Chapter 1

INTRODUCTION

1.1.1. Hypertension

High blood pressure (BP) is a major public health problem globally. The increase in blood pressure is considered to be a major risk factor in the development of cardiovascular diseases (CVD) leading cause of death worldwide, accounting WHO report an estimated 14 million deaths in 1990 and projected to cause 25 million deaths in 2020. The relationship between blood pressure and risk of CVD is continuous, consistent and independent of other risk factor. Hypertension is common in both developed and low- and middle-income countries (Kearney et al., 2005; Ong et. al., 2007). The recent study shows that nearly half of treated patients are not able to achieve desired blood pressure targets (Brown, 1997; Mancia et al., 1997).

The pressure exerted by the blood against the walls of the arteries is blood pressure. The higher the pressure, there are more chances of damage on the wall of artery. The pressure exerted on the vessel walls not only damages vessels but organs as well. The rates of cardiovascular disease double for each 20/10 mm Hg increment of blood pressure over 115/75 mm Hg (Chobanian et al., 2003). One of the most dreaded and a common complication of long-standing hypertension is atherosclerosis. High blood pressure decreases the coronary flow reserves and increases the myocardial oxygen demand. In addition, hypertension remodels the vessel, causes endothelial dysfunction and increases the collagen deposits in the artery (Rosendorff et al., 2007). The blood pressure is the leading cause of heart failure, which causes the myocardium to change structurally and also leads to impaired cardiac function. Stroke and encephalopathy are potential complications of long-standing hypertension. Stroke risk increases with proportional elevation in blood pressure – both systolic and diastolic. Controlling blood pressure is a major strategy in the reduction of stroke incidence. Kidney failure is another complication of long-standing hypertension. Hypertension is at times the primary cause of renal failure, but even if it is not, its presence increases the rate of kidney damage (NKUDIC 2007). Hypertension may increase the incidence of memory impairment. A recent study suggested that a history of hypertension is associated with an increase risk of mild cognitive impairment (Reitz et al., 2007).
addition, hypertension increases the incidence of aortic dissection, retinopathy and peripheral artery disease.

Hypertension is classified as primary hypertension and secondary hypertension. Primary or essential hypertension which accounts for more than 90% of cases of hypertension is diagnosed in the absence of an identifiable secondary cause. Primary hypertension is more common in adolescents and adults, and has multiple risk factors. Secondary hypertension indicates that the high blood pressure is a consequence of other condition like kidney disease or adrenal disease.

Blood pressure is reported as a systolic number over a diastolic number. The systolic number is the amount of pressure generated during a heart beat while diastolic pressure is the amount of pressure generated when the heart is relaxing between beats. Blood pressure is classified in one of four ways: normal, pre-hypertensive, stage I or stage II. According to the Seventh Report of the Joint National Committee on Detection, Education and Treatment of High Blood Pressure (JNC VII) (Chobanian et al., 2003), blood pressure is considered to be normal below 120/80 mmHg. Values between 120-139/80-89 mmHg are categorized as pre-hypertensive. Readings between 159-140/90-99 mmHg and more than 160/100 mmHg are considered to be stage I hypertension and stage II hypertension respectively.

1.1.2. Epidemiology

Hypertension is an increasingly important medical and public health issue. The prevalence of hypertension increases with advancing age to the point where more than half of people 60 to 69 years of age and approximately three to fourths of those 70 years of age and older are affected (Bert et al., 1995). Currently, the incidence of hypertension is not restricted to the elder people but increasing day by day among the young generations. The age related rise in systolic blood pressure (SBP) is primarily responsible for an increase in both incidence and prevalence of hypertension with increasing age (Franklin et al., 1997).

From the epidemiological point of view, the individual contribution of hypertension in the risk of cardiovascular diseases is difficult to estimate (Kannel, 2003). Since several other risk factors like obesity, diabetes mellitus, increased salt intake, hyperlipidaemia, smoking, lack of physical activity, psychological factors, age
and sex need to be considered (Kiritsi et al., 2008; Kalandidi et al., 1992). Each of these factors in the presence of high blood pressure can further increase the risk of cardiovascular diseases (Fig. 1.1) (Ellekjaer et al., 2001; Kannel, 2003).

![Diagram](image)

**Figure 1.1. A global brief of hypertension; World Health Day; April 2013; WHO**

According to WHO-ISH guidelines for the management of hypertension, patients with type 2 diabetes mellitus are 1.5-2 times more likely to present hypertension compared to the general population. This independent risk factor for cardiovascular diseases increases significantly the morbidity and the fatality rates (Kannel, 2003). This coexistence of hypertension and diabetes mellitus type 2 is more frequent in men and in lower socioeconomic levels. It increases with increasing age and in postmenopausal women after 50 years old (Turnbull et al., 2005).

Hypertension affects more than 1 billion people worldwide and among these more than 72 million people are from United States. Hypertension is a major public health problem in developing countries like India. The average prevalence of hypertension in India is 25% in urban and 10% in rural inhabitants (Gupta, 2004). Factors which are attributable to these changes are rapid urbanization, lifestyle changes, and dietary changes and increased life expectancy (Reddy and Katan, 2004). Estimates from the global burden of diseases, study suggest that by the year of 2020, India will
have more individuals with cardiovascular disease (CVD) than other region in the world. This is obvious from several Indian urban and rural studies.

1.1.3. Signs and symptoms

Hypertension is the silent killer because it appears without signs or symptoms. While no symptoms are present it is imperative for the clinician to perform a good history, physical examination and targeted diagnostic tests. The initial step in evaluating the hypertensive patient is to look for cardiovascular risk factors and treat if necessary. Secondly, attempt to determine if there is a specific cause of the hypertension and finally, evaluate for any complications of hypertension.

The history should draw out any signs or symptoms associated with complications of hypertension (American Heart Association). The patient should be questioned about any chest or abdominal pain, shortness of breath or dyspnea on exertion, vision changes, edema, weight gain, intermittent claudication (impairment in walking), or orthopnea (Fig. 1.2). The other risk factors like smoking, dyslipidemia, age, physical inactivity, obesity, family history and diabetes should also be taken into consideration.

![Overview of the most significant complications of high blood pressure](image)

Figure 1.2. Overview of the most significant complications of high blood pressure
In addition to checking blood pressure, the physical examination should also look for any causes or complication of hypertension. The legs should be evaluated for femoral bruits. The abdominal examination should look for any bruits, enlargement of the kidneys, masses or an abnormal aortic pulsation (Johnson et al., 2005). The neck should be examined for carotid bruits as well as any abnormality of the thyroid gland. The heart and cardiovascular system should be assessed for congestive heart failure.

The history and physical exam should also look for secondary causes of hypertension. Kidney disease, anaemia or an abdominal mass may suggest a renal pathology causing hypertension (Johnson et al., 2005). Thyroid dysfunction may be manifested by heat or cold intolerance, slow or fast heart rates, low energy levels or sweating. Reviewing the medications is important as many medications can lead to elevations in blood pressure including: non-steroidal anti-inflammatory medications, nasal decongestants or oral contraceptives. Sleep apnea is another cause of secondary hypertension. If the patient snores excessively or has daytime drowsiness than a referral for a sleep study may be warranted. Secondary hypertension is uncommon and not usually worked up for extensively unless a secondary cause is strongly suspected based on history and physical examinations.

Laboratory evaluation looks for causes of hypertension, cardiovascular risk factors and target organ damage (Laurent et al., 2001). Routine laboratory evaluation should include a urinalysis, kidney function test, lipoprotein levels, hematocrit, blood glucose level and serum potassium level. An electrocardiogram should be done to evaluate for any underlying cardiovascular disease. Low potassium levels may suggest hyper-aldosteronism. Decreased kidney function may suggest damage done to the kidney due to the effects of hypertension (Laurent et al., 2001). Hematuria or proteinuria on urine analysis implies damage to the tubules of the kidney. Fasting blood sugar evaluates for the presence of diabetes which, when combined with hypertension, significantly increases the risk of kidney damage and cardiovascular disease. Electrocardiogram is done to assess for abnormal heart rhythms or evidence of an old heart attack.

1.1.4. Pathophysiology

The chronic elevation of blood pressure causes organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and
systemic vascular resistance. Patients with arterial hypertension may have an increased cardiac output (CO), an increased systemic vascular resistance, or both. The CO is often elevated in younger age group, while in older patients increased vascular resistance and increased stiffness of the vasculature play an important role. The vascular tone is elevated due to increase of α-adrenoreceptor stimulation or increasing release angiotensin or endothelin. An increase in cytosolic calcium in vascular smooth muscle causes vasoconstriction. Various growth factors cause vascular remodelling. The increasing systemic vascular resistance and vascular stiffness create a load on the left ventricle, which induces left ventricular hypertrophy and left ventricular dysfunction (Foex and Sear, 2004).

In younger, the pulse pressure from left ventricle is relatively low and the wave reflected peripheral vasculature occur mainly after the end of systole, thus increasing pressure during the early part of diastole and improve coronary perfusion. With ageing, the stiffening of aorta and elastic property of aorta increases the pulse pressure. The movement of waves from early diastole to late systole causes left ventricular hypertrophy and finally coronary heart disease.

The autonomic nervous system plays an important role in the control of blood pressure. The increasing release of norepinephrine causes hypertension. Another feature of arterial hypertension is the decreased baroreceptor sensitivity. The renin–angiotensin system is also involved in some forms of hypertension (e.g. renovascular hypertension). Elderly or black patients are more prone to have low-renin hypertension. Others have high-renin hypertension and these are more likely to develop myocardial infarction and other cardiovascular complications (Oates, 1996).

1.1.5. Diagnosis of hypertension

The early detection of hypertension may possibly minimize the risk of heart attack, heart failure and stroke and kidney failure. All adults should check their blood pressure routinely and should know their blood pressure level. A baseline blood pressure should be established in all adults and reassessed periodically, commensurate with age and the presence of other risk factors (Canadian Hypertension Education Programme, 2007). Blood pressure measurements need to be recorded for several days before a diagnosis of hypertension can be made (Tab. 1.1).
Besides blood pressure measurement, following are the tests to be carried out for the early detection of hypertension:

- Urine analysis
- Blood chemistry (potassium, sodium, creatinine, glomerular filtration rate)
- Fasting blood glucose level
- Fasting total cholesterol,
- high-density lipoprotein (HDL), low-density lipoprotein, triglycerides
- Electrocardiogram (ECG)
- Diabetes

<table>
<thead>
<tr>
<th>Stages</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
</tr>
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<td>&lt; 80</td>
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<tr>
<td>Prehypertension</td>
<td>120 – 139</td>
<td>80 – 89</td>
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<tr>
<td>Stage 1 hypertension</td>
<td>140 – 159</td>
<td>90 – 99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥ 160</td>
<td>≥ 100</td>
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</table>

1.1.6. Management of hypertension

The treatment of hypertension has become a challenge with the finding that even small reductions in blood pressure can significantly reduce the risk of morbidity and mortality (Staessen et al., 2003). The management of hypertension involves pharmacological treatment, changes of life style or both. Reduction of body weight for obese patients, moderate consumption of alcohol and physical activity are all essential for decreasing BP and enhancing the efficacy of the pharmacotherapeutic regimens (Chobanian et al., 2003). There are number of blood pressure lowering medicines used by the patients for the rest of his/her life. However, patients might be able to stop the treatment, if the blood pressure level stayed under control for several years.

1.1.6.1. Non-pharmacological management: Non-pharmacological therapy (lifestyle management) plays an important role in both non-hypertensive and hypertensive individuals. In non-hypertensive individuals, including those with pre-hypertension, lifestyle modifications have the potential to prevent hypertension and
more importantly to reduce BP and lower the risk of BP-related clinical complications. Lifestyle modification can serve as initial treatment before the start of drug therapy in hypertensive individuals and as an adjunct to the drug therapy in persons already on medication. Treatment is successful when multiple factors in the patient’s life are addressed. Since, essential hypertension is considered as a result of interactions between genes and environment (Harrap, 2003). Important lifestyle or environmental factors are dietary excess of sodium and fat, dietary deficiency of potassium and fibre, alcohol intake, physical inactivity and psychological stress (Chobanian et al., 2003).

Dietary modifications are important for prevention and initial treatment of hypertension. Several animal studies, clinical trials and meta analysis suggests that with increase in dietary salt intake, blood pressure also increases (Sacks et al., 2001; MacGregor et al., 1989). In hypertensive patients, the dietary sodium intake should be limited to 65 to 100 mmol/day and diet should be low in saturated fat and cholesterol. Besides these fruits, vegetables, soluble fibres, whole grains and proteins from plant sources are highly recommended for the hypertensive patients (Appel et al., 2006). The Indian Council of Medical Research (ICMR) recommends 1.5 g/d (65 mmol/day) sodium as an adequate intake level, primarily to ensure nutrient adequacy (ICMR Dietary guideline, 2003). High potassium intake reduces the blood pressure. The preferred strategy to increase the potassium in the body is to consume foods such as fruits and vegetables rich in potassium.

Observational studies have documented a direct, dose-dependent relationship between alcohol intake and BP, particularly when the intake of alcohol increases above 2 drinks per day (Klatsky et al., 1977). Alcohol consumption should be limited to ≤ 2 alcoholic drinks per day in most men and ≤ 1 alcoholic drink per day in women and lighter-weight persons. A comprehensive dietary management would be the best approach to manage hypertension and to reduce overall cardiovascular risk. Besides these the weight management (Gupta et al., 2007), avoidance of smoking and tobacco, physical activity, yoga and stress management (Dickinson et al., 2006) can reduce BP as well as risk of cardiovascular mortality.

1.1.6.2. Pharmacological management: When non-pharmacological therapies show modest reductions in blood pressure, the pharmacotherapy is not adopted. But in many people the BP remains high despite appropriate non-pharmacological therapy.
Under these circumstances pharmacological approaches must be considered. According to the JNC-7 report, beta-blockers and thiazide diuretics are the suitable drugs for the first line treatment of hypertension. Current thinking is to start with angiotensin converting enzyme (ACE) inhibitors in young individuals and calcium channel blockers (CCB) in older individuals for the therapy of blood pressure until the targets are achieved (Williams, 2006).

**Diuretics:** Low-dose diuretics are effective and reduce the risk of stroke, coronary heart disease, congestive heart failure, and total mortality. Thiazides, loop diuretics and potassium sparing diuretics are also used successfully to reduce the risk of both hypokalaemia and hypomagnesaemia. The risk of sudden death is reduced when potassium-sparing diuretics are used. In the long-term use of spironolactones reduce morbidity and mortality in patients with heart failure (Messerli et al., 2003).

**Beta blockers:** Beta blockers are used for high sympathetic tone, angina and previous myocardial infarction. The low dose of beta blockers minimizes the risk of fatigue (an unpleasant effect of b-blockade), but addition of a diuretic or a calcium channel blocker is often beneficial. The most common side-effects like depression, fatigue, and sexual dysfunction have to be taken into consideration in the evaluation of the benefits of treatment. Over the past few years b-blockers have been used frequently in the management of heart failure, a known complication of arterial hypertension (Ong, 2007).

**Calcium channel blockers (CCB):** Calcium channel blockers can be divided into two category, dihydropyridines (e.g. nifedipine, nimodipine, amlodipine, felodipine) and non-dihydropyridines (verapamil, diltiazem). Both groups decrease peripheral vascular resistance but verapamil and diltiazem have negative inotropic and chronotropic effects. Calcium channel blockers are effective in the elderly and may be selected as mono therapy for patients with peripheral vascular disease or asthma as such patients do not tolerate b-blockers. Nifedipine is effective in severe hypertension and can be used sublingually; there is need for caution because of the risk of excessive hypotension (Ong, 2007). The newer “second generation” dihydropyridines (e.g. amlodipine, felodipine) are more vasoselective with lower negative inotropic effects. As well, reflex tachycardia is less prominent since fluctuations in plasma levels are less pronounced with these agents.
Angiotensin converting enzyme (ACE) inhibitors: ACE inhibitors are increasingly being used as first line therapy for hypertension. They have relatively few side-effects and contraindications except bilateral renal artery stenoses. Though ACE inhibitors are effective in unilateral renovascular hypertension, there is risk of ischemic atrophy. ACE inhibitors are first choice agents in diabetic hypertensive patients as they slow down the progression of renal dysfunction. In hypertension with heart failure, ACE inhibitors are also first choice drugs. Thus, this ACE inhibitor may exert a protective effect other than the reduction in blood pressure.

1.1.6.3. Mechanism of action of beta blockers (β-blockers): Beta-adrenoceptor antagonists produce competitive receptor antagonism and reduce blood pressure by decreasing cardiac output and also by reducing renin release from the kidneys. Pure β-blockers do not vasodilate. There are many β-blockers with differing pharmacological effects. Beta1-adrenoceptor selective (cardioselective) drugs (e.g. atenolol, bisoprolol) show selectivity for β1-adrenoceptors. Non-selective drugs (e.g. propranolol) are antagonists at both β1- and β2-adrenoceptors. Both non-selective and β1-selective drugs have the same effect on blood pressure. Vasodilator activity may also be produced by drugs with antagonist action at α-adrenoceptors (e.g. labetolol and carvedilol), or by those promoting endothelial nitric oxide production (e.g. nebivolol). Vasodilatation may be advantageous when treating hypertension (Ong, 2007; Toda, 2003).

1.1.6.4. Mechanism of action of calcium channel blockers: The CCBs work in hypertension largely by arterial vasodilatation, achieved by blocking the influx of calcium via transmembrane L type channels in the smooth muscle cells of resistance vessels. Some calcium channel blockers also act on the myocardium, and reduce heart rate and myocardial contractility. The consequent decrease in cardiac output also contributes to lowering of systemic blood pressure.

1.2.1. Sustained release dosage forms

During the last two decades the interest has been increase for developing sustained release drug delivery system. Various factors viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety have made the situation to develop these delivery
systems. The advantages of sustained release dosage forms are well known. Improved drug safety could often be achieved by controlling the rate of drug delivery from dosage form. Sustained release dosage forms are prepared by coating the drug by means of natural or synthetic polymers so that the release rate of the drug can be controlled. Sustained drug action can be achieved by maintaining a relatively constant, effective drug level in the body through pre-defined release rate.

1.2.2. Advantages of sustained release dosage forms

**Improved Patient Compliance:** Lack of compliance is generally observed with long term treatment of chronic disease like high blood pressure (Aulton, 2002). The success of drug therapy depends upon the ability of patient to comply with the regimen. The sustained release drug delivery system can improve the patient compliance to some extent.

**Reduced fluctuation in plasma drug concentration:** Administration of a drug in a conventional dosage form [except intravenous infusion at a constant rate] often results in the fluctuation of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics like absorption, distribution, elimination and dosing intervals. A well-designed sustained release drug delivery system can significantly reduce the dosing frequency and also maintain a steady drug concentration in blood circulation and target tissue cells (Aulton, 2002).

**Improved efficiency in treatment:** Sustained release products provides optimal therapeutic concentration of drug for long time as drug concentration lies within the minimum effective therapeutic concentration and minimum toxic level (Aulton, 2002).

**Reduced total dose:** Sustained release drug delivery systems reduce the quantity of drug administered per day treatment than the conventional oral dosage forms. This is not only reducing the cost of the treatment but also reduces the chances of systemic toxicity.

1.2.3. Challenges for developing sustained release dosage forms

Although, the sustained release delivery systems offer several advantages, there are many challenges too in their formulation development and use. Some of the challenges are as follows:
**Dose dumping:** Dose dumping is a phenomenon where, large quantities of drug in a sustained release formulation release rapidly (Aulton, 2002). This may lead to toxic quantities of the drug into the systemic circulation and it will be more fatal in case of potent drug having a narrow therapeutic index.

**Poor in vitro-in vivo correlation:** In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. The *in vitro* (dissolution rate) and *in vivo* (absorption) are difficult to correlate. When they do not correlate, there would be unsatisfactory *in vivo* performance (Aulton, 2002).

**Limited choice of selecting desired dose in the unit:** In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, they need to be swallowed or used without manipulation as fractions may damage the sustained action qualities.

**Patient variation:** The individual biological variations, co-administration of other drugs, presence or absence of food affect the drug release from dosage forms. This would also lead to variation in clinical response (Aulton, 2002).

1.2.4. **Criteria of drug for sustained release formulations**

**Desirable half-life:** The half-life of a drug is an index of its residence time in the body. The drugs with short half-life (less than 2) are good candidates for sustained release formulation.

**High therapeutic index:** Drugs with low therapeutic index are unsuitable for sustained release formulations as they have low safety of margin. The dose dumping may take place if the system collapsed in the body leading to fatalities.

**Desirable absorption and solubility characteristics:** Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into sustained release formulations is, therefore, unrealistic and may reduce overall absorption efficiency.

**Desirable absorption window:** Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the ‘absorption window’. Drugs exhibiting an absorption window are unsuitable candidates.
**First-pass clearance:** Drugs undergoing extensive first-pass elimination are not suitable for sustained release formulation.

### 1.2.5. Design and formulation of oral sustained release drug delivery system

The oral route of administration is the most preferred route due to flexibility in dosage form design, safety and patient compliance. Oral formulation also offers economical and effective solution to limitations of parenteral administration in addition to improved patient adherence and non-invasive administration (Shah et al., 2005; Oliveira et al., 2012; Paliwal et al., 2012). But the various biological factors like different pH of gastrointestinal tract, gastrointestinal motility, enzyme system highly influence drug release from its dosage forms.

The majority of the oral sustained release systems follow the mechanism of dissolution and diffusion or a combination of both. The sustained release delivery device, should release the drug by zero-order process which would result a blood level time profile similar to that after intravenous constant rate infusion. Drug Concentration (plasma) profile over time for conventional dosage form and sustained release dosage form are shown below (Fig.1.3).

![Figure 1.3. Comparison of conventional and controlled drug release profiles](image)

### 1.2.6. Factors influencing design of sustained release formulation (Aulton, 2002)

There is several factors influence the development of a sustained release dosage forms. When a drug is incorporated in the sustained release system the physicochemical properties of the drug, the dosage form design, physiology of gastrointestinal tract (intended for oral administration), the drug release mechanism, disease factors and biologic properties of the drug are taken into consideration.
**Physicochemical properties of the drug:** The physicochemical properties like aqueous solubility, stability, $pK_a$, partition coefficient and salt form affect the dosage form design. A highly soluble drug is absorbed by passive diffusion in intestine, can be considered a good candidate for modified release dosage form.

**Physiology of gastrointestinal tract and drug absorption:** The residence time of a dosage form in the gastrointestinal tract is influenced by both gastric emptying time and intestinal transit time. Solutions and pellets leave the stomach rapidly where as single dose can stay in the stomach up to 10 hours if taken after heavy meal.

**Drug release mechanisms:** Drug delivery systems can be designed to have either continuous release, a delayed GI transit while continuously releasing or delayed release.

**Biological factors:** Biological factors like, absorption, distribution, metabolism, duration of action, margin of safety, side effects of drug and disease states influence for the development of sustained dosage forms.

### 1.3. Poorly soluble drugs

Oral administration of poorly soluble drugs presents a significant challenge because of their irregular absorption in the gastrointestinal tract and low bioavailability. In recent years about 40% of drugs being in the development pipeline are poorly soluble. This increasing number of poorly soluble drugs requires innovative formulation approaches to reach a sufficiently high bioavailability after oral administration or at least to make available intravenously injectible forms. Various approaches have been developed to overcome the solubility problem of the poorly soluble drugs including salt formation, use of co-solvents, solubilisation, micronization and complexation with cyclodextrins (Lawrence and Rees, 2000; Stella and Rajewski, 1997). However, most of these techniques require more amount of additives limiting their use from the safety perspective.

It would be much more graceful to have one universal formulation approach to develop any poorly soluble drug. This is especially of interest for drugs being poorly soluble in aqueous media and simultaneously in organic media thus excluding all formulation approaches involving any solvent mixture. A classical formulation approach for such poorly soluble drugs is micronization that means conversion of the
coarse drug powder to an ultrafine (mean particle size range of about 2 to 5 mm) powder. The principle behind the micronization was to increase the dissolution velocity by increasing the surface area of the drug powder. In brief, micronization is the technology for BCS class II drugs, i.e. drugs with high permeability and low solubility to improve the bioavailability. Nowadays, many of the new drugs exhibit such a low solubility that micronization does not lead to a sufficiently high bioavailability. An effective way of alleviating these problems is by reducing the particle size within the nano-meter range, which leads to an enhanced dissolution rates and improved bioavailability (Jain, 2000).

1.4. Nanoparticles

As per the National Nanotechnology Initiative (NNI), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. The nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bioactive compounds. The drug may be adsorbed or covalently attached to the nanocarriers surface or else it can be encapsulated into it. Cell-specific targeting with nanocarriers may be accomplished by using active or passive mechanisms. The aims for nanoparticles entrapment of drugs are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drug to non-target organs. Both situations will result in an increase of therapeutic index, the margin between the doses resulting in a therapeutic efficacy and toxicity to other organ systems. For these aims, creation of long-lived and target-specific nanoparticles is needed (Wilczewska et al, 2012).

1.4. 1. Advantages of nanoparticles (Pangi et al., 2003)

1. Reduction of toxicity and occurrence of adverse reactions.
3. Controlled rate of drug release.
4. Specific site of drug release.
5. Greater patient convenience and / or better patient compliance.
6. Enhancement of the therapeutic effectiveness of the drug i.e., the overall pharmacological response per unit dose.

7. Method of preparations is reproducible.

8. Easy handling of nanoparticles prepared in the powder form.


11. No swallowing problems in case of oral administration.

1.4.2. Application of nanoparticles (Bharali DJ et al., 2009)

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<tr>
<th>S. No</th>
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<td>5-Fluorouracil</td>
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<td>4</td>
<td>To enhance therapeutic index</td>
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<td>5</td>
<td>To improve or enhance Bioavailability</td>
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<td>9</td>
<td>Miscellaneous</td>
<td>Cyclosporin-A, Somatoliberin</td>
</tr>
</tbody>
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**Therapeutic application** (Pangi et al., 2003)
### Application Purpose

<table>
<thead>
<tr>
<th>Application Purpose</th>
<th>Application Purpose</th>
</tr>
</thead>
<tbody>
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<td>Cancer Therapy</td>
<td>Targeting, reduced toxicity, enhanced uptake of antitumour agents, improved in vitro and in vivo stability</td>
</tr>
<tr>
<td>Intracellular</td>
<td>Target reticuloendothelial systems for intracellular targeting</td>
</tr>
<tr>
<td>Targeting</td>
<td>Infections</td>
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<tr>
<td>Prolonged systemic</td>
<td>Prolong systemic drug effect, avoid uptake by the reticuloendothelial system</td>
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<tr>
<td>Circulation</td>
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<tr>
<td>Vaccine adjuvant</td>
<td>Enhances immune response, alternate acceptable adjuvant</td>
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<tr>
<td>Peroral absorption</td>
<td>Enhanced bioavailability, protection from gastrointestinal enzymes.</td>
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<tr>
<td>Ocular delivery</td>
<td>Improved retention of drug or reduced wash out.</td>
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<tr>
<td>DNA delivery</td>
<td>Enhanced delivery and significantly higher expression levels.</td>
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<tr>
<td>Oligonucleotide delivery</td>
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<td>Other application</td>
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### 1.5. DRUG PROFILE

#### 1.5.1. NEBIVOLOL

Nebivolol is a third generation, highly selective β₁ adrenoceptor antagonist indicated for treatment of essential hypertension. Chemically nebivolol is 1-(6-fluoro-3, 4-dihydro-2H-1-benzopyran-2-yl)-2-[(2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)-2-hydroxyethyl)amino]ethan-1-ol (**Fig. 1.4**).

Molecular formula: C₂₂H₂₅F₂NO₄

Molecular weight: 405.435

Category: Oral antihypertensive

Dose: Initial dose 5-12.5 mg daily, in divided doses
Properties: Nebivolol is a white or almost white, crystalline powder. It is practically insoluble in water, chloroform and soluble in methanol, sparingly soluble in acetone and ethanol. It dissolves in dilute solutions of alkali hydroxides and freely soluble in dimethyl formamide. It has pKa value of 13.52. The drug should be stored in tightly-closed containers.

1.5.1.1. Mechanism of action

Nebivolol acts as anti-hypertensive agent with complimentary mechanism of actions. Clinically, nebivolol is administered as a racemic mixture of equal proportions of “d” and “l” isomers. The combination has greater antihypertensive activity than either enantiomer alone. Nebivolol binds to the β receptor on cell membrane leading to activation of adenyl cyclase resulting in accumulation secondary messenger cAMP. The cAMP dependent protein kinase helps in production of nitric oxide (NO). This mechanism leads to effective control of blood pressure by vasodilatation of blood vessels. It has a protective effect on left ventricular function. It reduces preload, afterload and increases stroke volume. It decreases pre-ejection period and lengthens left ventricular ejection time (Hilas and Ezzo, 2009). It also, decreases resting heart rate, total peripheral resistance and reduces exercise induced tachycardia (Bundkirchen et al., 2003).

1.5.1.2. Pharmacokinetics

Absorption: Nebivolol is rapidly absorbed after oral administration. The mean peak plasma drug concentration ($C_{\text{max}}$) is 1.42µg/L. The time to reach $T_{\text{max}}$ is 0.5-2h and is not affected by presence of food. For most individuals, steady state plasma concentration is achieved within 1 day for nebivolol and in a few days for active metabolites. Oral bioavailability is 12% in extensive metabolisers and 96% in poor
metabolisers, with plasma half-life of 10.3h and 31.9h respectively (Bundkirchen et al., 2003).

**Distribution**: The plasma protein binding is 98%, with limited distribution in adipose tissue due to its lipophilicity and hence no need for dosage adjustment in obese patients. The volume of distribution is being 695-2755 litres.

**Metabolism and Excretion**: It undergoes extensive first-pass metabolism and produces active β-blocking hydroxylated metabolites. The metabolism of nebivolol shows genetic polymorphism in gene encoding the CYP2D6 isoenzyme where individuals may be phenotypically divided as “poor” or “extensive” metabolizers. The poor metabolisers are unable to adequately hydroxylate aromatic moiety of the drug thus retaining high concentration of unchanged drug. In extensive metabolisers there is formation of the active hydroxyl metabolites, with low concentration of unchanged drug (Bundkirchen et al., 2003).

Elimination half-life of nebivolol is about 10h, increased by 5 times in poor metabolisers and for its metabolites it is about 24h 38% of dose is excreted in urine and 48% in faeces.

1.5.1.3. **Adverse effects**

The adverse effects with a frequency of 1-10% incidence included headache, dizziness, paraesthesias, dyspnoea, constipation, nausea, diarrhea, tiredness and oedema. The less frequently reported are impaired vision, bradycardia, heart failure, hypotension, bronchospasm, pruritus and impotence (Fogari et al., 1997).

1.5.1.4. **Drug Interaction**

Nebivolol interact with the following drugs and had adverse outcome in patients. Interaction with Amiodarone and Flecainide causes increased risk of myocardial depression, AV block and bradycardia. The calcium channel blockers like Verapamil and Deltiazem interact with the nebivolol and cause a trio-ventricular block and bradycardia (Fogari et al., 1997). The antihypertensive patients under treatment with SSRIs and Dextrometorphan may alter plasma drug concentration because nebivolol gets metabolized by the same isoenzyme.

1.5.1.5. **Contraindications**
Nebivolol is contraindicated in patients with:

- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome
- Second and third degree heart block
- History of bronchospasm and bronchial asthma.
- Untreated pheochromocytoma
- Metabolic acidosis.
- Hepatic insufficiency or impaired liver function
- Bradycardia
- Hypotension
- Pregnancy and lactation
- Severe peripheral circulatory disturbances

Nebivolol is used with caution in patients with:

- Raynaud's disease.
- First degree heart block.
- Prinzmetal's angina.
- Diabetes.
- Chronic obstructive pulmonary disease.
- History of psoriasis.

### 1.5.1.6. Use

Nebivolol is used to treat high blood pressure of unknown cause (essential hypertension), Angina pectoris and chronic heart failure (the heart is unable to properly pump blood around the body) in people aged 70 years or over. It is used to relax and widen blood vessels so that it is easier for heart to pump blood around the body and your blood pressure is reduced (Fogari et al., 1997).

### 1.5.2. FELODIPINE

Felodipine, a 1,4-dihydropyridine derivative calcium channel blocking agent, has been administered orally to treat hypertension. Chemically felodipine is 3-ethyl 5-methyl 4-(2, 3-dichlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate (Fig. 1.5).
This drug is classified according to the Biopharmaceutics Classification System as class II, indicating that it has very low water solubility and high permeability.

![Chemical structure of felodipine](image)

**Figure 1.5. Chemical structure of felodipine**

It is official in USP.

Molecular formula: C_{18}H_{19}Cl_{2}NO_{4}

Molecular weight : 384.254

Category : Oral antihypertensive

Dose : Initial dose 2.5-10 mg daily, in divided doses

Properties: Felodipine is a slightly yellowish, crystalline powder. It is practically insoluble in water, chloroform and soluble in dichloromethane and ethanol, sparingly soluble in acetone. It dissolves in dilute solutions of alkali hydroxides and freely soluble in di-methyl formamide. It has pKa value of 5.39. The drug should be stored in tightly-closed containers.

1.5.2.1. Mechanism of action

Felodipine acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, felodipine prevents calcium-dependent myocyte contraction and vasoconstriction. Felodipine is the most potent CCB in use and is unique in that it exhibits fluorescent activity (Dunselman, 1991). In addition to binding to L-type calcium channels, felodipine binds to a number of calcium-binding proteins, exhibits competitive antagonism of the mineralcorticoid receptor, inhibits the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase, and blocks calcium influx through voltage-gated T-type calcium channels. Felodipine is used to treat mild to moderate essential hypertension.
1.5.2.2. Pharmacokinetics

**Absorption:** Felodipine is completely absorbed from the gastrointestinal tract; however, extensive first-pass metabolism through the portal circulation results in a low systemic availability of 15%. Oral bioavailability is 12% in extensive metabolisers and 96% in poor metabolisers, with plasma half-life of 17.5h and 31.5h respectively. Bioavailability is unaffected by food (Kim, 2006).

**Distribution:** The plasma protein binding is 92%, with limited distribution in adipose tissue due to its lipophilicity and hence no need for dosage adjustment in obese patients. The volume of distribution is being 10 L/kg (Kim, 2006).

**Metabolism and Excretion:**

The felodipine is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of felodipine is approximately 20%. Mean peak concentrations following the administration of felodipine are reached in 2.5 to 5 h. Both peak plasma concentration and the area under the plasma concentration time curve increase linearly with dose up to 20 mg. Felodipine is greater than 99% bound to plasma proteins (Dunselman, 1991). The plasma concentration of felodipine declined tri-exponentially with mean disposition half lives of 4.8 min, 1.5 h and 9.1 h. The mean contributions of the three individual phases to overall AUC were 15, 40 and 45% respectively, in the order of increasing t\(_1/2\). After oral administration of the immediate-release formulation, the plasma level of felodipine also declined poly-exponentially with a mean terminal t\(_1/2\) of 11 to 16 h. The mean peak and trough steady-state plasma concentrations achieved after felodipine formulation given once a day to normal humans. The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min, and the apparent volume of distribution is about 10 L/kg (Saltiel et al., 1988).

The renal vascular resistance is reduced by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis and kaliuresis have been observed during the first week of therapy. No significant effects on the serum electrolytes were observed during short and long term therapy. The clinical trials in patients with hypertension, increases in plasma nor-adrenaline levels have been observed.
1.5.2.3. **Adverse effects**

The adverse effects with a frequency of 1-10% incidence included headache, dizziness, paraesthesias, dyspnoea, constipation, nausea, diarrhea, tiredness and oedema. The less frequently reported are impaired vision, bradycardia, heart failure, hypotension, bronchospasm, pruritus and impotence (Dunselman, 1991).

1.5.2.4. **Drug Interaction**

Cimetidine, ketoconazole, itraconazole, and erythromycin can block the breakdown of felodipine, resulting in higher blood concentrations of felodipine and drops in blood pressure. Carbamazepine, phenobarbital, or phenytoin can lower felodipine blood concentrations. Therefore, higher doses of felodipine may be necessary in patients receiving these medications. Taking felodipine with grapefruit juice increases its absorption and may lead to sudden drops in blood pressure. Felodipine may increase blood concentrations of tacrolimus. Tacrolimus blood concentrations should be monitored and the dose should be modified as necessary (Saltiel et al., 1988).

1.5.2.5. **Contraindications**

Felodipine is contraindicated in patients with:

- Uncontrolled heart failure
- Sick sinus syndrome
- History of bronchospasm and bronchial asthma.
- Untreated pheochromocytoma
- Hepatic insufficiency or impaired liver function
- Pregnancy and lactation
- Severe peripheral circulatory disturbances

Felodipine is used with caution in patients with:

- First degree heart block.
- Prinzmetal's angina.
- Diabetes.
- Chronic obstructive pulmonary disease.
1.5.2.6. Use

Felodipine is used to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Felodipine is known as calcium channel blocker. By blocking calcium, this medication relaxes and widens blood vessels so blood can flow more easily. This medication may also be used to prevent angina (Saltiel et al., 1988).

1.6. POLYMER PROFILE

1.6.1. EUDRAGIT® RS100

Eudragit® RS 100 is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable. IUPAC name is Poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (Fig. 1.6).

![Chemical structure of Eudragit® RS 100](image)

**Figure 1.6. Chemical structure of Eudragit® RS 100**

It is official in Ph. Eur., USP/NF and JPE.

**Physical properties:** It is a solid substance in form of colourless, clear to cloudy granules with a faint amine-like odour.

- Weight average molar mass: \(~32,000 \text{ g/mol}\)
- Alkali Value: 15.2 mg KOH/ g polymer
- Glass Transition Temperature (Tg): \(~ 65^\circ C\)
- Product Form: Granules
Stored at controlled room temperature. Protect against moisture. Any storage between 8°C and 25°C fulfils this requirement.

**Molecular weight:** Approx. 150,000.

**Description:** Colourless, clear to cloudy granules with a faint amine-like odour.

**Solubility:** 1 g of the substances dissolves in 7 g aqueous methanol, ethanol and isopropyl alcohol (containing approx. 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions. The substances are practically insoluble in petroleum ether, 1 N sodium hydroxide and water (Sahoo et al., 2005).

**Test solution:** A 12.5 % solution of the dry substance is used for the test solution: a quantity of the substance of corresponding to 12.5 g dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

**Particle size:** Particle size is determined according to Ph. Eur. 2.1.4 or USP <811>.

**Dry substance / Residue on evaporation:** Not less than 97.0 % 1 g of the substances is dried in an oven for 5h in vacuum at 80 °C.

**Storage:** Storage between 8°C and 25°C. Eudragit® RS 100 tends to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again. Minimum stability dates are given on the product labels and batch-related Certificates of Analysis.

1.6.2. **PLGA- POLY (LACTIDE- CO- GLYCOLIC ACID)**

Biopolymers are a class of biodegradable and biocompatible polymers used in the medical and pharmaceutical industries. The most common example is PLGA. Different ratios of PLGA are available like PLGA (75:25), PLGA (50:50) & PLGA (85:15) means are copolymer which can be represented as 75% lactic acid and 25% glycolic acid, 50% lactic acid and 50% glycolic acid and 85% lactic acid and 15% glycolic acid. The polymers are generally prepared from polymerization of the cyclic dimers of the two components (Miller et al., 1977, Danhiera et al., 2012).
Figure 1.7. Chemical structure of Poly (lactide-co-glycolic acid)

Standard Specification for poly (glycolide) and poly(glycolide-co-lactide) resins for surgical implants with mole fractions greater than or equal to 70 % glycolide.

Physical properties: Standard grade of PLGA is an almost colourless or light tan solid manufactured in transparent pellet form. PLGA is easily decomposed into glycolic acid and lactic acid by reaction with water (Makadia et al., 2011).

It is official in Ph. Eur., USP/NF, JPE.

Chemical Formula: \((C_4H_4O_4)x \,(C_6H_8O_4)y\)

Color: white to light tan

Odor: Odorless

Tg (Glass Transition): °C 45-55

Solubility: \(CH_2Cl_2, CHCl_3, DMF, DMSO, THF\)

Grade: Standard grade “PLGA 50-50” is a product with the decomposition rate of one month (Makadia et al., 2011).

1.6.3. ETHYL CELLULOSE

Ethyl cellulose is a derivative of cellulose in which a defined percentage of the hydroxyl groups of the repeating glucose units are substituted with ethyl ether groups. It is a naturally occurring polymer. Cellulose is treated with an alkaline solution to produce alkali cellulose, which is reacted with ethyl chloride yielding ethyl cellulose.

Figure 1.8. Chemical structure of Ethyl cellulose

Physical properties: Ethyl cellulose is an inert, hydrophobic polymer and is essentially tasteless, odourless, colourless, non-caloric, and physiologically inert. The glass
transition temperature is 130 °C. It is practically insoluble in water but soluble in ether, chloroform and carbon disulfide (Verma et al., 2014).
It has long been used for tablet and pellet coating, tablet binder, to prepare microcapsules and microspheres, and both as film- and matrix- forming material for sustained-release dosage forms. Ethyl cellulose also masks the taste of bitter actives, enhance the strength and appearance of tablets and capsules, and enable controlled release formulations.

**Storage**: Ethyl cellulose should be stored at temperature not exceeding 32 °C in a dry area away from all sources of heat.

### 1.6.4. CHITOSAN

Chitosan is a linear polysaccharide composed of randomly distributed β-linked D-glucosamine and N-acetyl-D-glucosamine. Chitosan is a naturally occurring polysaccharide and the deacetylated product of chitin. As a positively charged biopolymer, chitosan is bioadhesive and readily binds to negatively charged surfaces such as mucosal membranes. Chitosan enhances the transport of polar drugs across epithelial surfaces, and is biocompatible and biodegradable (Rinaudo, 2006).

![Chemical structure of Chitosan](image)

**Physical properties**: Chitosan is odourless, tasteless and slightly crystalline in “native” state. The glass transition temperature of chitosan is 40 °C. It is soluble in dilute acids such as acetic acid, formic acid etc. It is soluble in water at acidic (pH) (Bagre et al., 2013).

Chitosan is the only pseudo-natural cationic polymer, finds many applications. It is widely used as filler in tablets; as a carrier in controlled-release drugs; to improve the way certain drugs dissolve; and to mask bitter tastes in solutions taken by mouth.

**Storage**: Chitosan is stored in normal room temperature not exceeding 45 °C in closed container.