearate through 30 mesh screen and diluted with weighted quantity of blended materials.

- Magnesium Stearate 0.260 gm
- Purified Talc 0.500 gm

- Blend of Step 1 5.000 gm

We added to Step 1 and blended manually for 1 minute in PE bag

Step 3

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 4

Compression force and checked the following physical parameters

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

Average Weight : 194.00 mg to 206.00 mg (± 3% of the calculated weight)

Uniformity of weight : 185 mg to 215 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 4.00mm ± 5%

Friability : Not more than 0.8% w/w

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

Step 5

After satisfactory result, the compression machine was run

7.1.3 Formulation 3 (Direct Compression Methods)

APIs: Atenolol-Amlodipine (Amlodipine besylate).

Excipients:

- Avicel 101(microcrystalline cellulose)
- Colloidal silicon dioxide (Aerosil 200)
- Purified Talc
- Dihydrous dibasic Calcium phosphate
- Pregelatinized Starch
- 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
Pregelatinized Starch	Binder/Diluent
Magnesium stearate	Lubricant

mula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate	3.658	7.316 mg
2	Atenolol	25.25	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 102)	14.692	29.384 mg
4	Dibasic Calcium Phosphate Anhy.	47.50	95.000 mg
5	Pregelatinized Starch	5.00	10.000 mg
6	Colloidal Silicondioxide (Aerosil 200)	2.000	4.000 mg
7	Purified Talc	1.250	2.500 mg
8	Magnesium Stearate	0.650	1.300 mg
		100.000	200.000 mg

Step 1

A) We sieved weighed quantity of following materials through 20 mesh and took into glass beaker

- Atenolol 10.100 gm
- Dibasic Calcium Phosphate Anhy. 19.000 gm
- Pregelatinized Starch 2.000 gm

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

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

- Mixture of Step 1(A) approx. 10.00 gm
- Amlodipine Besylate 1.463 gm
- Avicel PH 102 5.877 gm
- Colloidal Silicondioxide 0.800 gm

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

We transferred to Step 1(A) and mixed manually for 10 minutes in PE bag.

Step 2

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

- Magnesium Stearate 0.260 gm
- Purified Talc 0.500 gm
- Blend of Step 1 5.000 gm

We added to Step 1 and blended manually for 1 minutes in PE bag

Step 3

We compressed the blended 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 4

Compression force and checked the following physical parameters

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

Average Weight: 194.00 mg to 206.00 mg (± 3% of the calculated weight)

Uniformity of weight: 185 mg to 215 mg (± 7.5% of the average weight)

Hardness : Not less than 40 N

Thickness : 3.50 mm ± 5%

Friability : Not more than 0.8% w/w

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

Step 5

After satisfactory result, the compression machine was run

7.1.4 Formulation 4 (Wet Granulation Technique)

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

mula/ Composition

No.	Name of Ingredients	% w/w	Quantity/ Tablet
1	Amlodipine Besylate	3.252	7.316 mg
2	Atenolol	22.444	50.500 mg
3	Microcrystalline Cellulose (Avicel PH 101)	16.860	37.934 mg
4	Dibasic Calcium Phosphate Dihy.	44.444	100.000 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	1.000	2.250 mg
9	Magnesium Stearate	1.778	4.000 mg
		100.000	225.000 mg

Step 1

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

- Atenolol 10.100 gm
- Dibasic Calcium Phosphate Dihy. 20.000 gm
- Avicel PH 01 7.587 gm

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

LOD at 105^{O}C: 1.83%

Step 2

We took 20 cm3 water in a beaker, add 1.600 gm Maize starch and stir to make slurry, heat the slurry to make clear paste, cool 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 20min minutes, after 20min minutes we passed the semidried mass through 20 mesh, finally drying the semidried granules for 15 minutes at moisture content of 1.50 to 2.50% (LOD at 105^{O}C) and kept into PE bag.
LOD at 105^{O}C: 1.10%

Step 4

We sieved weighted quantity of following materials through 30 mesh (if necessary) and took into glass beaker

- Amlodipine Besylate 1.463 gm
- Maize Starch (Dried) 2.400 gm
- Colloidal Silicondioxide 0.600 gm

We mixed manually for 5 minutes with the help of glass rod. We added granules of Step 3 10.00 gm and mixed for 5 minutes with glass rod.
We transferred to Step 3 and mix manually for 10 minutes in PE bag

Step 5

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

Magnesium Stearate 0.800 gm
Purified Talc 0.450 gm
Blend of Step 3 5.000 gm

We added to Step 3 and blended manually for 1 minutes in PE bag

Step 6

We compressed the blended 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)
Uniformity of weight : 208 mg to 242mg (± 7.5% of the average weight)
Hardness : Not less than 40 N
Thickness : 3.95 mm ± 5%
Friability : Not more than 0.8% w/w
DT in water at $37^{O}C$: Not more than 15 minutes

Step 8

After satisfactory result, the compression machine was run

7.1.5 Formulation 5 (Wet Granulation Technique)

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 $\leq$ 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) 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:

a) Appearance : White to off-white colored, biconvex oval shaped both side plain tablet
b) Average Weight: 218 mg to 232 mg (± 3% of the calculated weight acc)
c) Uniformity of weight : 208 mg to 242 mg (± 7.5% of the average weight)
d) Hardness : Not less than 40 N
e) Thickness : 3.80 mm to 4.20 mm (4.00 mm ± 5%)
f) 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

Equipments used in all these formulations were: Shimadzu UV Spectrophotometer (Shimadzu, Model UV-160A, Tokyo, Japan); Sartorius electronic balance, Slide callipers, Logan hardness tester, Roche friabilator, tablet punch machine, dissolution tester, disintegration tester, as well as all other rudimentary laboratory equipments.

7.2 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

Step1

The dissolution medium was made: 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 sodium acetate is alkaline. Then we slowly added aqueous solution of acetic acid of 1N to the sodium acetate solution until the pH fell to 4.6. This was done with the help of the pH probe. Thus we got the dissolution medium: sodium acetate buffer.

Step 2

We then distributed the dissolution medium 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 each generic (Amdocal Plus 50, Fixocard 50 and tablet X).

Step 3

The samples were taken at 10, 20, 30, 40, 50, and 60 min after the start of the test. 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.

Step 4

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 8
Results and Discussion

Formulation 1 (using Direct Compression)

Physical Properties (Core Tablet)

Test Parameters	Specifications	Results
Appearance	White to off-white colored, biconvex oval shaped both side plain tablet	complies
Average weight	194 mg to 206 mg (± 3% of the calculated weight)	193.5 mg
Uniformity of weight	185 mg to 215 mg (± 7.5% of the average weight)	181-203mg
LOD at 105°C	Not more than 5.0%	4.23%
Hardness	Not less than 40 N	94-116N
Thickness	3.85 mm ± 5%	3.82-4.02
Friability	Not more than 0.8% w/w	0.0106%
DT in water at 37°C	Not more than 15 minutes	7-8 mins

Conclusion:

Material flow was inadequate. Weight variation needed to be improved.

Formulation 2 (using Direct Compression)

Physical Properties (Core Tablet)

Test Parameters	Specifications	Results
Appearance	White to off-white colored, biconvex oval shaped both side plain tablet	Complies
Average weight	194 mg to 206 mg (± 3% of the calculated weight)	198.28mg
Uniformity of weight	185 mg to 215 mg (± 7.5% of the average weight)	190-210mg
LOD at 105°C	Not more than 5.0%	5.14%

Hardness	Not less than 40 N	60-70N
Thickness	4.00 mm ± 5%	3.95-4.20mm
Friability	Not more than 0.8% w/w	0.08%
DT in water at 37°C	Not more than 15 minutes	>15 min (17-20mins)

Conclusion:

Disintegration time much higher than specified

Formulation 3 (using Direct Compression)

Physical Properties (Core Tablet)

Test Parameters	Specifications	Results
Appearance	White to off-white colored, biconvex oval shaped both side plain tablet	Complies
Average weight	194 mg to 206 mg (± 3% of the calculated weight)	199.1mg
Uniformity of weight	185 mg to 215 mg (± 7.5% of the average weight)	193-200mg
LOD at 105°C	Not more than 5.0%	1.60%
Hardness	Not less than 40 N	60-70N
Thickness	3.50 mm ± 5%	3.46- 3.52mm
Friability	Not more than 0.8% w/w	0.062%
DT in water at 37°C	Not more than 15 minutes	2-4min

Conclusion:

Material flow was inadequate. Sticks with die wall and punch tip.

Formulation 4 (Wet Granulation)

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	218mg to 232 mg (± 3% of the calculated weight)	230.00mg
Uniformity of weight	208 mg to 242 mg (± 7.5% of the average weight)	222-239mg
LOD at 105^{O}C	Not more than 5.0%	1.69%
Hardness	Not less than 40 N	88-103N
Thickness	.....3.95.... mm ± 5%	3.95-4.02mm
Friability	Not more than 0.8% w/w	0.00%
DT in water at 37^{O}C	Not more than 15 minutes	2-3%

Conclusions:

Strongly sticks to die wall.

Formulation 5 (Wet Granulation)

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.

Discussion

As we can see, modifications in ingredients of the individual formulations as well as in techniques gave us a suitable immediate release dosage form. Addition of maize starch (both as paste and dried) and dihydrous dibasic calcium phosphate proved to be useful. Wet Granulation technique was more effective than direct compression.

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 are:

At 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

At 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

At 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

At 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

At 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

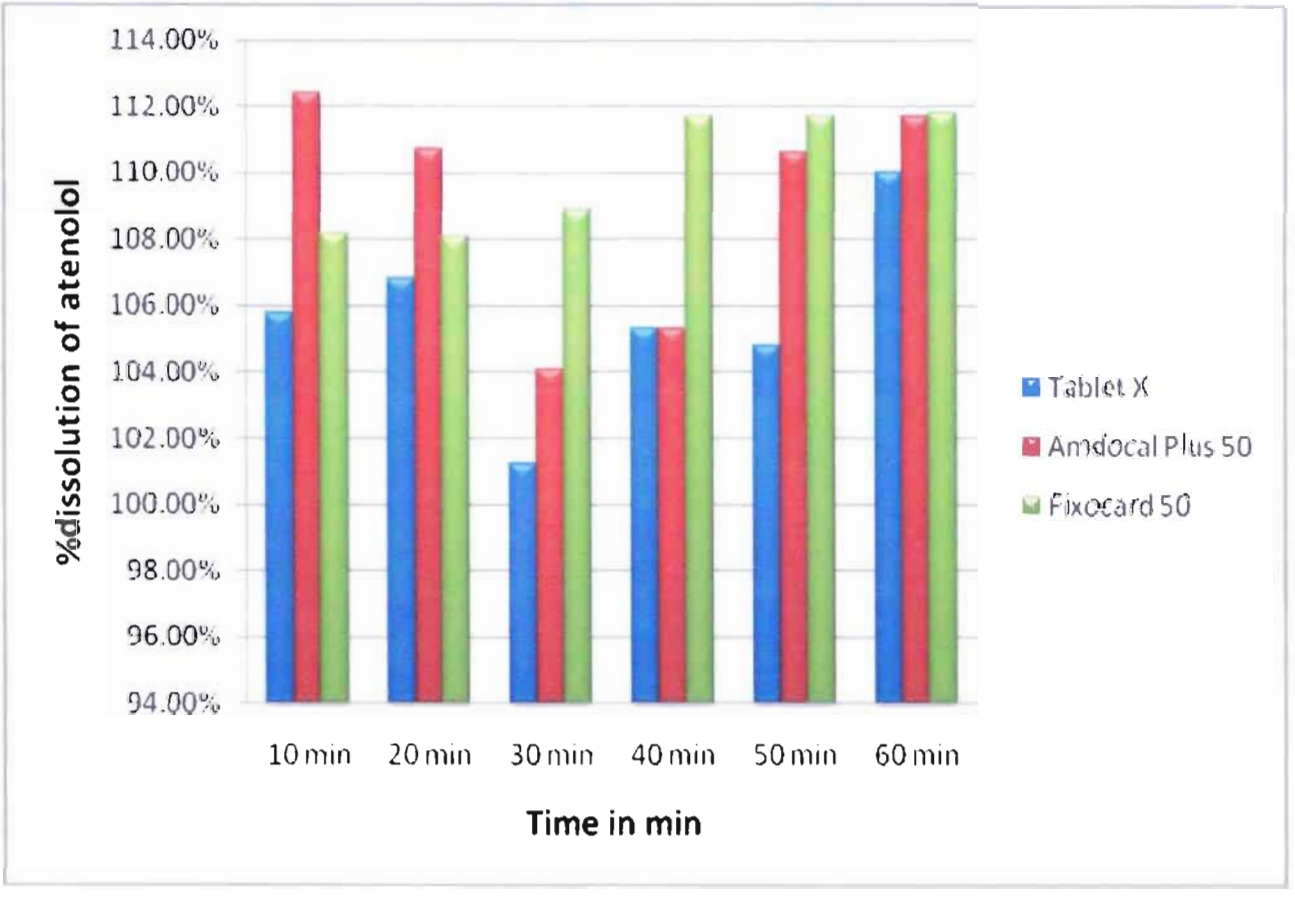


Fig: Graph showing the % dissolution rates of atenolol

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

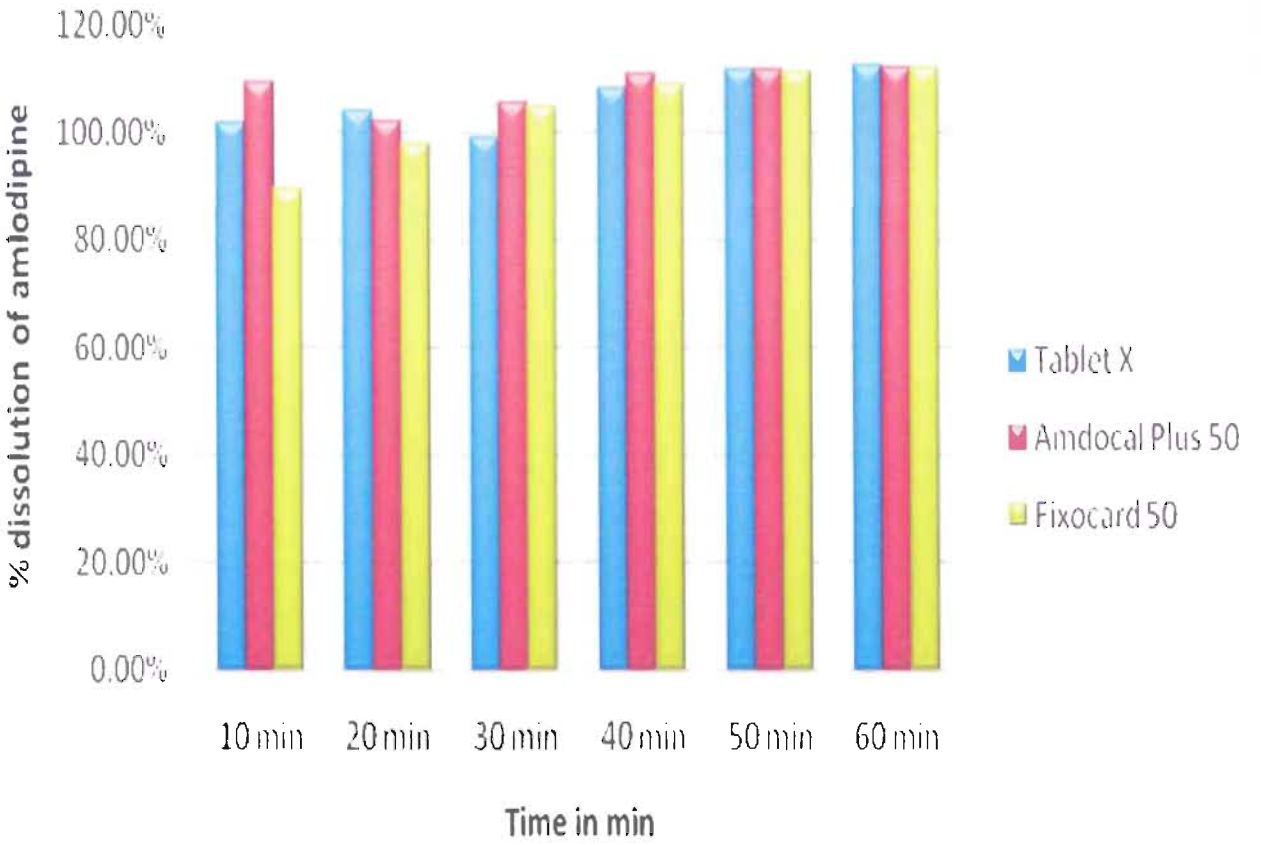


Fig: Graph showing the % dissolution rates of amlodipine

Discussion and conclusion:

As we can see that by the end of 10 mins, almost 100% of the atenolol and amlodipine from all three drugs have dissolute according to the rates of dissolution on the graphs . 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. Thus we can say that they have better efficacy and bioavailability. They have insignificant difference between their dissolution rates so it is tough to deduce which drug is better than the other. But even then, all three drugs prove that they aresuitable for immediate release dosage forms and their formulations are 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 the other two market products.

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