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IN VITRO DISSOLUTION OF SUSTAINED-RELEASE NIFEDIPINE BRANDS MARKETED IN THE KUMASI METROPOLIS

BY

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DECLARATION

I hereby declare that this thesis is my own work for the Master of Philosophy degree in Pharmaceutics and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the university, except where due acknowledgement has been made in the text.

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DEDICATION

This thesis is dedicated to my dear husband, Richard Osei-Asare and my entire family for their love and constant support in all my endeavours, especially in this academic programme.

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To God be the glory, great things He has done! What shall I render to my God for His loving kindness to me? I shall praise Him for as long as I live. His faithfulness is my shield and rampart.

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ABSTRACT

With the advent pattern of generic prescribing and substitution in developing countries like Ghana, there has been an influx of a wide variety of antihypertensive drug brands on the market. The study was aimed at establishing the most prescribed sustained-release (SR) antihypertensive drug in the Kumasi Metropolis and evaluation of the quality of selected brands of this drug by *in vitro* dissolution studies and to establish whether the selected brands were interchangeable based on analysis of the dissolution patterns. The survey was conducted for 66 doctors in 50 hospitals and 150 patients within the Kumasi metropolis, based on hypertension management. Information gathered from the survey was edited, coded and analyzed using the version 16 of Statistical Package for Social Science, SPSS software. The drug Nifedipine SR ranked first on the list as the most stocked and used SR antihypertensive drug. Twelve brands of Nifedipine SR comprising 20 mg (8 brands) and 30 mg (4 brands) were purchased from randomly selected pharmacies within the Kumasi metropolis and coded as brands A, B, C, D, E, F, G, H, I, J, K and L. On the subject of SR brands interchangeability, 60% of prescribers and 41% of patients were of the opinion that all brands of SR nifedipine brands were indeed interchangeable. Patients' perception on interchangeability might have been influenced by their experience in the use of the drugs whereas doctors' perception might have been influenced by their knowledge of drug contents and general experience in practice. The twelve coated tablet brands were analyzed for weight uniformity and content. All the twelve brands passed the BP weight uniformity test and 9 passed the USP test for Assay. Dissolution testing was conducted using the USP dissolution test 2, paddle method at 18 time points to obtain their dissolution profiles which were subjected to analysis involving model-independent methods and model dependent methods. For the *in vitro* USP dissolution test conducted, 7 out of the 12 brands passed all the 3 time-points specified

(3hours, 6hours and 12 hours). Further analysis by fit factors showed that brands B, C and D (30 mg) were interchangeable. However, the pairs of 20 mg brands considered similar included brands E &K, E & L, G&H, G&I, and G &J. Based on the analysis of the release profiles in the light of distinct kinetic models, brands A, B, C, D, E, I and K were considered similar because their drug release kinetic followed Higuchi's model. Brands H and J were considered similar because their drug release kinetics followed Hixson-Crowell kinetic model. Therefore, few SR nifedipine brands were similar and could be interchanged, whereas majority of the selected brands could not.

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CHAPTER ONE

INTRODUCTION

Hypertension is the most common cardiovascular condition in the world and the problem of defining a strategy for control confronts all societies. Hypertension is characterized by pathological elevation of blood pressure in the arteriolar system of the blood vessels. It may be classified as essential or secondary. Essential hypertension is the term for pathological increase in blood pressure with unknown cause. It accounts for about 95% of cases. Secondary hypertension is the term for high blood pressure with a known direct cause, such as kidney disease, tumours, or birth control pills (Carretero and Oparil, 2000). Moreover, high blood pressure may be controlled by changing lifestyle, with medicines or a combination of the two. Among the medical options to manage hypertension include several classes of drugs such as angiotensin converting enzyme inhibitors e.g. losartan, beta-blockers e.g. atenolol, diuretics e.g. bendrofluazide, calcium channel blockers e.g. nifedipine.

Calcium-channel blockers slow the movement of calcium into the smooth-muscle cells of the heart and blood vessels. This weakens heart muscle contractions and dilates blood vessels and thereby lowers blood pressure. Other examples of calcium-channel blockers include felodipine (plendil), amlodipine (norvasc), and many more. Hypertension has been confirmed as a common worldwide major public health problem. Wolf-Maier *et al.*, (2003) revealed in a study that the prevalence of hypertension was found to be 28% in North America and 44% in Western Europe.

In Africa, hypertension has also been widely reported and is the most common cause of cardiovascular morbidity on the continent (Cooper *et al.*, 2003). Earlier studies conducted in developing countries such as Nigeria, Ghana, Cameroun, the Gambia, Sierra Leone, Liberia and Senegal have shown a high (and rising) prevalence of hypertension

generally, and a consistently higher prevalence in urban than in rural areas. They have also shown low rates of detection and correspondingly low rates of treatment and control. Clearly, therefore, there is a pressing need for robust strategies to deal with this serious threat to the health of the people of sub-Saharan Africa (Amoah, 2003).

The current prevalence of hypertension in many developing countries, particularly in urban societies, is reported to be already as high as is seen in developed countries (Addo *et al.*, 2007). In Ghana, it has been reported in a study that the prevalence of hypertension among populations was comparable to that reported from Europe and North America (Kearney *et al.*, 2004). The prevalence of hypertension is expected to increase even further in the absence of broad and effective preventive measures (Chobanian *et al.*, 2003).

Reports of some community surveys, done in Kumasi in the Ashanti Region and in Accra (Greater Accra Region) have all confirmed the high prevalence of hypertension in Ghana but worrisome low rates of detection, treatment, and control (Cappuccio *et al.*, 2004; Amoah, 2003). In a study involving four rural communities in the Ga district of the Greater Accra region, only 30(32.3%) of the 93 found to be hypertensive were aware they had high blood pressure. Of these, only 16.7% had their BP under control (Addo *et al.*, 2006).

1.1 Problem statement

An increased burden of hypertension should be expected in Ghana as life expectancy increases and with rapid urbanization. Without adequate detection and control, this will translate into higher numbers of stroke and other adverse health outcomes for which hypertension is an established risk factor. A review of population-based studies conducted on hypertension in Ghana has identified a number of studies conducted since 1973, involving rural as well as urban adults. The rates of detection, treatment and control

were low in all such reported studies. The prevention and control of hypertension in Ghana is therefore very crucial (Addo et al., 2012).

Non-adherence of therapy plays a very significant part in low control rates. Among the possible causes affecting the success of medical treatment outcomes in Ghana and worldwide is the pervasive problem of non-adherence. On average, one third to one half of patients do not comply with prescribed treatment regimens (Rosamond *et al.*, 2007).

Munger *et al*., (2007), examined the prevalence of non-adherence among various patient populations, with a specific focus on antihypertensive medications and showed that many factors such as age, choice of drug, cost of drug, forgetfulness, non-compliance, adverse effects, co-morbid conditions involving use of multiple drug therapy, tolerability of drug, all contributed to the pervasive problem of non-adherence.

Hakonsen and Toverud, 2011 in a study also revealed that among hypertension patients, generics substitution has also been an important reason for intentional non-adherence since a fraction of the respondents (33%) reported that it was more demanding to keep track of their medication after substitution. Such negative attitudes and experiences with generics substitution led to intentional non-adherence. Therefore, the choice and use therefore, of a convenient dosage form that addresses the patient challenges like cost and frequency of drug administration is very necessary to improve upon control rates of the disease.

Recent pharmacotherapeutic advances in the treatment of hypertension have included the development of sustained-release (SR) dosage formulations, providing patients with the convenience of once daily administration (Skaer *et al.*, 1993). The concept of sustained-release was developed to eliminate the need for multiple dosage regimens for chronic cases like hypertension management which particularly requires constant drug-blood levels over a long period of time. Other potential benefits of sustained-release anti-

hypertensive drugs include reduced dosing frequency, enhanced compliance and convenience, reduced toxicity, stable drug levels, uniform drug effect, and decreased total dose (Gohil *et al.*, 2013). Sustained-release (SR) antihypertensives, therefore, when employed in hypertension management, would be very useful as they confer many advantages in addressing the issues of low control rate noted in earlier cited studies in Ghana. If they can be useful alternatives to the conventional types, their quality must be verified.

With the influx of a variety of imported brands of SR antihypertensive drugs (generics) on the Ghanaian market, the prescriber and pharmacist have been faced with the challenge of selecting from among many brands of SR drugs, one of acceptable quality that will ensure good bioavailability within its expected time-frame and thereby yield high treatment outcome. Coupled with the effect of climatic (temperature) changes and variable storage conditions for these products, example, nifedipine (a photosensitive product), the need for regular post- market surveillance in assessing their quality becomes necessary.

Generic drug use, with a few exceptions, has been promoted in western countries by allowing pharmacists to substitute drugs defined as therapeutically equivalent generics. In Canada for example, drug product interchangeability decisions can be based on Health Canada's Declaration of Equivalence, as indicated by the identification of a Canadian Reference Product on a Notice of Compliance for a generic drug. Furthermore, according to their Health Professions Act, an "Interchangeable drug" means a drug that contains the same amount of the same active ingredients, possesses comparable pharmacokinetic properties, has the same clinically significant formulation characteristics and has to be administered in the same way as the drug prescribed (Drug interchangeability update, 2011). In Ghana today, there is no such detailed drug product interchangeability policy as

practiced in Canada. However, the existence of the Ghana National Drug Policy (2004) allows for the selection and prescribing of drugs by their generic or international non-proprietary (INN)-generic names. Prescribers therefore have no control over brands of SR antihypertensive given to hypertension patients at the pharmacies. Scarcity of one product, due to challenges of the drug supply management in health institutions, may cause a patient to be switched over from one brand to another of the same drug (generic). Consequently, due to differences in manufacturing variables of these products and variation in their storage conditions, differences in bioavailability may be observed among brands of a particular SR drug product. The question of interchangeability or substitution among brands has become an issue (Paveliu *et al*., 2011).

The need therefore to employ dissolution testing, as a quality control procedure to detect the influence of critical manufacturing variables on products and to gather the recent evidence about the quality of these imported SR nifedipine brands in Ghana, using Kumasi as case study is of great necessity.

1.2 Aims and objectives:

The study aims at establishing the most prescribed sustained-release antihypertensive drug in use in the Kumasi Metropolis and assessing the quality of the selected brands of the most used SR antihypertensive drug within the metropolis by *in vitro* dissolution studies. The study will also establish whether the selected brands are interchangeable based on analysis of the dissolution data.

Specific objectives:

- To determine the most preferred SR antihypertensive drug brands by doctors and patients and for what reasons, using purposeful sampling procedure.
- To assess whether doctors and patients think the various SR brands of the most preferred drug are interchangeable?
- To identify the brands with excellent drug-release properties and which meet required pharmacopoeia specifications.
- To ascertain whether SR brands are interchangeable based on analysis of their dissolution profiles by model- independent and model-dependent approaches.

1.3 Scope of the study:

The Research design was in two parts: Survey and Experiment.

1.3.1 Survey:

This was done to collect primary data on the most prescribed sustained-release (SR) antihypertensive drug commercially marketed in the Kumasi Metropolis and the preferred SR brands by doctors and patients and for what reasons. Patients and prescribers were assessed on their views about interchangeability of SR brands.

Sampling method and Sampling size: Purposive sampling was used for 73 pharmacies, 50 hospitals and 66 Doctors. Selection was based on hypertension management. Patients (150) were selected purposively based on the use of SR brand for disease control.

Data collection method: After being able to secure ethical clearance from the Committee on Human Research and Publication Ethics, (CHRPE), KNUST, and from the Komfo Anokye Teaching Hospital, (KATH) as well as official permission from medical administrators of the selected hospitals and clinics, commencement of the survey was made possible. An initial pilot study was done to randomly collect data on various groups

of SR anti-hypertensive drugs stocked in community pharmacies, hospitals and clinics within the Kumasi Metropolis. A well-structured questionnaire was used to collect data from prescribers and patients at the selected hospitals. Data processing and analysis for the survey was done using the version 16 of the Statistical Package for Social Science, (SPSS) software.

1.3.2 Experimental:

This work was done at the Ernest Chemist Ltd Laboratory, in Tema- Ghana. Laboratory analysis included;

Assessment of physical parameters included test for uniformity of weight and assay according to USP specifications, as applicable for the 12 brands which were all coated tablets. Dissolution Studies was conducted using the USP-Type 2 dissolution method (paddle type) and High performance liquid chromatography, HPLC (from Agilent technologies, Germany).

Comparison of the various dissolution profiles obtained for the brands selected for similarity was done using three main approaches. These were:

United States Pharmacopoeial (USP) method: all the 20 mg and 30 mg brands which passed the USP dissolution acceptance criteria at all the three time-points specified (3, 6 and 12 hours) were considered as similar.

Model independent approach (fit factors): The dissolution profiles of all possible pairs of pharmaceutical equivalents were compared by similarity factor (f2) and difference factor (f1), for equivalence of the dissolution profiles among paired brands.

Model-dependent approach: The dissolution data were fitted in various kinetic dissolution models such as zero-order, first order, Higuchi, Hixson-Crowell and

Korsmeyer-Peppas models to describe the release kinetics and the mechanism of drug release for the analyzed brands.

1.4 Justification

- This study will in effect provide information on SR anti-hypertensive drugs (Nifedipine brands) marketed in Ghana to improve their use.
- It will help doctors and patients to improve upon hypertension management using SR Nifedipine anti-hypertensive.
- It will provide useful information to Drug and Therapeutic Committees of health institutions in selecting effective Nifedipine SR brands for stocking and subsequent use in their health institutions.
- It will also contribute to current literature on control of hypertension with SR Nifedipine brands.

CHAPTER TWO

LITERATURE REVIEW

2.1 Hypertension:

2.1.1 Overview

Hypertension, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Hypertension is generally characterized by a pathological elevation of blood pressure in the arteriolar system of blood vessels (Chobanian *et al.*, 2003). The heart is therefore required to work harder than normal to circulate blood through the blood vessels.

2.1.2 Signs and symptoms

The presence of the disease is rarely accompanied by any symptoms (asymptomatic) and therefore has been named the "silent killer". It is the major risk factor for cardiovascular morbidity and mortality (Gavras, 2009). However, among the common signs and symptoms experienced include headaches (which occurs in the morning at the back of the head), lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears) and altered vision or fainting episodes (Fisher, 2005).

The symptoms of hypertension have been attributed to anxiety than the high blood pressure itself (Marshall *et al*., 2012).

2.1.4 Types of Hypertension

Two major types of hypertension exist. These are:

Primary or essential hypertension and Secondary hypertension.

Primary (essential) hypertension is the most common form of hypertension and has no known cause. It accounts for 90%–95% of all cases of hypertension (Carretero and Oparil, 2000).

Although it has frequently been indicated that the causes of essential hypertension are not known, this is only partially true because we have little information on genetic variations or genes that are over expressed or under expressed as well as the intermediary phenotypes that they regulate to cause high blood (Luft, 1998).

Secondary hypertension results from an identifiable cause. It is often caused by reversible factors, and is sometimes curable. Other causes include renal disease or endocrine conditions such as Cushing's syndrome, hyperthyroidism, hypothyroidism and acromegaly (Dluhy and Williams, 1998).

The causes of secondary hypertension have been attributed to other factors such as obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive liquorice consumption and certain prescription medicines such as (pseudoephedrine in cough and cold medications , Non-steroidal anti-inflammatory drugs such as naproxen), herbal remedies and illegal drugs (Grossman and Messerli, 2012).

2.1.5 Predisposing factors to hypertension

The predisposing factors that cause hypertension include inherited, behavioural, and environmental components (Carretero and Oparil, 2000).

Among the factors that increase BP, include obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging and perhaps sedentary lifestyle, stress, low potassium intake, and low calcium intake (Sever and Poulter, 1989).

Furthermore, many of these factors are additive, such as obesity and alcohol intake. The genetic alterations responsible for inherited “essential” hypertension remain largely unknown (Luft, 1998).

In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable (Vasan *et al.*, 2003). Insulin resistance

which is common in obesity and a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension (Sorof and Daniels, 2002). Electrocardiogram (EKG/ECG) testing is done to check for evidence that the heart is under strain from high blood pressure. It reveals the existence of left ventricular hypertrophy or whether the heart has experienced silent heart attack. Signs of heart enlargement or damage to the heart can be detected by chest X-ray or an echocardiogram (O'Brien *et al*., 2007).

2.1.6 Definition/classification of hypertension in adults

According to the National institute for health and clinical excellence, (NICE, 2011) guideline draft for consultation, the various classifications for hypertension have been defined as shown in table 2.1.

Table 2.1 Classification of hypertension by National Institute for Health and Clinical Excellence (NICE, 2011).

Classification	Definition
Stage1 hypertension	Initial clinic blood pressure 140/90 mmHg or higher and subsequent ambulatory blood pressure monitoring(ABPM) daytime average or home blood pressure monitoring(HBPM) average blood pressure135/85 mmHg or higher.
Stage 2 hypertension	Initial clinic blood pressure 160/100mmHg or higher and subsequent ABPM daytime average or HBPM average blood pressure150/95 mmHg or higher.
Severe hypertension	Clinic blood pressure 180/110mmHg or higher.

2.1.6 Prevention of hypertension

The concept of preventing hypertension is an important goal in overall efforts to control blood pressure and reduce the incidence of hypertension-related cardiovascular and renal complications and outcomes (Slama *et al.,* 2002).

Among the lifestyle changes recommended in the guidelines for the primary prevention of hypertension by the British Hypertension Society guidelines (Williams et al., 2004) include the following:

- Maintain normal body weight for adults (e.g. Body mass index 20–25 kg/m^2)
- Reduce dietary sodium intake to <100 mmol/day (<6 g of sodium chloride or <2.4 g of sodium per day)
- Engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week)
- Limit alcohol consumption to not more than 3 units/day in men and no more than 2 units/day in women
- Consume a diet rich in fruit and vegetables (e.g. at least five portions per day);
- Effective lifestyle modification may lower blood pressure as much an individual antihypertensive drug. Combinations of two or more lifestyle modifications can achieve even better results (Williams, *et al.,* 2004).

2.1.7 Management of hypertension

Hypertension can be managed in two ways:

- Lifestyle changes (as first line of treatment)
- Combination of lifestyle changes and drug therapy when only lifestyle changes do not adequately control the hypertension.

2.1.8 Lifestyle modifications

Healthy lifestyle changes are an important first step for lowering blood pressure. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication (Blumenthal *et al.*, 2010).

It has been proven in a study (Dietary Approaches to Stop Hypertension, DASH) that a diet low in sodium and high in fruits, vegetables, and calcium is helpful in treating hypertension (Appel *et al.*, 1997).

Different programs aimed to reduce psychological stress such a biofeedback, relaxation or meditations are advertised to reduce hypertension. However, overall efficacy is not greater than health education (Greenhalgh *et al.*, 2009).

2.1.9 Medications for hypertension

Several classes of antihypertensive drugs exist for treating hypertension. The ultimate public health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. It has been proven beyond a doubt that blood pressure reduction is associated with reduced cardiovascular morbidity and mortality (Lewington *et al*., 2002). For most individuals, the aim of treatment should be to reduce blood pressure to <140/90 mmHg for most individuals, but for those with diabetes or kidney disease (some medical professionals recommend keeping levels below 120/80 mmHg). If the blood pressure goal is not met, a change in treatment should be made as therapeutic inertia is a clear impediment to blood pressure control (Eni *et al*., 2006). Treatment guidelines on the choice of medications for treating hypertension for various sub-groups have changed over time and differ between countries. The best first line agent has been disputed. Low dose thiazide-based diuretic has been proposed as first line treatment by the World Health Organization, the Cochrane collaboration and the United States guidelines support (Klarenbach *et al.*, 2010).

2.1.9.1 Calcium channel blockers

CCBs which include both dihydropyridines (DHPs) e.g., nifedipine and amlodipine and non-dihydropyridines (verapamil and diltiazem), are among the most widely prescribed agents for the management of essential hypertension. Several large outcome risk trials and comprehensive meta-analyses have found that CCBs reduce the cardiovascular morbidity and mortality associated with uncontrolled hypertension, including stroke (Basile, 2004). Among the preferred combination drug options for managing hypertension include renin–angiotensin system inhibitors and calcium channel blockers, or renin–angiotensin system inhibitors and diuretics (Sever and Messerli, 2011). Other acceptable combinations include calcium channel blockers and diuretics, beta-blockers and diuretics, dihydropyridine calcium channel blockers and beta-blockers, or dihydropyridine calcium channel blockers with either verapamil or diltiazem (Musini *et al.,* 2009). In America the recommended BP goal is advised as <140/90 mm Hg with thiazide diuretics being the first line medication. Calcium-channel blockers are advocated as first line with targets of clinic readings <150/90, or <145/85 on ambulatory or home blood pressure monitoring in the revised UK guidelines (Aronow *et al.,* 2011).

2.1.10 Epidemiology

Nearly one billion people or 26% of the adult population of the world by the year 2000 had hypertension. This situation was observed in both developed (333 million) and undeveloped (639 million) countries (Burt *et al.,* 1995). Hypertension recorded in US adults (34% of the population) and African American adults have among the highest rates of hypertension in the world at 44 % (Lloyd-Jones *et al.,* 2010).

2.1.10.1 Hypertension situation in Ghana

Hypertensive renal disease has been found to be a common complication in both Kumasi and Accra. This was reported in the study of the health burden of cardiovascular diseases in Accra and was to form the basis for setting up a hypertension control program (Plange-Rule *et al* 1999, Mate-Kole *et al.*, 1990). Reports of some community surveys, done in Kumasi (Ashanti Region), and in Accra (Greater Accra Region) have both confirmed the high prevalence of hypertension in Ghana but worrisome low rates of detection, treatment, and control (Cappuccio *et al.*, 2004, Amoah, 2003). The prevalence rate of hypertension in four rural districts in Accra, Ghana has shown an increase of nearly 8 times than what it was thirty years ago and the prevalence rate has nearly doubled than what was declared (Addo *et al.*, 2006).

An increase in morbidity associated with hypertension does not only reflect a high prevalence of hypertension, but is also an indication of inadequate rates of detection, treatment and control. In an examination of postmortem records in the teaching hospital in Accra between 1994 and 1998, 11 % of deaths in adults aged 20 years or more were due to stroke, most of which were hemorrhagic (Wiredu and Nyame, 2001).

Hypertension was a predominant factor in these strokes. A study had also been done to assess the prevalence, detection, management, and control of hypertension among men and women living in rural and semi-urban villages in the Ashanti Region of Ghana, West Africa. Results from the survey revealed that hypertension is common in adults in Ghana, particularly in urban areas. Rates of detection are suboptimal in both men and women, especially in rural areas. Generally, adequate treatment of high BP is at a very low level. Overall 22.0% (64/291) were aware of being hypertensive, 11.3% (33/291) were on antihypertensive treatment but only 2.8% of the total (8/291) had their blood pressure adequately controlled. Figure 2.1 demonstrates this (Cappucio *et al.*, 2004).

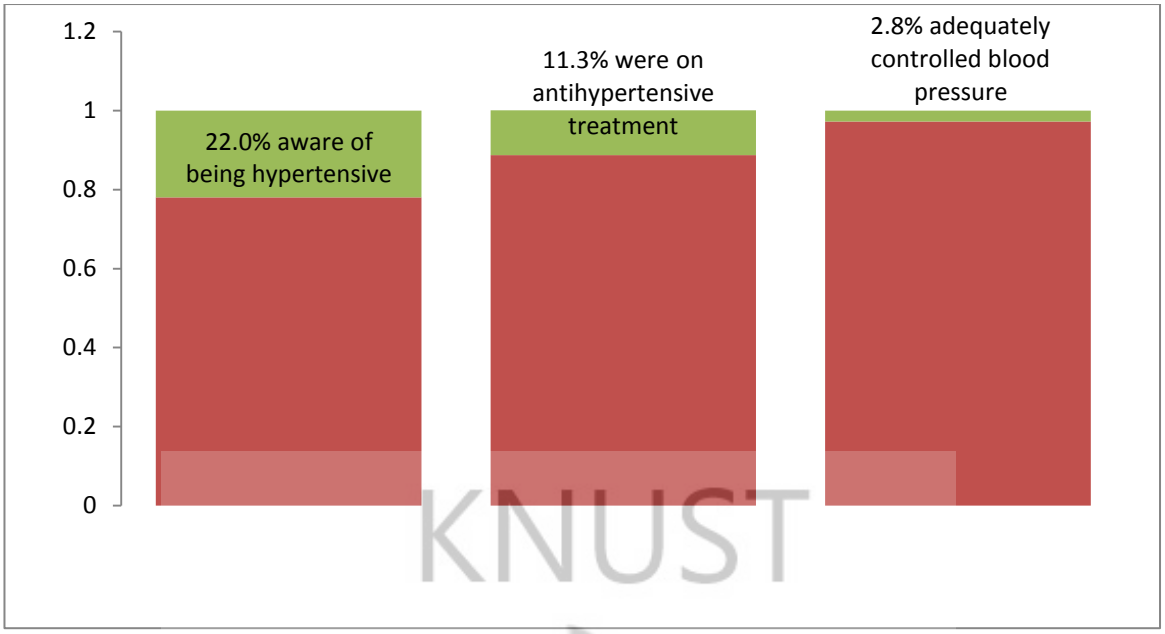

Figure 2.1 Survey findings on prevalence, detection, management and control of hypertension in rural and urban villages in the Ashanti region (Ghana) in 2004.

Another study has been done to review patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care a randomized clinical trial using electronic monitoring. This was done at the Hypertension Unit H360, University of Ottawa Heart Institute, and Ontario. Results of the study revealed that compliance were significantly better with once daily (sustained-release) than a twice daily (conventional drug) therapy antihypertensive. The results further suggested that the negative consequences of partial compliance for blood pressure control can be offset by choosing agents with duration of action well beyond the dosing interval (Leenen *et al.*, 1997).

In Ghana, one among several findings on the contributory factors to the low treatment and control rates has revealed that the high cost of antihypertensive medications contributes to non-adherence. For example, 93% of patients in Ghana were noncompliant with their antihypertensive regimens, and 96% of these patients cited unaffordable drug prices as the main reason for non-compliance (Buabeng *et al.*, 2004).

Non-adherence of therapy plays a very significant part in low control rates (Munger *et al.*, 2007). The choice therefore of a convenient dosage form that addresses the patient challenges like cost and frequency of drug administration is very necessary to optimize treatment outcomes. The findings of the above studies support the fact that Sustained-release (SR) antihypertensives existing on the Ghanaian market today have a role to play in curbing the menace of non-adherence in hypertension management.

2.1.11 Overview of calcium channel blockers in hypertension management:

2.1.11.1Calcium–channel blockers

Calcium-channel blockers (see Table1) slow the movement of calcium into the smooth-muscle cells of the heart and blood vessels. This weakens heart muscle contractions and dilates blood vessels, lowering blood pressure. Because calcium-channel blockers also slow nerve impulses in the heart, they are often prescribed for arrhythmias (Elliott, 2011).

Table 2.2 Calcium channel blockers

Generic name	Brand name	Side effects
Amlodipine	Norvasc	Headache, dizziness, edema, and heartburn. Nifedipine can cause palpitations. Diltiazem and verapamil can cause constipation and a slowed heartbeat.
Diltiazem	Cardizem, Dilacor, others	
Felodipine	Plendil	
Isradipine	DynaCirc	
Nicardipine	Cardene, Cardene SR	
Nifedipine	Adalat CC, Procardia XL	

2.1.11.2 Nifedipine

Nifedipine, chemically dimethyl-2, 6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate, has an empirical formula of $C_{17}H_{18}N_2O_6$ and molecular weight 346.3.

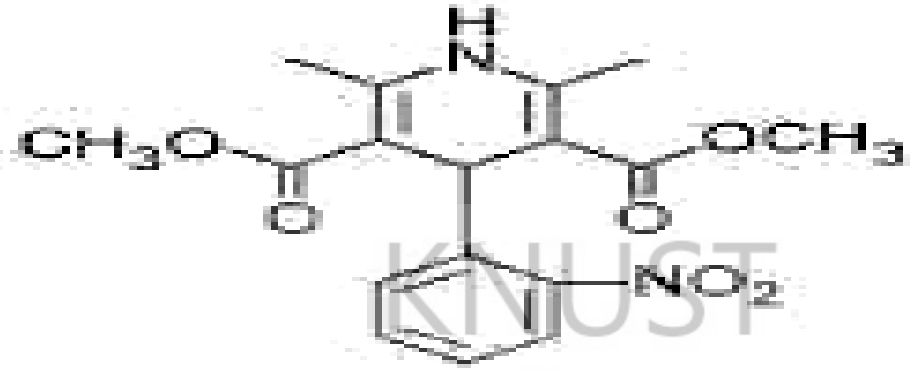

Figure 2.2 Structure of Nifedipine

It is commonly available in capsule and extended-release tablet dosage forms as 30 mg and 60 mg of active drug substance (Lubsen *et al.*, 1998). Nifedipine , which occurs as a yellow crystalline powder, has a melting point of 172°C to 174°C and is practically insoluble in water, sparingly soluble in dehydrated alcohol and freely soluble in acetone (Sweetman, 2009).

Nifedipine is sensitive to daylight or to certain wavelengths of artificial light and therefore must be protected way from light. The pharmacological activity of its photo-reactive by-products (nitrosophenylpyridine and nitrophenylpyridine) is highly diminutized (Al-Turk *et al.*, 1989).

The drug is official in the United States Pharmacopoeia (USP) , which recommends high performance liquid chromatography (HPLC) for its assay (both the pure drug and its dosage forms), and in the BP (British Pharmacopoeia) which recommends redox titration using cerium sulphate and HPLC for the assay of the drug and its dosage forms, , respectively.

2.1.11.3 Pharmacokinetic activity of nifedipine

Nifedipine is rapidly and almost completely absorbed from the gastrointestinal tract but undergoes extensive hepatic first-pass metabolism. Bioavailability of oral capsules is between 45% and 75% but is lower for longer-acting formulations. Peak blood concentrations were reported to occur 30 minutes after oral doses of capsules. It is about 92% to 98% bound to plasma proteins and is distributed into breast milk. It is extensively metabolised in the liver, and 70% to 80% of a dose is excreted in the urine almost entirely as inactive metabolites. The half-life is about 2 hours after intravenous doses or oral capsules (Sweetman, 2009).

It is a poorly soluble drug and its absorption from gastrointestinal tract is limited by dissolution rate. Absorption of Nifedipine is poor following administration orally via immediate release dosage forms. It exhibits 45-65% oral bioavability due to hepatic first pass metabolism. Although sublingual nifedipine had been used previously in hypertensive emergencies, its use has been abandoned because research has revealed it as dangerous (Grossman *et al.,* 1996). Clinical experiences gained with oral nifedipine formulations with immediate-release (IR) characteristics clearly show that a steep rise in the drug plasma concentration results in an increase in heart rate and drug-specific side effects (Soons *et al.,* 1992).

2.1.11.4 History of nifedipine

The first brand of Nifedipine, initially was an innovation drug by the German pharmaceutical company Bayer, with most initial studies being performed in the early 1970s (Vater *et al.,*1972). The study was a meta-analysis, and demonstrated harm mainly in short-acting forms of Nifedipine (that could cause large fluctuations in blood pressure) and at high doses of 80 mg a day and more (Opie and Messerli, 1995).

2.1.11.5 Uses of nifedipine

Nifedipine, the prototypical 1, 4-dihydropyridine, is a calcium channel blocker with peripheral and coronary vasodilator activity. Nifedipine is officially used for long-term treatment of systemic hypertension and angina pectoris (especially in Prinzmetal's angina). Its uses result primarily in vasodilatation, with reduced peripheral resistance, blood pressure, and afterload; increased coronary blood flow; and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output. It acts by inhibiting the trans-membrane influx of calcium into cardiac and vascular smooth muscle cells (Simon and Levenson, 2003).

In recent times, it has been found useful for other indications such as Raynaud's phenomenon, premature labor, and painful spasms of the esophagus such as in cancer and tetanus patients. Topical Nifedipine has been shown to be as effective for anal fissures as topical nitrates (Ezri and Susmallian, 2003).

2.1.11.6 Dosing of nifedipine

The recommended starting dose for immediate-release nifedipine capsules is 10 mg, taken 3 times daily. With the extended-release version, the recommended starting Nifedipine dosage is 30 to 60 mg, taken once daily. After taking the first few doses of the drug, patients usually feel dizzy or faint tachycardia (fast heart rate). These problems are encountered less in the sustained-release preparations of Nifedipine such as Adalat OROS (Brown *et al*., 2000).

Extended release formulations of Nifedipine advisedly should be taken on an empty stomach. Patients are advised to avoid anything containing grapefruit or grapefruit juice, as they raise blood Nifedipine levels (Odou *et al*., 2005).

Toxicity due to acute over dosage with Nifedipine, either accidentally or intentionally, and via either oral or parenteral administration has been experienced in a number of

persons using the drug. The adverse effects include lethargy, bradycardia, marked hypotension and loss of consciousness. The drug may be quantitated in blood or plasma to confirm a diagnosis of poisoning in hospitalized patients or to assist in a medico-legal death investigation. Chromatography and specimen concentrations (in the range 100-1000μg/L) are some of the analytical methods used to investigate (Baselt, 2008).

2.1.11.7 *In vitro* analytical procedures for nifedipine

The stability study of nifedipine in an electrolyte solution used to induce cardioplegia suggests that it degraded more rapidly at 25^0C than at 40^0C. However, even when protected from light and refrigerated, nifedipine concentration declined to approximately 90% of its original value within 6 hours of preparation (Bottorff, 1984).

Detailed survey of literature for nifedipine revealed several methods that have been reported for the assay of nifedipine either alone or in combined form in drug formulations. These analytical techniques include UV-Visible (Vis) spectrophotometry (Kasture and Ramteke, 2005), HPLC (Potter and Hulm, 1988), high performance thin layer chromatography (Patravale *et al.*, 2000), micellar electrokinetic chromatography (Bretnall *et al.*, 1995) and electroanalytical methods (Ghoneim *et al.*, 2003).

Various attempts have been made to evaluate and compare the quality of some marketed brands of nifedipine in various countries. Examples among many include the following:

- Sharma and Gupta, 2006 did *in vitro* comparative evaluation of five leading brands of Nifedipine soft gelatin capsule with respect to compliance with prescribed standards of Indian Pharmacopoeia.
- Oyeniyi and Ayorinde, 2012 did pharmaceutical evaluation of some commercial brands of 20 mg nifedipineSR brands in commercial city of Kano, Nigeria.

- Ashwini *et al*., 2013 recently has conducted *in vitro* release comparison of nifedipine from marketed and prepared controlled release formulations by mathematical modeling to verify on the possibility of switching among brands.

The various research findings confirmed variation in the quality of products due to varying manufacturing variables among the manufacturing companies as well as the adverse effect of poor storage condition on the nifedipine drug.

2.1.12 Novel drug-delivery systems for hypertension

The combination of drugs with different mechanisms of action has become an alternative to improve blood pressure reduction and control, enhance adherence to the treatment and reduce adverse events (Oigman *et al*., 2010).

The recent application of novel controlled-release drug-delivery systems in the treatment of hypertension include biotechnical use of chemical-dispensing systems such as the multiple-unit pellet system for propranolol and metoprolol succinate, one system comprising sustained-release beads and the other utilizing the patented Geomatrix extended-release system (Diltiazem), the transdermal therapeutic system for Clonidine and ,the gastrointestinal therapeutic system, GITS for Nifedipine (Prisant *et al.*, 1992).

The most common oral sustained-release formulations included the wax-matrix system, the gastrointestinal therapeutic system (GITS), and the spheroidal oral drug absorption system (SODAS). The wax-matrix delivery system is limited by the occurrence of "dose-dumping." In a low-pH setting, the wax-matrix formulation may dissolve too rapidly, liberating the entire dose in a short period of time (Prisant *et al.*, 1992).

2.1.13 Modified-release dosage forms (MR)

The conventional release formulations of some drugs have undergone modification by virtue of their rate of release of active drug substance. Such modifications may have a

number of objectives, such as maintaining therapeutic activity for an extended time, reducing toxic effects, protecting the active substance against degradation due to low pH, targeting the active substance to a predefined segment of the gastrointestinal tract for local treatment or targeting active substance release at specified time-points (Patil *et al.*, 2011).

Modified release dosage forms are drug delivery systems (DDS) which, by virtue of formulation and product design, provide drug release in a modified form distinct from that of the conventional dosage forms. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug delivery System (Jha, 2012). Tablets and capsules which are designed to provide modified release often have the letters MR, LA, XL, CR or SR in their names e.g. Nifecard XL, Sometimes the words 'slow' or 'retard' can be used to denote modified release e.g. Diclomax retard, Voltarol retard and Slow (Patil *et al.*, 2011).

2.1.14 Modified-release (MR) dosage forms design

A comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions is considered as vital in the successful formulation of an MR device. Multi-particulate dosage forms have been shown to be less prone to food effects than monolithics and are often the preferred formulation for extended and/or delayed release. Film coating is an ideal process for the production of extended release multi-particulate dosage forms (e.g. drug-loaded pellets, granules, mini-tablets and drug crystals). For application in extended release delivery systems, film coats with well-characterized permeability properties are essential (Kenyon *et al.*, 1995).

Classification: Modified Release dosage form may be classified according to Rathbone *et al.*, 2003 as:

A. Delayed release (timed-release)

B. Extended release (e.g. sustained release, Controlled release)

2.1.14.1 Extended-release

Extended release formulations are pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds (Kumar *et al*., 2012).

It is a controlled-release formulation designed to release the medication in a controlled manner, at pre-determined rate, duration and location in the body to achieve and maintain optimum therapeutic blood levels of drug. The following terms have been applied to "extended" or "sustained" drug delivery systems (Gohil *et al.,* 2013):

Sustained-release (SR)

Controlled-release (CR)

Extended release (ER)

Prolonged-release (PR)

The US FDA defines ER dosage form as: one that allows a reduction in dosing frequency to that presented by a conventional dosage form such as a solution or an immediate release dosage forms (Singhvi and Singh, 2011). The effect of extended release of drug over a number of hours in ER preparations can be accomplished by combining the drug with release-retardant materials to form a matrix core. Release-modifying film coatings (e.g. enteric coating) have two cores containing the drug to delay the release of the drug for a period of time (Kenyon *et al.*, 1995).

2.1.14.1.1 Terminologies for extended-release formulations

Various terms (and abbreviations) have been used interchangeably to describe modified-release dosage forms. These include: sustained release (SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA). Individual products bearing these descriptions may differ in design and performance and must be examined individually to ascertain their respective features (Tiwari *et al.,* 2003).

2.1.14.1.2 Rationale for extended-release dosage-forms

Drugs that are not inherently long lasting require multiple daily dosing to achieve the desired therapeutic effects. Multiple daily dosing is often inconvenient and can result in missed doses, made-up doses and patient non-compliant with therapeutic regimen. Blood levels of drugs from conventional immediate-release dosage forms taken more than once daily following definite schedule usually demonstrate sequential peaks and troughs (valleys) associated with each dose.

The rational design of MR systems, where biological, physicochemical and physico-mechanical considerations have been taken into account during formulation of MR dosage form, has alleviated the risk of 'dose dumping' *in vivo* (Kenyon *et al.,* 1995).

2.1.14.2 Controlled release dosage forms:

They are class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower than normal manner for longer period of time (Tiwari *et al.,* 2003).

2.1.14.2.1 Controlled-release drug design

Controlled-release (CR) matrix systems are designed to continuously deliver and maintain a drug concentration at a desired level in the body. Advantages of such systems

include: the maintenance of plasma drug concentrations in a therapeutically desired range and a reduction in toxic side effects, improved patience compliance and a reduction in the required administration frequency (Tiwari *et al.*, 2003)

The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Typically the basis for such matrices are cellulose ether polymers such as hydroxypropyl methylcellulose (HPMC), which form a pseudo gel layer on the surface of the tablet when exposed to water. Drug release from the system can then occur by two mechanisms: erosion of the gel layer (poorly water-soluble drugs) and dissolution and diffusion through the hydrated gel layer of soluble drugs (Kenyon *et al.*, 1995).

When developing a CR drug, it is common practice to design multiple formulations with different release profiles. While it is hoped that one of these designs will provide the desired pharmacokinetic (PK) profile when tested *in vivo*, further alteration of the formulations may be required. Reliable *in vitro* dissolution techniques should provide information on the stability of the product, enable accurate quality control testing, and in many cases, establish *in vitro–in vivo* correlations (IVIVC). Of these, an IVIVC is highly advantageous as it allows drug companies to adjust formulations without the need for further *in vivo* testing (Prisant *et al.*, 2003).

2.1.14.3 Delayed-release

An important MR technology is delayed release through application of gastro-resistant coatings. In this case, a coating layer is applied to the dosage form, either multiparticulate or monolithic, providing protection to the stomach from the drug or protecting the drug from exposure to acidic gastric fluids. The majority of modern enteric coatings rely on polymers containing carboxylic acid groups as the functional moiety. These groups remain unionised in the low pH environment of the stomach but start to ionise as the

dosage form passes into the small intestine. As the pH level rises above the point of dissolution, the polymer is ionised and the drug is released (Lee and Robinson, 2000).

2.1.14.4 Sustained release:

These are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug (Bhargava *et al.*, 2013).

2.1.14.4.1 Advantages of sustained--release drugs

Sustained-release drugs are considered better formulation alternatives for drugs with short half-life and which require repeated dosing. Their potential advantages according to Prisant and Elliot, (2003) include the following:

Better patient compliance is ensured by eliminating the need for frequent daily administration of a drug, helping patients with co-morbid condition to adhere better to treatment when on several other classes of drugs either hypertensive drugs or non-hypertensive drugs.

The incidence and intensity of side-effects related to high serum drug concentration resulting from the administration of conventional dosage forms is attenuated.

Better economy is assured since average cost of treatment over an extended period may be less compared with the conventional types.

2.1.15 Novel drug-delivery systems for nifedipine

Nifedipine has also undergone novel formulation designs regarding its mode of release. These include:

- Development of Nifedipine-loaded coated gelatin microcapsule as a long acting oral delivery (Li *et al.*, 2009).

- Development of novel spray coated soft elastic gelatin capsule sustained release formulations of Nifedipine (Fahmy *et al.,* 2009).
- Development of Gastro-Intestinal Therapeutic System (GITS) (Chung *et al.*, 1987).

A more novel release system is Gastro-Intestinal Therapeutic System, (GITS); developed by Bayer which provides a 24-hour continuous release through an osmotic push system The formulation design of the nifedipine GITS involves an osmotic pump process which provides approximately zero-order delivery of the drug. This mechanism serves to prevent the possibility of dose dumping, but more importantly allows for maintenance of the relatively constant plasma drug concentrations assumed necessary to maintain smooth control of blood pressure (Brown *et al.*, 2000).

The GITS formulation consists of a two-layer core of nifedipine and osmotic polymer surrounded by a semi-permeable membrane. The membrane incorporates a precisely laser-drilled hole (*Chung et al.,* 1987). When the tablet is swallowed, water is absorbed from the gastrointestinal (GI) tract through the semi-permeable membrane and the nifedipine-containing core forms a suspension, which is extruded through the laser-drilled hole at a constant rate by the expanding polymer core layer. The GITS formulation provides drug concentrations which reach a plateau within 6 hours after administration of a single dose, and continue at that concentration until at least 24 hours after administration. In this way large fluctuations in plasma drug concentrations are avoided, which may improve the efficacy and tolerability of the drug (Grundy and Foster, 1996).

2.1.15.1 Sustained-release nifedipine formulation design

Most commonly used method to control the drug release of SR formulations is incorporation of drug in a matrix system. The direct compressed matrix tablet has been

used for decades due to its simplicity and cost efficiency in comparison with other drug delivery systems.

Nonionic cellulose ethers and hydroxypropyl methyl cellulose (Hypromellose, HPMC) have been widely studied for their application in oral sustained release formulations (Rajabi-Siahboomi and Jordan, 2000). HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods (Reddy *et al.,* 2003).

The adjustment of the polymer concentration, the type, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates (Bravo *et al.,* 2002).

2.2 *In vitro/in vivo* correlation for nifedipine SR drugs

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance. New drug applications (NDAs) submitted to the Food and Drug Administration (FDA) contain bioavailability data and *in vitro* dissolution data, which, together with chemistry, manufacturing, and controls (CMC) data, characterize the quality and performance of the drug product. Establishment of an *in vitro-in vivo* correlation (IVIVC) could facilitate drug development by reducing the number of *in vivo* studies required for confirming both the safety and the efficacy of a drug product or the bioequivalence of products containing the same drug (Nagabandi *et al.,* 2010).

Wonneman *et al.,* 2006 did a research to compare the rate and extent of nifedipine bioavailability after single dose administration of Adalat OROS 30 (Reference product) and Nifedipine Sandoz retard 30 tablets (Test product). The *in vitro* dissolution testing done characteristics showed a significant pH dependency with the Test product whereas drug release with the Reference product was independent of experimental conditions. Similarly *in vivo* study conducted confirmed significant food interaction effect on bioavailability of the test drug which showed higher nifedipine plasma concentration (Cmax) compared to the reference product. The differences observed between the two products suggested a possible direct therapeutic relevance when switching from one formulation to the other and, in particular, when administration conditions changed (i.e. administration in the fasting state and administration with a fatty meal). Since the pharmacological and therapeutic actions of nifedipine are closely associated with the concentration, the results confirmed the relationship between the *in vitro* dissolution profile results and the effects of the drug *in vivo*.

Ashwini *et al.,* 2013, in another study involving the *in vitro* dissolution comparison among nifedipine formulated and marketed brands confirmed the need for controlled release formulations to be formulated in such a way that they remained independent of these variable factors, encountered most commonly when administered through per oral route in order to ensure a reliable *in vivo* performance. This is in view of the different drug release profiles exhibited by a particular formulation under different chemical environments and in different physical states owing to the nature of excipients and the method of manufacturing.

Furthermore, according to Freitag, 2001, the main applications of an *in vitro/in vivo* correlation are the setting of dissolution specifications for new drug products and the possibility of granting biowaivers for changes in the manufacturing of a new drug.

2.3 Dissolution theory

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium. As an *in vitro* laboratory test method, it is designed to demonstrate how efficiently an active drug substance is extracted out of oral dosage forms like capsules and tablets (Dressman, 2000).

The basic step in drug dissolution is the reaction of the solid drug with the fluid and/or the components of the dissolution medium. This reaction takes place at the solid—liquid interface and therefore dissolution kinetics are dependent on three factors, namely:

the flow rate of the dissolution medium toward the solid—liquid interface, the reaction rate at the interface, and the molecular diffusion of the dissolved drug molecules from the interface toward the bulk solution dissolution mechanism.

Scientists have reviewed the factors which can affect the dissolution of tablets and these include the stirring speed, temperature, viscosity, pH, composition of the dissolution medium and the presence or absence of wetting agents (Singhvi and Singh, 2011). The goal of dissolution testing is to assure the pharmaceutical quality of the product and also the reliability of a product's biopharmaceutical characteristics such as rate and extent of absorption. It is desirable therefore to develop dissolution tests that can assess the ability of the dosage form to release the drug completely and to simultaneously indicate how the product will perform *in vivo* (Dressman, 2000).

For drug dosage forms to be efficacious, the active drug substance must be absorbed into the systemic circulation so that it can be transported to its site of activity. The overall efficiency of a drug to be absorbed into the systemic circulation (bioavailability) depends on two major steps: dissolution and absorption, or permeability, as defined within Food and Drug Administration (FDA) guidelines concerned with the Biopharmaceutics Classification System (BCS) (Benet, 2010).

The first step which is dissolution is the process of extracting the drug substance out of the dosage form solid-state matrix into solution within the gastrointestinal tract. The second step, which is absorption, involves transporting the drug substance from the gastrointestinal tract into the systemic circulation. The objective in dissolution is to develop a discriminatory method that is sensitive to variables that affect the dissolution rate. Such variables may include characteristics of the active pharmaceutical ingredient (API) e.g. particle size, crystal form, bulk density, drug product composition (e.g. drug loading and the identity, type and levels of excipients), the product manufacturing process (e.g. compression forces, equipment) and the effects of stability storage conditions (Tadey and Carr, 2009).

2.3.1 Importance of dissolution

Drug dissolution testing is routinely used in the pharmaceutical industry to provide critical *in vitro* drug release information for both quality control i.e., to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, i.e., to predict *in vivo* drug release profiles (Bai and Armenante, 2011). It serves as a quality control test in support of routine manufacture to establish lot-to-lot performance consistencies. In fact, this test method is considered so useful that it is a standard compendia method published by the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia (BP) and the Japanese Pharmacopoeia (JP) (Hauck *et al.,* 2005).

In pharmaceutical industry, *in vitro* dissolution test is performed early in order to validate initial screening among potential formulations to detect the influence of critical manufacturing variables and to help in the selection of the candidate formulation (Chevalier *et al.,* 2009). Dissolution testing is an essential requirement for the development, establishment of *in vitro* dissolution and *in vivo* performance (IVIVR),

registration and quality control of solid oral dosage forms (Pillay and Fassihi, 1998). The use of dissolution test can speed up the formulation development, enabling a prompt identification of potential problems in drug release (Snyder *et al.,* 2008). *In vitro* release testing is also a very important tool for batch to batch quality control. *In vitro* dissolution tests are important in the development and ultimately in the quality control (QC) of a solid dosage form (Siewert *et al.,* 2003).

2.3.2 Types of dissolution apparatus

An effective dissolution procedure is dependent on system hydrodynamics, which in turn depends on apparatus data due to the nature of dissolution testing (Uddin *et al.,* 2011).

USP describes the various apparatuses used in dissolution studies, and has been recently harmonized with the European Pharmacopoeia and the Japanese Pharmacopoeia (Long and Chen 2009). In United States Pharmacopeia (USP) General Chapter Dissolution, there are four dissolution apparatuses standardized and specified (USP, 2011).They are namely:

USP Dissolution Apparatus 1 – Basket method (Sinko, 2010).

USP Dissolution Apparatus 2 – Paddle method (Dyas and Shah, 2007)

USP Dissolution Apparatus 3 - Reciprocating Cylinder method(Yu *et al* , 2002)

USP Dissolution Apparatus 4 - Flow-Through Cell method (Moller,1983)

USP Dissolution Apparatus 2 is the most widely used apparatus among these four.

The rotating basket and the paddle (apparatus 2, USP) devices are easy to use, robust and adequately standardized apparatuses. They have a general acceptance worldwide and recommended by various guidelines as first choice for the *in vitro* dissolution testing of immediate as well as controlled/modified-release preparations (FIP Guidelines, 1997, Uddin *et al.,* 2011).

USP Apparatus 3 is generally preferred when a pH gradient is required and offers advantages such as ease of setup, operation, and sampling relative to USP Apparatus 4. USP Apparatus 4 is particularly applicable for the dissolution of very poorly soluble drug substances, because it allows for continuous introduction of fresh medium during the test (Uddin *et al.*, 2011).

Figure 2.3 USP Apparatus 2 (Paddle)

Figure 2.4 USP Apparatus 3 (The reciprocating cylinder)

2.3.3 Selection of dissolution conditions

The development of a dissolution procedure involves selecting the dissolution media, apparatus type and hydrodynamics (agitation rate) appropriate for the product (Das and Gupta, 1988). Both the FDA and USP have published guidelines on developing suitable dissolution methodology. Sufficient information about the drugs substance properties (solution stability, solubility, particle size, polymorphism, permeability, and site of absorption) that are likely to affect the *in vitro* dissolution behaviour should be obtained (Brown *et al.*, 2004).

Some decisions regarding method parameters will be determined by drug product characteristics, such as the type of dosage form (tablet, capsule, and suspension), the number of strengths, and the desired release mechanism and profile (immediate, delayed,

or extended release) (Tadey and Carr, 2009). A systematic approach, based on sound scientific and regulatory principles, should be applied in developing a dissolution method. It is also extremely important for dissolution method development chemists to work closely with input from their counterparts in pharmaceutics and process development. Failure to do this during method development may result in a method that is not relevant for the dosage form (Tadey and Carr, 2009).

2.3.4 Dissolution test acceptance criteria

For dissolution tests, acceptance criteria are set on the basis of requirements for a percent quantity of drug to be released after a certain period of time in the dissolution apparatus. Acceptance criteria must be established on this basis of six individual dosage units used for each test. Specifications for extended release products are based on three or four time points. The requirements are based on ranges for the intermediate time points but for the final time point, they are usually based on a single value. Therefore, the acceptance criteria at each stage are expressed in terms of variances around ranges for intermediate time points and minimum acceptable release at the final time points (Babu, 2011).

2.3.5 Dissolution profile

Dissolution profile refers to the curve of the mean dissolution rate (cumulative percentage dissolved) over time. A dissolution profile can characterize the product more precisely than a single point dissolution test under appropriate test conditions (Costa and Lobo, 2001).

2.3.6 Dissolution profiles comparison

The common methods for the comparison of *in vitro* dissolution profiles include:

Model-dependent methods (Polli *et al.,* 1997).

Model-independent methods (Moore and Flanner, 1996).

2.3.6.1 Model-dependent methods:

Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q= f (t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson-Crowell, Weibull, Higuchi, Baker-Lonsdale, Korsmeyer-Peppas and Hopfenberg models. Other release parameters, such as dissolution time (tx%), assay time (tx min), dissolution efficiency(ED), difference factor (f1), similarity factor (f2) and Rescigno index (xi1 and xi2) can be used to characterize drug dissolution/release profiles (Costa and Lobo, 2001).

2.3.6.2 Model independent methods (Fit factors approach)

The similarity factor, f2 exists as the simplest among several methods investigated for dissolution profile comparison. Moore and Flanner, 1996 proposed a model independent mathematical approach to compare the dissolution profile using two factors, f1 and f2. By the fit factor method, profile comparisons are based on the difference factor (f1), which calculates the percent difference between the two curves at each time point, and the similarity factor (f2), which is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves (Shah *et al.*, 1998).

2.3.7 Analysis of dissolved sample

Two common ways of analyzing dissolved drug samples is the Direct ultraviolet/visible (UV/VIS) spectrophotometry and high pressure liquid chromatography (HPLC). UV/VIS should be considered as a first choice for routine quality control release testing because it is faster and more efficient (Tadey and Carr, 2009).

2.3.8 HPLC analysis

High-performance liquid chromatography (sometimes referred to as high-pressure liquid chromatography), HPLC, is a chromatographic technique used to separate a mixture of compounds in analytical chemistry and biochemistry with the purpose of identifying, quantifying or purifying the individual components of the mixture. The exceptional separation capabilities of the HPLC (higher specificity, sensitivity as well as its applicability in formulations with multiple API's or very low dose) gives it an edge over UV spectrometry (Levin, 2010).

2.3.8.1 Uses of HPLC

HPLC has many general uses including medical e.g. detecting vitamin D levels in blood serum (Saenger *et al.*, 2006), legal e.g. detecting performance enhancement drugs in urine (Lai *et al.*, 1997), research e.g. separating the components of a complex biological sample or of similar synthetic chemicals from each other and manufacturing e.g. during the production process of pharmaceutical and biological products Lisitskaya *et al.*, 2012).

Identification (ID) of individual compounds in the sample

The most common parameter for compound ID is its retention time (the time it takes for that specific compound to elute from the column after injection) depending on the detector used, compound ID is also based on the chemical structure, molecular weight or some other molecular parameter (Tsao *et al.*, 2003).

Quantification

This involves the measurement of the amount of a compound in a sample (concentration) meaning, how much is there? There are two main ways to interpret a chromatogram (i.e. perform quantification)

Determination of the peak height of a chromatographic peak as measured from the baseline;

Determination of the peak area: In order to make a quantitative assessment of the compound, a sample with a known amount of the compound of interest is injected and its peak height or peak area is measured. In many cases, there is a linear relationship between the height or area and the amount of sample (Prazeres *et al.*, 1998).

2.3.8.2 Basic components of HPLC equipment

The schematic of an HPLC instrument typically includes a sampler, pumps, and a detector. The sampler brings the sample mixture into the mobile phase stream which carries it into the column. The pumps deliver the desired flow and composition of the mobile phase through the column. Most HPLC instruments also have a column oven that allows for adjusting the temperature at which the separation is performed (Levin, 2010).

2.3.8.3 Basic operating principles of HPLC

HPLC is a separation technique that involves injection of a small volume of liquid sample into a column (tube packed with tiny particles 3 to 5 microns (μm) in diameter) called the stationary phase. The individual components of the sample are moved down the column with a liquid (mobile phase) forced through the column by high pressure delivered by a pump.

These components of the sample are separated from one another by the column packing that involves various chemical and/or physical interactions between their molecules and the packing particles. Detection of the separated components occurs at the exit of the column by a flow-through device (detector), which measures their amount. A Liquid chromatogram is the output from this detector (Ahuja and Dong, 2005).

2.3.8.4 Isocratic elution

A separation in which the mobile phase composition remains constant throughout the procedure is termed isocratic (meaning constant composition. It has proven typically

effective in the separation of sample components that are not very dissimilar in their affinity for the stationary phase (i.e. simple preparations). It has also proven useful in quality control applications that support and are in close proximity to a manufacturing process. In isocratic elution, peak width increases with retention time linearly according to the equation for the number of theoretical plates, N. This leads to the disadvantage that late-eluting peaks get very flat and broad. Their shape and width may keep them from being recognized as peaks (Shrivastava and Gupta, 2012).

2.3.8.5 Gradient elution

The composition of the mobile phase may vary during the chromatographic analysis. This is termed as gradient elution. In gradient elution the composition of the mobile phase is varied typically from low to high eluting strength. The eluting strength of the mobile phase is reflected by analyte retention times with high eluting strength producing fast elution and short retention times). It is considered best for the analysis of complex samples and in method development for unknown mixtures. Gradient elution decreases the retention of the later-eluting components so that they elute faster, giving narrower (and taller) peaks for most components. This also improves the peak shape for tailed peaks, as the increasing concentration of the organic eluent pushes the tailing part of a peak forward. This also increases the peak height (the peak looks sharper), which is important in trace analysis. The gradient program may include sudden "steep" increases in the percentage of the organic component, or different slopes at different times – all according to the desire for optimum separation in minimum time (Snyder *et al.*, 2008).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

3.1.1 Reagents

All the reagents used for the experiment were of analytical grade and obtained from the chemical store of Ernest chemists manufacturing division, Tema. The reagents were all imported from Merck Specialties Private Ltd, Mumbai, India. USP Nifedipine RS was a free gift from Sharon Bio-Medicine Ltd (Taloja in Mumbai, India). The Dibasic Sodium Phosphate, Citric acid and Phosphoric Acid which formed the buffer solutions were always freshly prepared with distilled water before use. Other reagents used included Sodium Lauryl Sulphate powder, Acetonitrile (HPLC and analar grades), Methanol, Methanolic Potassium Hydrochloride, Sulphuric acid S, Acetone, Sodium Nitrite R, Naphthylethylene Diamine Dihydrochlorate R., Ammonium Sulphamate R, 2-Methyl-2-Propanol solution, Perchloric acid solution R. 0.1M, Cerium Sulphate and Ferroin R indicator.Whatman No. 1 filter paper was also used. Twelve brands of sustained-release (SR) nifedipine consisting of two innovator brands (Adalat 20 mg and 30 mg purchased from selected community and hospital pharmacies are shown in Table 3.1).

Table 3.1 Nifedipine SR brands marketed in the Kumasi metropolis

Drug name	Strength (mg)	Code	Country of origin	Batch no.	Man. Date	Expiry date
Adalat 30	30	A	Germany	Bxg5jy1	09/12	09/15
Nifecard Xl	30	B	Slovenia	Cv4547	08/12	08/15
Caredin 30	30	C	England	310472	05/11	04/14
Cardovasc Xl	30	D	India	19c14	09/12	09/15
Adalat 20	20	E	Germany	Bxfg4e1	06/12	06/15
Cordipin Retard	20	F	Slovenia	Vii080	09/11	09/14
Caredin 20	20	G	England	620002	01/11	12/14
Nifedi-denk	20	H	Germany	17016	12/11	11/14
Nepine SR	20	I	England	410267	09/11	09/14
Carditas Retard	20	J	India	Vmo264	03/11	02/14
Nifin 20	20	K	India	Nf-023	06/12	07/15
Nifidose	20	L	India	E0102l	08/11	08/14

Source: Survey 1 (2012)

3.1.2 USP nifedipine reference sample, (RS)

Information on the Nifedipine powder obtained for use as the reference standard (RS) for the dissolution study was captured as follows:

Date of analysis: 06/12/12

Raw material: Nifedipine Crude (Ph.Eur)

Batch number: SBML/NFD/11004

Date of manufacturing: 08/11

Date of expiry: 07/16

Supplier: Sharon Bio-Medicine Ltd, API Unit 11, L-6, MIDC, Taloja, India.

Content: 98% to 102 % (dried substance) complies with BP, 2011 AS Ph. Eur Monograph 0672

3.2 Equipment

Laboratory grade general glassware (Borosil ™,Germany), Magnetic stirrer(Stuart, Britain), Mettler-Toledo weighing balance(Switzerland), Agilent Technologies 1200 series HPLC equipment(Germany),Agilent Prep C-18, Scalar column (4.6x 25-cm analytical column containing L1 packing and a 2.1-mm*3-cm guard column, containing L1 packing (from Agilent technologies, Germany), Erweka dissolution apparatus (paddle-type, by Copley Scientific Britain), Amber-coloured vials (Germany), Syringe membrane-filter (AutoPack™ GXF/0.45um nylon membrane, USA), Injectable syringe (10ml),Orbital shaker SSL1(Stuart, Germany), pH Meter (H12215, Hanna instruments, Germany), Heraeus oven (Britain), Micrometer screw gauge, Mortar and pestle(China).

General Precaution:

All assays and tests were conducted under low actinic light due to the photosensitive nature of Nifedipine to daylight and certain wavelengths of artificial light (USP, 2007).

3.3 Methods

The Research design was in two parts: Survey and Experiment.

The survey confined itself to the aim and objectives of the study which sought to determine the most prescribed SR drug brand commercially marketed in the Kumasi Metropolis; to determine the most preferred SR brands of this drug by doctors and patients and for what reasons, and to assess doctors and patients views on brand interchangeability of the most prescribed drug. This was followed with laboratory experiment centred on the last two specific objectives which were to identify the brands (as collated from the survey) which had excellent drug-release properties and which met

required pharmacopoeia specifications, and to ascertain whether SR brands are interchangeable based on analysis of their dissolution data.

3.4 Methodology 1 (Survey)

Before commencement of the survey, ethical clearance was sought from the Committee on Human Research and Publication Ethics (CHRPE) at the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi and the Komfo Anokye Teaching Hospital, KATH. Official permission was also sought from the medical administrators of the selected hospitals and clinics within the Kumasi metropolis.

Before the survey was administered, the objectives of the study were explained to the patients. Interviews took place in a private area within the health facilities.

Questionnaires were anonymous, with no personal identifying information recorded on them. Study participants were assured a strict confidentiality of the information they provided.

3.4.1 The Study Prefecture

The survey was conducted in the Kumasi Metropolis which is one of Ghana's 30 political and administrative districts and the capital city of the Ashanti Region, located in the south-central part of the country. Kumasi is located in the transitional forest zone and is about 270 kilometers north of the national capital, Accra. The metropolis has an area of about 254 square kilometers. With a 5.4% annual growth rate, Kumasi Metropolis is the most populous district in the Ashanti, representing 42.6% of the total population of the region (GSS, 2012; MOH/GHS, 2008)

Health services within the metropolis are organized around 5 Sub-Metro health teams namely, Bantama, Asokwa, Manhyia North, Manhyia South and Subin. Health facilities in the city exist in both the public and private sectors. Notable among them are the Komfo

Anokye Teaching Hospital (KATH), which is one of the two (2) national autonomous hospitals, four (4) quasi health institutions, five (5) health Care Centres owned by the Church of Christ and the Seventh-Day Adventist Church. There also exist 13 industrial Clinics in the metropolis and over two hundred (200) known private health institutions. There is an even distribution of all these facilities in space. With the passage of the National Health Insurance Bill in 2005, the Kumasi Metropolis had four District Mutual Health Insurance Schemes in operation (DMHIS) in the four Sub Metropolitan District Councils, namely; Subin, Bantama, Manhyia and Asokwa. This is expected to improve the accessibility to health care delivery in the Kumasi Metropolis (MOH/GHS, 2008).

3.4.2 Sampling procedure

Purposive sampling was used for 73 community pharmacies, 50 hospitals and 66 doctors within the metropolis. Selection was based on hypertension management. 150 patients were selected purposively based on the use of SR brand for the disease control. The selection of community pharmacies was done by referring to an updated list of all registered pharmacies within the metropolis obtained from the pharmacy council office in Kumasi during the survey period (2nd December, 2011 – 5th March, 2012). The selection of facilities ensured that each Kumasi sub-metropolis area was represented as shown in Figure 2.5.

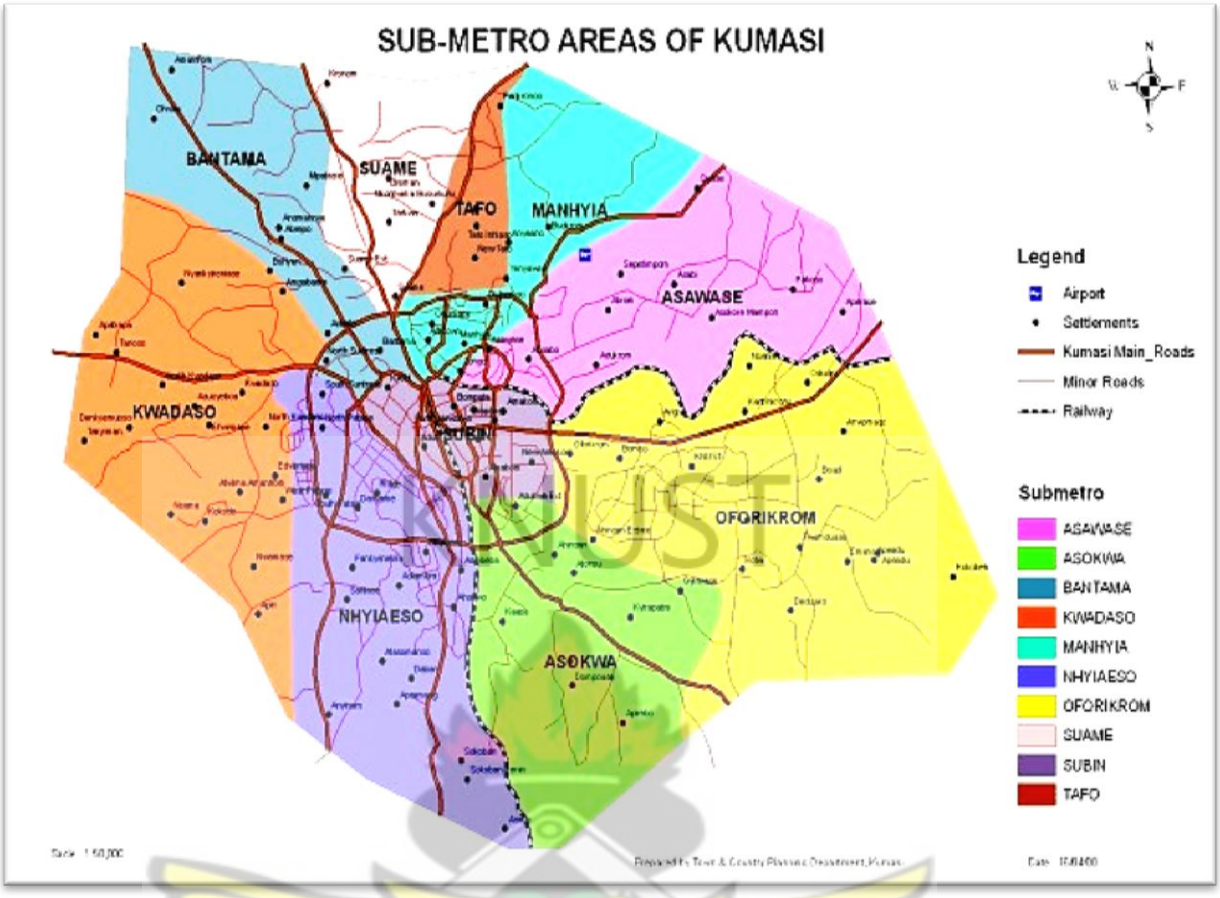

Figure 2.5 Sub-metro areas of Kumasi

Source: Google images

3.4.3 Data collection method

An initial pilot survey was done with the aid of an interview guide to collect data on the various types of SR antihypertensive drugs stocked in government and quasi government hospitals/clinics, private hospitals/clinics and community pharmacies within the metropolis as shown in Appendix 2. Nifedipine drug SR ranked first on the list as the most stocked SR antihypertensive drug. A list of the names of the various brands of nifedipine (20 mg and 30 mg) stocked in 73 community pharmacies and 50 hospitals and clinics within the metropolis was captured in the questionnaire to make it easier for prescribers and patients to recollect brand names easily. Samples (brands) for the study were purchased randomly from among the various community pharmacies and

pharmacies within the government and private hospitals/clinics selected from the four sub-metro health areas organized within the metropolis. Information was obtained from respondents: doctors who handled hypertensive cases and hypertensive patients (from outpatient departments). They were interviewed via interviewer administered structured questionnaires as shown in Appendix 3 and 4. The average interview time was about twenty minutes per respondent.

3.4.4 Data processing and analysis

Information gathered from the survey was edited, coded and analyzed using the version 16 of Statistical Package for Social Science, SPSS software. The presentation of data was done through frequency tabulations and/or percentages.

3.5 Methodology 2(laboratory experiment)

This work was done at the Quality Assurance Department of Ernest Chemist Ltd Manufacturing Division, Tema- Ghana. Analysis included;

Assessment of physical parameters: appearance, uniformity of weight and assay.

- Dissolution Studies was done using the USP-Type 2 dissolution method (paddle type) and HPLC for analysis (USP, 2007).

The reference standard obtained was analysed to confirm its authenticity and suitability for the intended purpose via tests recommended by the BP for nifedipine. These included:

- tests for identification(appearance, solubility, colour)
- assay
- loss on drying

3.5.1 Tests for identification of Nifedipine RS

The Nifedipine reference standard was then subjected to identification tests as specified in the USP (2007), Clarkes (2004) and BP (2011) as follows:

CHARACTERS:

- *Appearance*: The appearance of the nifedipine powder was observed with the naked eye for the colour and form of particles. Visual observation of yellow, crystalline powder complied with the USP specification on appearance (USP, 2007).
- *Solubility*: Procedure for the solubility of the nifedipine powder involved the addition of about 10 ml each of water, acetone and ethanol to about 1.000 g of nifedipine powder. The nifedipine powder was practically insoluble in water, freely soluble in Acetone and sparingly soluble in ethanol. This confirmed its compliance with USP specification on solubility (USP, 2007).
- *Colour tests*: the Nifedipine powder (0.1g) turned orange upon the addition of 5 ml methanolic Potassium Hydrochloride and Sulphuric Acid. And therefore complied with the colour test as specified. (Clarke's Analysis of drugs and poisons, 2004)

BP Identification test (D): This was done as follows:

To 25 mg of Nifedipine powder in a test tube, 10 ml of a mixture of 1.5 volumes of HCl R, 3.5 volumes of water R and 5 Volumes of alcohol R was added. The content of the test-tube was subjected to gentle heating to dissolve. Zinc R, in granules (0.5 g) was added and the contents allowed to stand for 5 minutes with occasional swirling. Upon filtering into a second test tube, 5 ml of 10 g/l solution of sodium nitrite R was added to the filtrate and allowed to stand for 2 minutes. Two millilitres (2 ml) of a 50 g/l solution of Ammonium sulphamate was added and the test tube was shaken vigorously with care. Two milliliters (2 ml) of a 5 g/l solution of Naphthylethylene diamine dihydrochlorate R was then added. The appearance of an intense red colour which developed and persisted for not less than 5 minutes confirmed compliance of the Nifedipine powder with

specification (BP, 2011). Therefore the Nifedipine powder complied with the Identity test D in BP, 2011.

3.5.2 Assay of the nifedipine reference powder

Two weighed amounts of the reference standard (0.1318 g and 0.1333 g) were separately dissolved in a mixture of 25 ml of 2-methyl-2-propanol and 25 ml of perchloric acid solution. Each was titrated with 0.1 M Cerium Sulphate using 0.1 ml of Ferroin R as indicator, until a pink colour disappeared. The titrations were done slowly towards the end. A blank titration was then carried out (BP, 2011). The percentage of active content value of 101.39% shows compliance with BP specification (BP 2011) as shown in 4.1.

3.5.3 Loss on drying of nifedipine powder

One gram of Nifedipine powder (1 g) was subjected to drying in a Heraeus oven (Germany) for two hours at a specified temperature of 105^{o}C. The weight of the dried sample after the two hours showed a maximum loss on drying as 0.5%, showing compliance with the USP specification on loss on drying (USP, 2007).

3.5.4 Uniformity of weight of selected brands

Twenty tablets each from each of the twelve brands were randomly selected. For each brand, the 20 tablets were weighed together on a Mettler-Toledo weighing balance, after which the average tablet weight was calculated. The tablets were then weighed individually and recorded. The deviation of each of the individual tablet weight from the average weight of 20 tablets per brand was determined (example as shown in Appendix 5 table 1).

3.5.5 Assays of the selected 12 brands of nifedipineSR tablets

The content of active ingredient (assay) for each of the twelve brands was determined by HPLC method, using the Agilent Technologies 1200 series HPLC equipment. The 12 brands comprised 2 innovator brands and 10 branded generics. The assay was conducted promptly after preparation of the standard and assay solutions as directed by the USP.

Plate 2.1 Snapshot of assay test samples

3.5.5.1 Mobile phase preparation for use as diluent

Distilled water of volume 250 ml; 125 ml acetonitrile and 125 ml methanol were measured with a measuring cylinder into a 500 ml standard volumetric flask and mixed thoroughly to obtain the specified ratio of 50:25:25 of water: acetonitrile and methanol, respectively.

3.5.5.2 Standard preparation

USP Nifedipine RS, 100 mg was dissolved in 100 ml of methanol to obtain a solution of concentration 1 mg/ml. This was quantitatively diluted with mobile phase (diluent prepared containing 250 ml of water,125 ml of Acetonitrile and 125 ml of Methanol) to obtain a solution having a concentration of 0.1 mg/ml.

3.5.5.3 Assay preparation

Selection of tablets randomly (25 tablets of the 20 mg Nifedipine tablets and 20 tablets of the 30 mg nifedipine tablets) from each respective brand were weighed and finely powdered with the aid of a ceramic mortar and pestle.

Powder equivalent to 420 mg of Nifedipine from each brand was transferred to a 250 ml volumetric flask containing 130 ml of water. This was shaken in an orbital shaker and a mixture of the acetonitrile and methanol (1:1) was added to make up to volume, and stirred for 30 minutes. The resultant solution was centrifuged to obtain a clear supernatant stock solution. A volume of the stock solution (3.0 ml) was transferred into a 50 ml volumetric flask and diluted with mobile phase to volume. This was mixed and filtered using a whatman no. 1 filter paper to obtain a solution of concentration of about 0.1 mg Nifedipine per ml.

3.5.5.4 Chromatographic procedure for assay

The Chromatographic system was set up as follows: the wavelength for the detector was set at 265-nm and pressure of 73 bars. The column used was Agilent Prep C-18, scalar column (4.6x 25-cm analytical column containing L1 packing), and a 2.1-mm*3-cm guard column, containing L1 packing. A column efficiency of not less than 4000 theoretical plates with tailing factor of not more than 1.5 was also set. Relative standard deviation for replicate injections was not more than 1% and a flow rate of 1.5 ml/min for an injection volume of 25 µl was set. The run time for analysis was set as 6 minutes.

The pump was set up to deliver a mobile phase composition of water, acetonitrile and methanol (50:25:25), which was filtered and degassed automatically by the in-built degasser of the HPLC equipment.

Plate 2.2 Snapshot of dissolution apparatus used

Before starting the various runs for the assay determination, a straight horizontal baseline was obtained. The assay preparations were however transferred into the amber coloured vials via syringe membrane filters to exclude any particles (as from excipients). These were all well labeled and arranged into the auto sampler unit of the Agilent technology 1200 Series HPLC equipment. The system was set up to run and record chromatograms sequentially according to the arrangement and labeling of the standard and assay preparations placed within the autosampler. The area under the curve (AUC) for each of the brands analysed was expressed as a percentage of the AUC of the standard to obtain the percentage drug content (assay value) for each brand, as shown in Table 4.1.

3.5.6 *In vitro* Dissolution study (USP test 2)

This test was carried out using the paddle method (USP test 2) for *in vitro* dissolution of extended release nifedipine (USP, 2007). The dissolution buffer and medium were freshly prepared always and used. Preparation of the buffer and dissolution medium are shown in Appendix 1.

3.5.6.1 Dissolution testing procedure

The water bath was filled to the marked capacity. Each of the seven vessels (round bottom beakers) of the dissolution apparatus was filled with 900 ml of the dissolution medium prepared of pH of 6.8. The thermostat of the apparatus was switched on and the system was allowed to stand for 2 hours for the temperature of the water in the bath and beakers to equilibrate around 37± 0.5^{O}C.The paddle heights were adjusted such that each paddle was 2 cm above the bottom of the dissolution vessel. One dosage unit was placed in each of the six vessels and the stirrers and timer switched on simultaneously. Stirring was maintained at a paddle speed of 50 revolutions per minute. Care was taken to exclude air bubbles from the surface of the dosage unit. At specified intervals of 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 hours,, respectively after start of dissolution, 8 ml of sample was withdrawn (from a zone midway between the surface of the dissolution medium and the top of the rotating paddle blade, not less than 1 cm from the vessel wall from each dissolution vessel) and filtered into labeled conical flasks.

To replace the 8 ml of sample withdrawn from each of the six vessels, 8 ml of the dissolution medium from the seventh vessel was added to each vessel from which the volume was withdrawn in order to maintain sink conditions. The vessels were kept covered for the duration of the test and the temperature of the medium maintained at 37 ± 0.5^{O}C at all times.

3.5.6.2 Preparation of standard nifedipine

For each of the 20 mg tablet in 900 ml of dissolution medium, its concentration was 0.0022%.This concentration of the standard was prepared by weighing and dissolving 0.1 g of Nifedipine RS in about 5 ml of methanol(to enhance solubility of the powder) in a 100 ml volumetric flask and making it up to volume with dissolution medium. This was labeled as A. From flask A, 2.2 ml of solution was pipetted and made up to 100 ml with

more dissolution medium in another volumetric flask, labeled as B to obtain the final concentration of 0.0022%.

For each of the 30 mg tablet in 900 ml of dissolution medium, its concentration was 0.0033%.This concentration of the standard was prepared by weighing and dissolving 0.1 g of Nifedipine RS in about 5 ml of methanol and making it up to 100 ml with dissolution medium in a volumetric flask labeled as C. A further 3.3 ml of solution was pipetted from C and made up to 100 ml with more dissolution medium to get the final concentration needed (0.0033%).

3.5.6.3 Chromatographic analysis

Chromatographic system: The liquid chromatograph was equipped with a 350-nm detector and a 4.00-mm x 125-mm column that contains 3-um packing L1.Key input of parameters for the chromatographic system software included: a temperature setting of 40^{O}C, an injection volume of 25 ul, a flow rate of 1.5ml/min, column efficiency allowed was not less than 2000 theoretical plates and tailing factor of not more than 1.5.

Procedure: The pump was set up to deliver a mobile phase composition of acetonitrile and water (70:30), which were filtered and degassed automatically by the in-built degasser. With the aid of a syringe membrane filter, dissolved drug samples of brands in the labeled conical flasks were transferred into amber-coloured vials and placed at their designated areas within the HPLC auto sampler chamber. The prepared standard solutions (for the 20 mg and 30 mg), respectively were transferred into amber-coloured vials and placed at their designated positions in the auto sampler chamber of the HPLC equipment.

A straight horizontal baseline was first obtained after setting up the parameters for the chromatographic run. The system was programmed to run and record chromatograms sequentially according to the arrangement and labeling of the standard and dissolved brand preparations placed within the auto sampler. Responses for the various peaks were

measured as Area under the curve (AUC). In order to obtain the cumulative percentage of drug dissolved for each brand, the AUC for each of the dissolved brands at each time point was expressed as a percentage of the AUC of the standard taking cognizance of the correction factor as shown in 4.3.

Plate 2.3 Snapshot of HPLC apparatus used

3.5.7Analysis of dissolution data

The HPLC primary data was entered into Microsoft Excel 2007 professional Edition which was used to calculate the percent dissolved of the active pharmaceutical ingredient (API) for all the 12 brands of nifedipine SR brands. It was also used in the calculation of similarity, f2 and difference, f1 factors as well as the graphs of the various kinetic models including their coefficient of determination, R^2.

CHAPTER FOUR

RESULTS/CALCULATIONS

Table 4.1 Health centers and SR drugs in stock

Health centre	SR drug	Frequency	Rank
Community pharmacy (N=73)	**Nifedipine**	50	1
	Indapamide	13	2
	Atenolol	7	3
	Diltiazem HCl	3	4
Government/Quasi government hospitals (N=13)	**Nifedipine**	10	1
	Indapamide	2	2
	Atenolol	1	3
	Diltiazem HCl	0	4
Private hospitals (N=37)	**Nifedipine**	30	1
	Indapamide	5	2
	Atenolol	2	3
	Diltiazem HCl	0	4

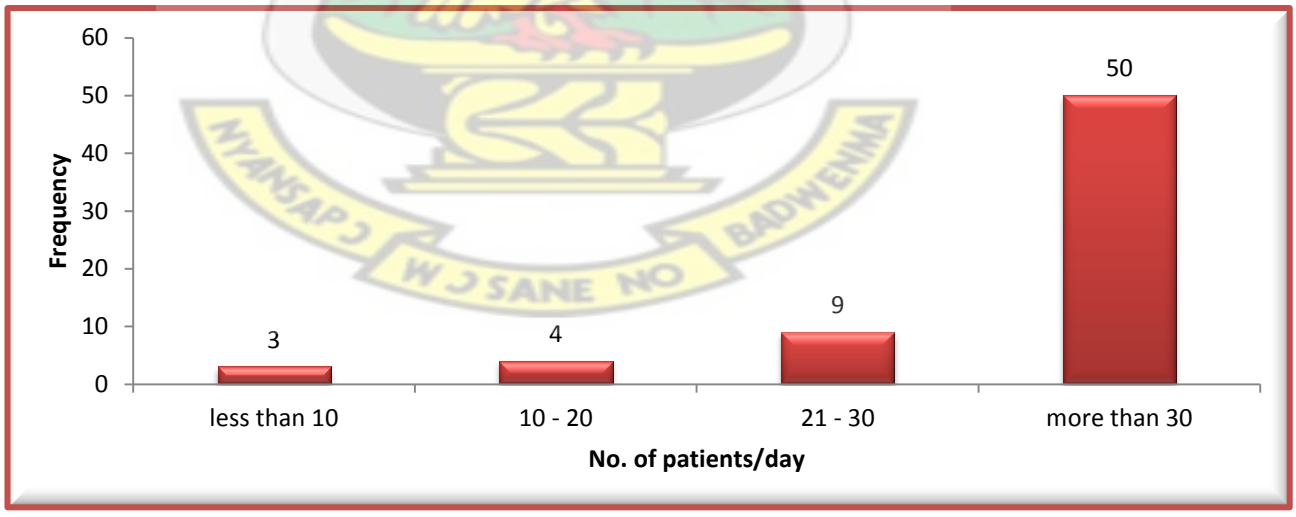

Figure 4.1 Number of hypertensive cases received by Respondent Doctors per day

Table 4.2 Patients knowledge on SR brands

Statement:	Yes (%)	No (%)
I can identify the SR brand I use	111 (74)	39 (26)
I receive the same SR brand every time	44 (40)	67 (60)
I worry about not receiving same brand	64 (96)	3 (4)

Table 4.3 Patients' main concerns for not receiving same brands of SR nifedipine

Concern	Frequency	Rank
Side effects	25	1
Efficacy	18	2
Availability	13	3
Affordability	8	4

Table 4.4 Classes of hypertensive patients preferred for SR by doctors

Patient Category	Frequency*	Rank
Moderate	65	1
Severe	51	2
Mild	35	3

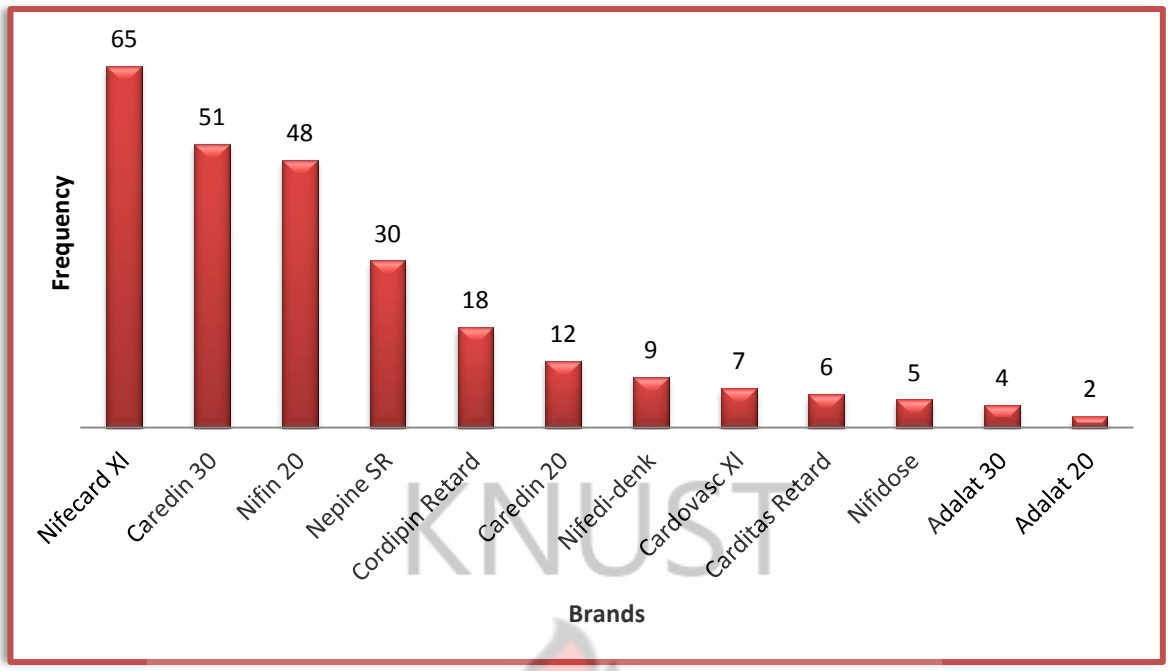

Figure 4.2 Rank of SR brands preferred and used by patients in the Kumasi metropolis

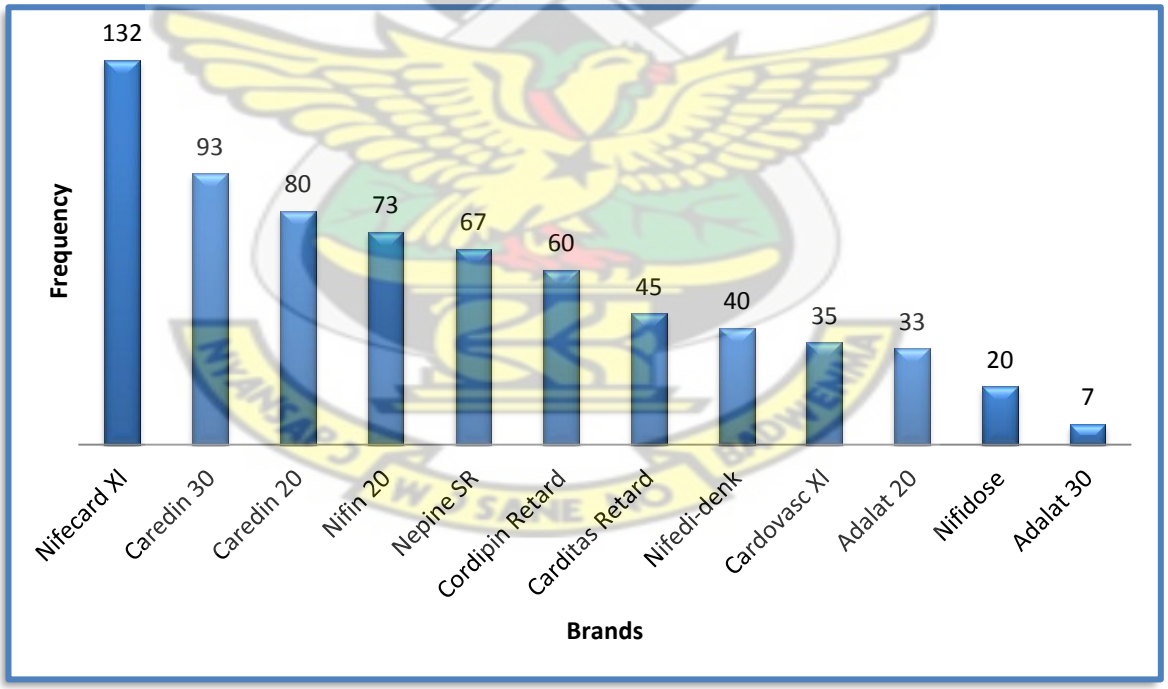

Figure 4.3 Rank of SR Nifedipine brands preferred and prescribed by doctors in the Kumasi metropolis

Table 4.5 Reasons for preference of SR Nifedipine brands by doctors and patients

Actors	Reason for preference	Frequency*	Rank
Doctors (N=66)	Perceived Efficacy	49	1
	Compliance	47	2
	Tolerability	39	3
	Availability	26	4
	Insurance coverage	15	5
Patients (N=150)	Affordability	105	1
	Availability	87	2
	Insurance coverage	72	3
	Tolerability	69	4
	Efficacy	63	5
	Compliance	50	6

Table 4.6 Respondents attitude towards brand interchangeability of SR Nifedipine

Actor	Attitude Statement	Percent
Patients	SR nifedipine brands are interchangeable because they have the same active ingredients and strengths	30
	Different attributes of brands make them not interchangeable	28
	Different manufacturers of various brands have different specifications rendering drugs non-interchangeable	31
	All brands are interchangeable since they are supplied by NHIS as substitutable brands	11
Doctors	SR brands are interchangeable since our training allows for generic prescription	24
	SR brands can be interchanged when their names, strengths and administration modes are similar	36
	Psychological factors, different tolerability and efficacy makes them non-interchangeable	40

Table 4.7 Physical characteristics of SR brands

S/No.	Brand code	Colour	Shape	Nature Of Surface	Cavity Profiles
1	A	Brown	Round	Smooth	Normal Convex
2	B	Brown	Round	Smooth	Normal Convex
3	C	Pink	Round	Smooth	Shallow Convex
4	D	Yellow	Round	Smooth	Shallow Convex
5	E	Yellow	Round	Smooth	Bevel And Convex
6	F	Orange	Round	Smooth	Shallow And Convex
7	G	Golden Brown	Oblong	Smooth	Shallow And Convex
8	H	Golden Brown	Round	Smooth	Shallow And Convex
9	I	Orange	Round	Smooth	Scored, Shallow Faced
10	J	Golden Brown	Round	Smooth	Shallow Convex
11	K	Golden Brown	Round	Smooth	Normal Convex
12	L	Orange	Round	Smooth	Normal Convex

Table 4.8 Weight Variation for the brands

Brand	Weight of 20 tablets (X)	Average weight (X/20)	BP % deviation	Standard deviation (±)	BP weight range	Actual weight range	Compliance with BP weight variation
A	5.9772	0.2984	0.0500	0.00135	0.2835-0.3133	0.2969-0.3018	**Passed**
B	8.3366	0.4168	0.0500	0.00650	0.3960-0.4377	0.3992-0.4109	**Passed**
C	5.9452	0.2973	0.0500	0.00484	0.2824-0.3121	0.2908-0.3035	**Passed**
D	3.9048	0.1952	0.0750	0.00260	0.1806-0.2099	0.1918-0.1983	**Passed**
E	1.6860	0.0843	0.0750	0.00178	0.0780-0.0906	0.0830-0.0894	**Passed**
F	1.8885	0.0944	0.0750	0.00146	0.0874-0.0992	0.0919-0.0959	**Passed**
G	2.5097	0.1255	0.0750	0.00197	0.1161-0.1348	0.1225-0.1280	**Passed**
H	3.6291	0.1815	0.0750	0.00162	0.1679-0.1905	0.1794-0.1840	**Passed**
I	1.8205	0.0910	0.0750	0.00209	0.0842-0.0978	0.0870-0.0931	**Passed**
J	2.5520	0.1275	0.0750	0.00165	0.1180-0.1372	0.1250-0.1298	**Passed**
K	3.1125	0.1556	0.0750	0.00464	0.1439-0.1673	0.1507-0.1618	**Passed**
L	6.4244	0.3212	0.0500	0.01481	0.3051-0.3373	0.2837-0.3587	**Passed**

4.1 Assay of the nifedipine reference standard, RS

Blank titre (Volume,V) =14.9 ml

Titre volume 1(V_1) = 22.8 ml

Titre volume 2 (V_2) = 22.9 ml

Factor of 0.1M cerium sulphate = 0.976

Given that 1ml is equivalent to 0.01732 g of nifedipine

Amount of nifedipine = (V_1 – V)* Amount of nifedipine in 1ml * Factor of 0.1M cerium sulphate

Amount of nifedipine (sample 1) = (22.8-14.9) * 0.976*0.01732

= 7.9 * 0.976 * 0.01732

= 0.13354413 g

Percentage content, (%) = 0.13354413*100/0.1318 = 101.32%

Amount of nifedipine (sample 2) = (22.9-14.9)* 0.976 *0.01732

= 8 * 0.976 * 0.01732

= 0.13523456 g

% content = 0.13523456*100 / 0.1333 = 101.45%

Average % content = (101.32 + 101.45)/2 = 101.39%

BP limits = 98% - 102%.

4.2 Sample calculation for percentage active content of the nifedipine brands

(As shown in table 4.9)

Assay value (Percentage active content) = AUC of brand/ AUC of Standard * 100

Where AUC = Area under curve on HPLC chromatogram

But AUC of Standard = 12,963.56

Assay value for A = 14,055.61 / 12,963.56 * 100 = 108.4%

Table 4.9 Results of assays of selected brands

Code	Average content	Average content (%)
A	14,052.98	108.40
B	14,774.55	113.97
C	12,765.76	98.47
D	12,924.36	99.70
E	13,226.02	102.02
F	13,860.70	107.00
G	13,253.12	102.23
H	14,447.84	111.45
I	13,165.16	101.56
J	13,223.25	102.00
K	14,968.88	115.47
L	13,210.16	101.90

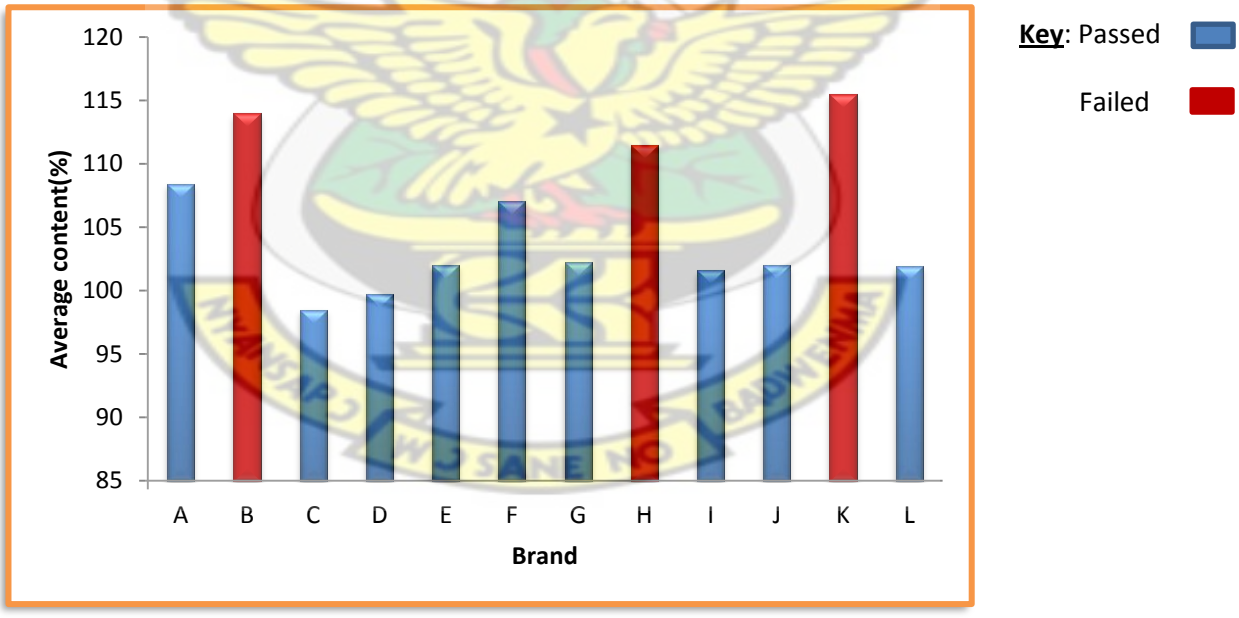

Figure 4.4 Assays of selected brands using USP, 2007.

(Acceptance range: 90% - 110%)

4.3 Sample calculation for average cumulative drug dissolved at each time point

Correction factor (CF_{tn}) = (volume pipetted/bath volume) * $cAUC_{tn-1}$

AUC = Area under the curve

Where cAUC = corrected area under the curve

CF_{tn} = correction factor at time point, n

$CAUC_{tn-1}$ = cumulative drug release at most previous time

Volume pipetted = 8 mls

Dissolution medium volume = 900 mls

$CF_{0.25\ hrs}$ = (8/900) * 0 = 0

$CF_{0.50\ hrs}$ = (8/900) * 6.30 = 0.06

Corrected AUC = Correction factor + AUC

cAUC at 0.25 hrs. = 0 + 6.3 = 6.3

cAUC at 0.50 hrs. = 8.9 + 0.06 = 8.96

Average cAUC = (sum of cAUC for vessels 1, 2, 3, 4, 5, 6) / 6

Average cAUC brand A at 0.25 hrs. = 6.30 + 5.86 + 5.25 + 5.99 + 6.12 + 4.60 = 5.69

NB: Average AUC for brand A is shown in Appendix 5B.

4.4 Sample calculation for percentage drug dissolved at each time point

(As shown in tables 4.10 and 4.11)

% Cumulative drug released = (Mean AUC of sample/ Mean AUC of reference standard)*100

Where AUC = Area under curve

Mean AUC of sample = Mean cumulative drug dissolved (sample)

Mean AUC of standard = Mean AUC obtained in HPLC analysis for standard

Mean AUC of standard for Brands A, B, C, and D is 363.76

Mean AUC of standard for Brands E, F, G, H, I, J, K and L is 230.6

% Corrected AUC for brand A = 100 * 5.69/363.76 = 1.61

% Corrected AUC for brand E = 100 * 8.09/230.6 = 3.51

Table 4.10 Percentage drug dissolved of 30 mg nifedipine brands

TIME/hrs.	PERCENTAGE DRUG DISSOLVED			
	A	B	C	D
0.25	1.61	1.13	1.01	1.15
0.50	2.56	1.89	1.31	1.93
0.75	6.07	2.87	1.38	2.84
1	12.51	11.74	13.36	11.78
1.5	18.91	19.45	15.42	19.30
2	23.47	25.86	19.37	26.14
3	29.78	27.09	26.74	30.62
4	47.50	43.54	34.92	39.85
6	64.98	48.35	50.66	42.94
8	74.03	54.80	54.81	49.71
10	89.42	72.10	64.51	65.79
12	99.85	89.40	81.98	75.72
14	100.00	92.90	82.14	85.62
16	100.02	93.54	85.39	89.57
18	100.01	98.31	87.12	90.73
20	100.01	98.40	88.07	90.09
22	100.10	98.40	88.98	91.54
24	100.10	97.93	88.89	90.94

Table 4.11 Percentage drug dissolved of 20 mg nifedipine brands

TIME/hrs.	PERCENTAGE DRUG DISSOLVED FOR 20 mg NIFEDIPINE BRANDS							
	E	F	G	H	I	J	K	L
0.25	3.51	1.76	0.00	1.17	0.00	0.00	0.00	0.00
0.50	4.01	11.62	1.26	2.69	4.19	0.00	0.00	3.08
0.75	6.19	42.41	4.00	3.97	4.84	0.00	4.70	6.18
1	12.22	60.55	9.37	6.31	10.65	6.56	6.60	12.22
1.5	16.02	64.36	12.47	9.58	17.38	7.76	9.21	19.75
2	20.80	69.55	13.13	12.89	22.59	15.63	19.93	28.64
3	29.76	73.83	24.59	21.73	26.21	25.18	26.45	38.40
4	52.88	79.32	31.22	30.51	41.43	40.19	53.55	53.44
6	64.54	83.66	45.23	46.15	49.61	53.39	80.98	66.43
8	81.03	83.34	62.57	57.32	60.65	71.17	92.55	74.20
10	91.49	83.21	70.26	65.85	70.13	83.25	99.28	79.92
12	100.09	84.93	89.02	67.55	82.46	92.27	99.56	86.78
14	99.99	82.13	92.30	70.90	83.21	92.08	99.70	92.71
16	99.98	82.43	93.12	72.31	83.18	91.99	99.84	99.53
18	100.07	82.43	92.98	72.76	83.25	92.68	99.85	100.46
20	100.02	81.88	93.01	73.33	83.47	92.14	99.94	100.20
22	100.03	81.89	92.90	73.27	83.44	93.11	99.80	100.36
24	100.01	84.09	93.14	73.37	83.55	92.30	99.98	100.28

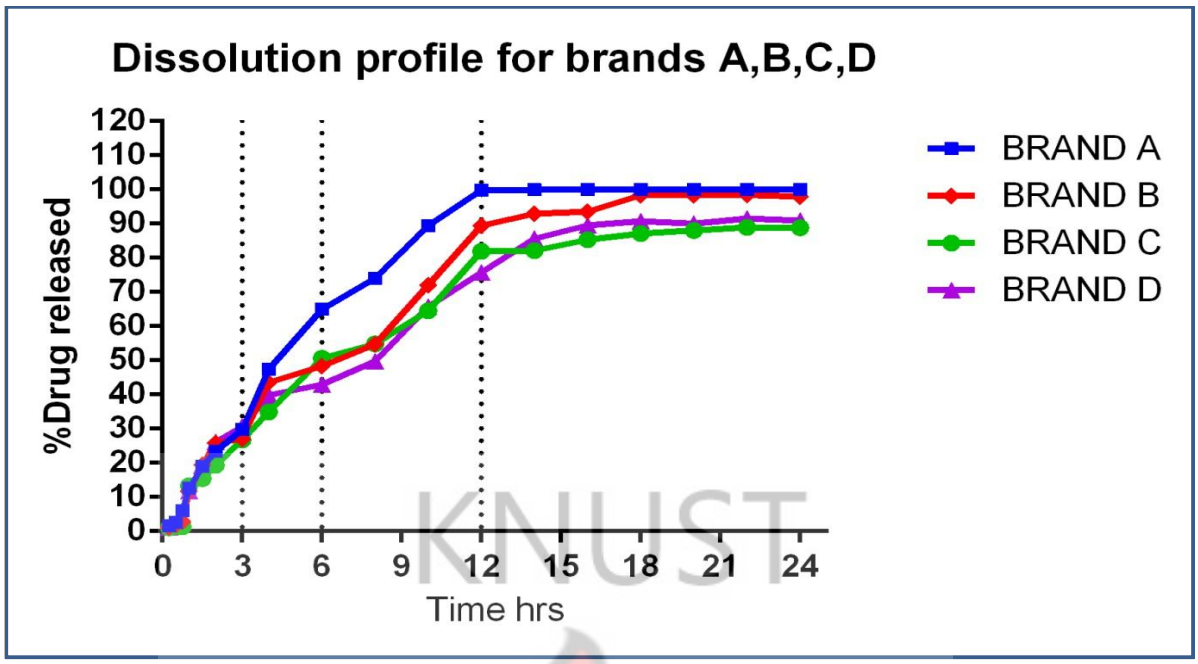

Figure 4.5 dissolution curve for brands (30 mg)

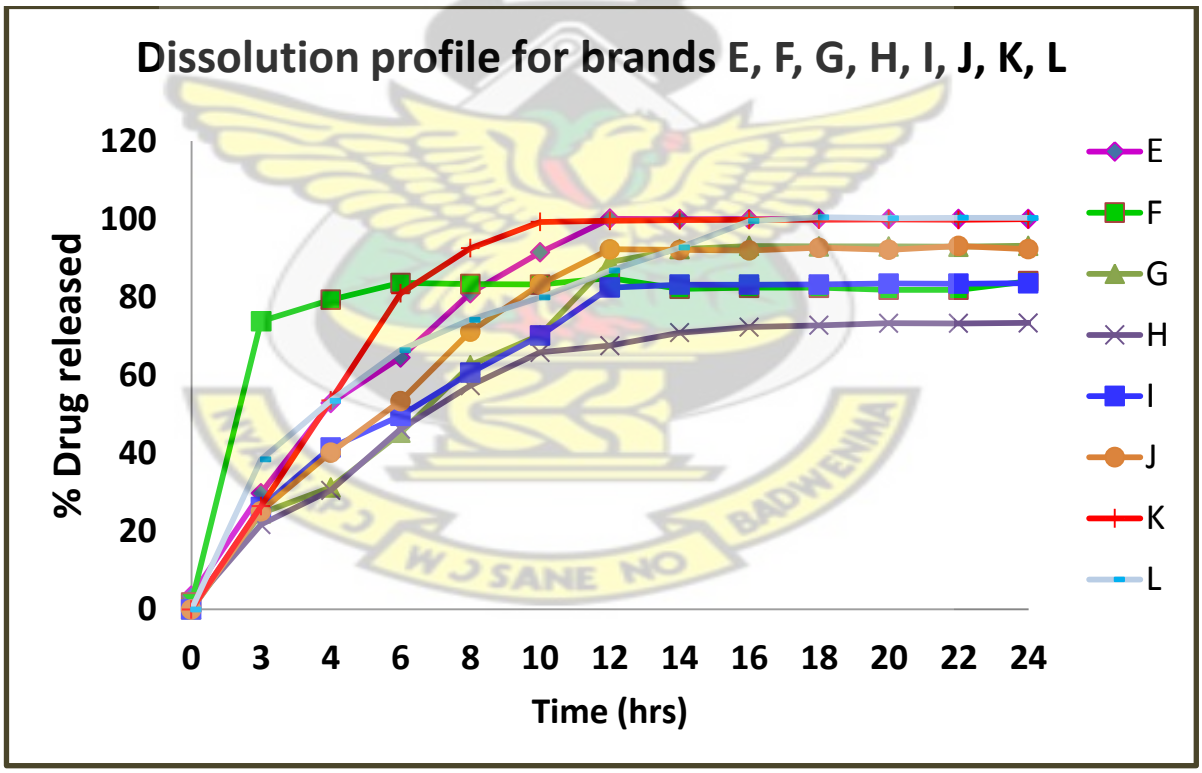

Figure 4.6 dissolution curve for brands (20 mg)

Table 4.12 USP (2007) Parameters of percentage drug release of the 12 brands

BRAND	3 hrs.	6 hrs.	12 hrs.	Remark
A	29.78	64.98	99.85	Passed
B	27.09	48.35	89.40	Passed
C	26.74	50.66	81.98	Passed
D	30.62	42.94	75.72	Failed
E	29.76	64.54	100.09	Passed
F	73.83	83.66	84.93	Failed
G	24.59	45.23	89.02	Passed
H	21.73	46.15	67.55	Failed
I	26.21	49.61	82.46	Passed
J	25.18	53.39	92.27	Passed
K	26.45	80.98	99.56	Failed
L	38.40	66.43	86.78	Failed

USP acceptance criteria: 3 hours (10% – 30%), 6hours (40% -65%), 12 hours (>80%)

Passed = brands which passed at all three time points

Failed = brands which did not pass all three time- points

Table 4.13 Sample calculations of fit factors

Reference sample: Sample A, Test sample: Sample B				
Time hrs	**Reference**	**Test**	**Reference - Test**	**$(R_t - T_t)^2$**
0.25	1.61	1.13	0.48	0.2318
0.5	2.56	1.89	0.67	0.4501
0.75	6.07	2.87	3.20	10.2372
1	12.51	11.74	0.78	0.6031
1.30	18.91	19.45	0.54	0.2942
2	23.47	25.86	2.38	5.6858
3	29.78	27.09	2.70	7.2801
4	47.50	43.54	3.96	15.6837
6	64.98	48.35	16.63	276.5185
8	74.03	54.80	19.23	369.9000
10	89.42	72.10	17.32	299.9845
12	99.85	89.40	10.45	109.2619
sum	**Rt=470.6935**	**T_t=398.1989**	**$\sum(R_t - T_t)$=78.3485**	**$\sum(R_t - T_t)^2$=1096.1310**
	N	**12**		
	f2	**51**		
	f1	**18**		

4.5 Sample calculation of difference factor

$$f_1 = \left\{ \frac{[\sum_{t=1} n|R_t - T_t|]}{\left[\frac{\sum_{t=1} n(R_t + T_t)}{2}\right]} \right\} * 100$$ ----------equation 1

Where;

f1 = difference factor

n = Number of dissolution time points.

Rt = Reference dissolution value at time, t

Tt = Test dissolution value at time, t

From table 4.13, calculation of f1 using equation 1 is as follows:

$\sum (R_t - T_t) = 78.3485$

$R_t = 470.6935$ $T_t = 398.1989$

$\sum (R_t + T_t)/2 = (470.6935 + 398.1989)/2 = 434.4462$

f1 = (78.3485/ 434.4462) * 100

f1 = 0.180340989 * 100 = 18

Therefore f1 = 18

4.6 Sample calculation of similarity factor

- $$f_2 = 50 * log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1} n\,(R_t - T_t)^2\right]^{-0.5} * 100\right\}$$ ------equation 2

Where;

f1 = similarity factor

n = Number of dissolution time points.

Rt = Reference dissolution value at time, t

Tt = Test dissolution value at time, t

From table 4.13, calculation of f2 using equation 2 is as follows

n = 12

$\sum (R_T - T_t)^2 = 1096.1310$

$f = 50 * \log \{[1+ (1/12) * 1096.1310]^{-0.5} * 100\}$

$f2 = 50 * \log \{[1+ 0.08333 * 1096.1310]^{-0.5} * 100\}$

$f2 = 50 * \log \{[1 + 91.3442135]^{-0.5} * 100\}$

$f2 = 50 * \log \{[92.3442135]^{-0.5} * 100\}$

f2 = 50 * log {0.104062716 * 100}

f2 = 50 * log 10.4062716

f2 = 50 * 1.017295

f2 = 50.86476

f2 = 51

Therefore f2 = 51

Table 4.14 Similarity and difference factors for brands, 30 mg

REFERENCE	TEST	f2	f1	COMMENT
A	B	51	18	Dissimilar
A	C	46	26	Dissimilar
A	D	43	26	Dissimilar
B	A	51	18	Dissimilar
B	C	66	11	Similar
B	D	64	10	Similar
C	A	46	26	Dissimilar
C	B	66	11	Similar
C	D	67	12	Similar
D	A	43	26	Dissimilar
D	B	64	10	Similar
D	C	67	12	Similar

Similar means f1 = 0-15 and f2 =50-100

Table 4.15 Similarity and difference factors for 20 mg brands

Ref	Test	F2	F1	Comment		Ref	Test	F2	F1	Comment
E	F	25	50	Dissimilar		I	E	47	23	Dissimilar
E	G	45	28	Dissimilar		I	F	23	62	Dissimilar
E	H	39	39	Dissimilar		I	G	65	12	Similar
E	I	47	23	Dissimilar		I	H	58	19	Dissimilar
E	J	55	20	Dissimilar		I	J	57	18	Similar
E	K	58	13	Similar		I	K	39	32	Dissimilar
E	L	59	12	Similar		I	L	53	19	Dissimilar
F	E	25	50	Dissimilar		J	E	55	20	Dissimilar
F	G	21	70	Dissimilar		J	F	22	63	Dissimilar
F	H	20	78	Dissimilar		J	G	60	15	Similar
F	I	23	62	Dissimilar		J	H	49	25	Dissimilar
Ref	Test	F2	F1	Comment		Ref	Test	F2	F1	Comment
F	J	22	63	Dissimilar		J	I	57	18	Similar
F	K	24	53	Dissimilar		J	K	46	22	Dissimilar
F	L	27	45	Dissimilar		J	L	52	21	Dissimilar
G	E	45	28	Dissimilar		K	E	58	13	Similar
G	F	21	70	Dissimilar		K	F	24	53	Dissimilar
G	H	58	13	Similar		K	G	38	34	Dissimilar
G	I	65	12	Similar		K	H	34	43	Dissimilar
G	J	60	15	Similar		K	I	39	32	Dissimilar
G	K	38	34	Dissimilar		K	J	46	22	Dissimilar
G	L	46	27	Dissimilar		K	L	48	22	Dissimilar
H	E	39	39	Dissimilar		L	E	59	12	Similar
H	F	20	78	Dissimilar		L	F	27	45	Dissimilar
H	G	58	13	Similar		L	G	46	27	Dissimilar
H	I	58	19	Dissimilar		L	H	42	37	Dissimilar
H	J	49	25	Dissimilar		L	I	53	19	Dissimilar
H	K	34	43	Dissimilar		L	J	52	21	Dissimilar
H	L	42	37	Dissimilar		L	K	48	22	Dissimilar

Similar means f1 = 0-15 and f2 = 50-100

4.7 Analysis of dissolution profile using release kinetics

4.7.1 Zero order kinetics

$Qt = K_0 t$

Where Q = amount of drug release in time t

K_0 = zero order rate constant expressed in unit of concentration/time

t = release time

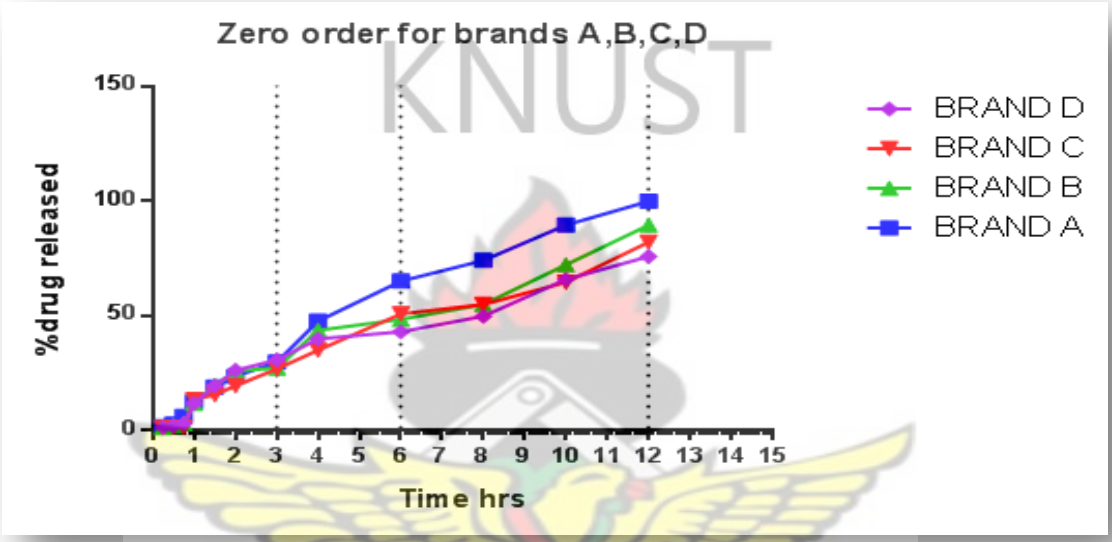

Figure 4.7 Zero order kinetic plot for brands A, B, C, D

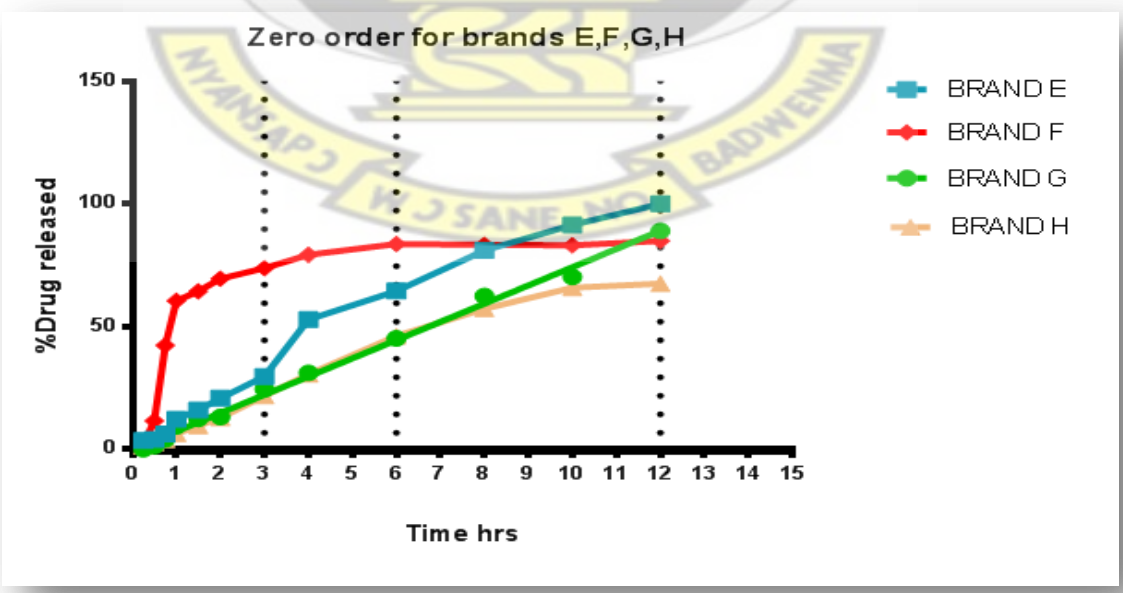

Figure 4.8 Zero order kinetic plot for brands E, F, G, and H

Figure 4.9 Zero order kinetic plot for brands I, J, K and L

4.7.2 First order kinetics

First order kinetics Log Q=Log Q_0+Kt/2.303

Where Q_0= is the initial concentration of drug

K= is the first order rate constant

t =release time

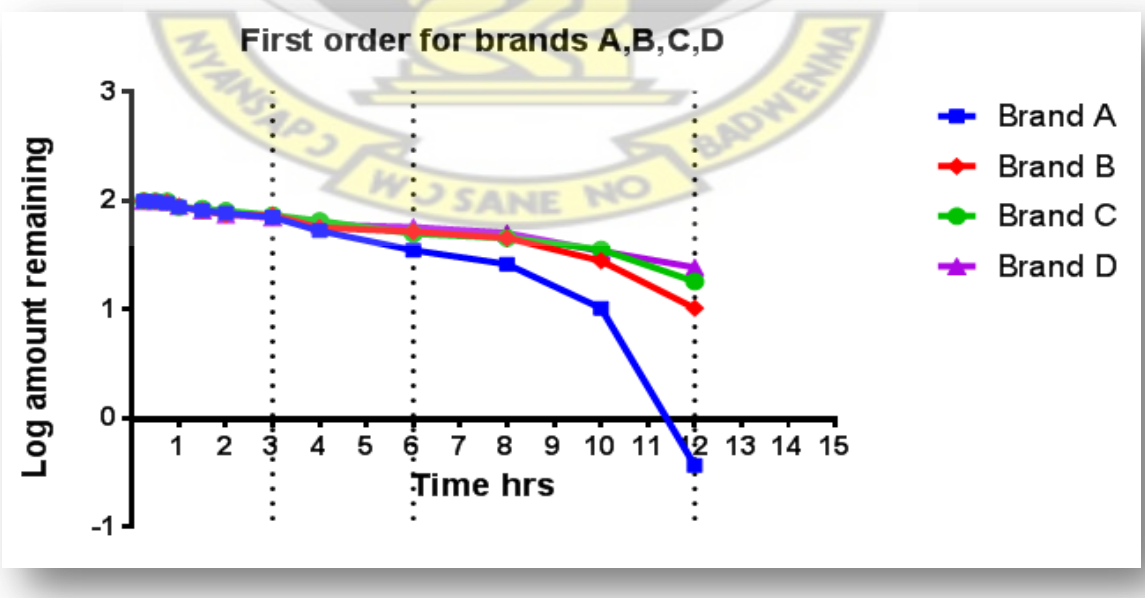

Figure 4.10 First order kinetic plot for brands A, B, C, D

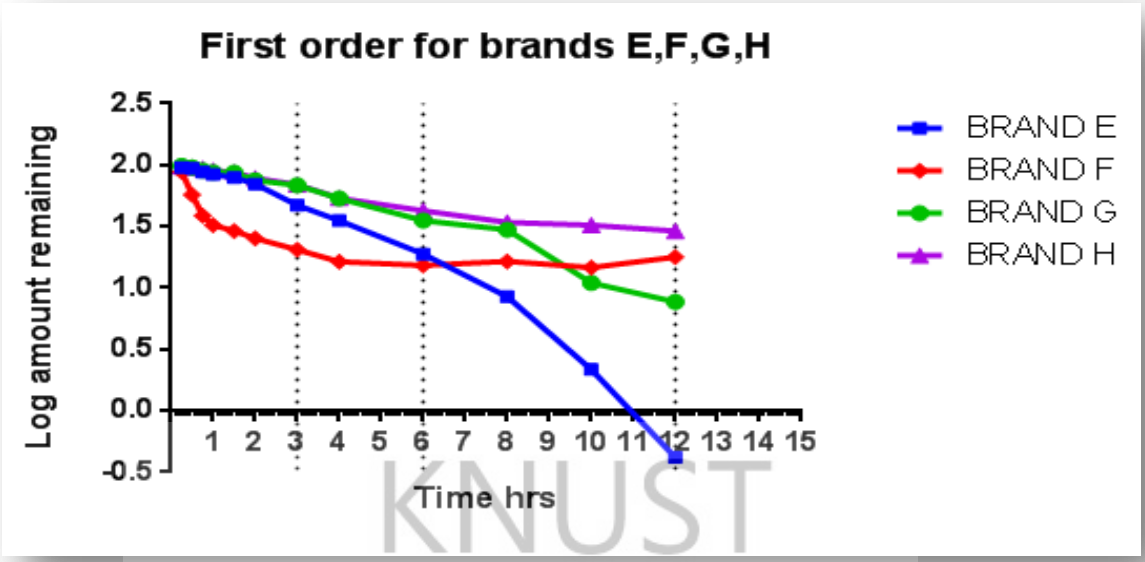

Figure 4.11 First order kinetic plot for brands E, F, G, and H

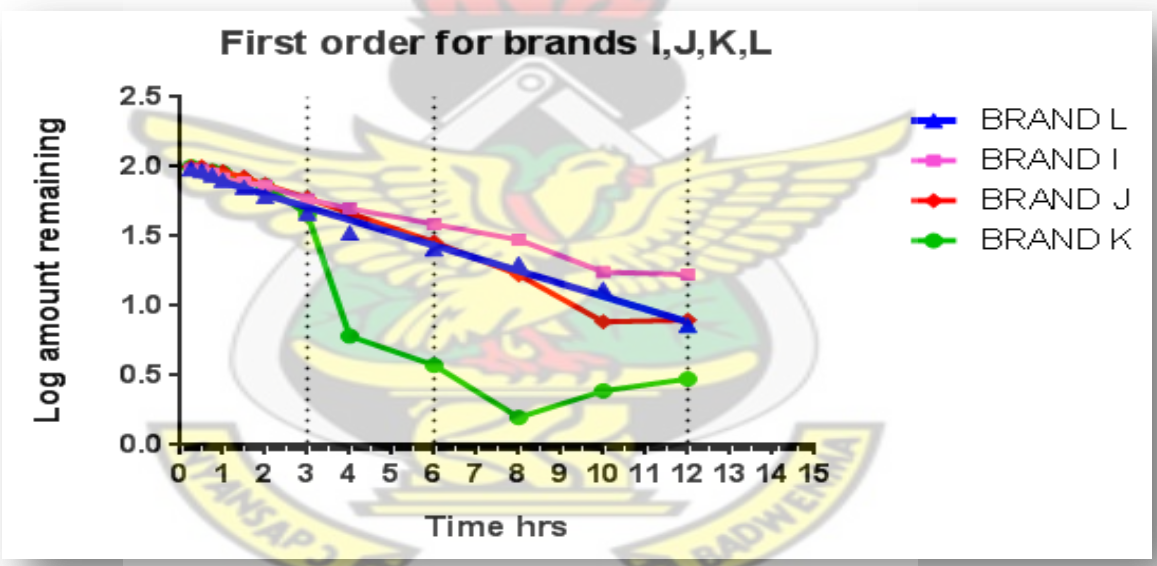

Figure 4.12 First order kinetic plot for brands I, J, K and L

4.7.3 Higuchi model

Higuchi kinetics $Q = kt^{1/2}$

Where k = Release rate constant

t = release time

Hence the release rate is proportional to the reciprocal of the square root of time.

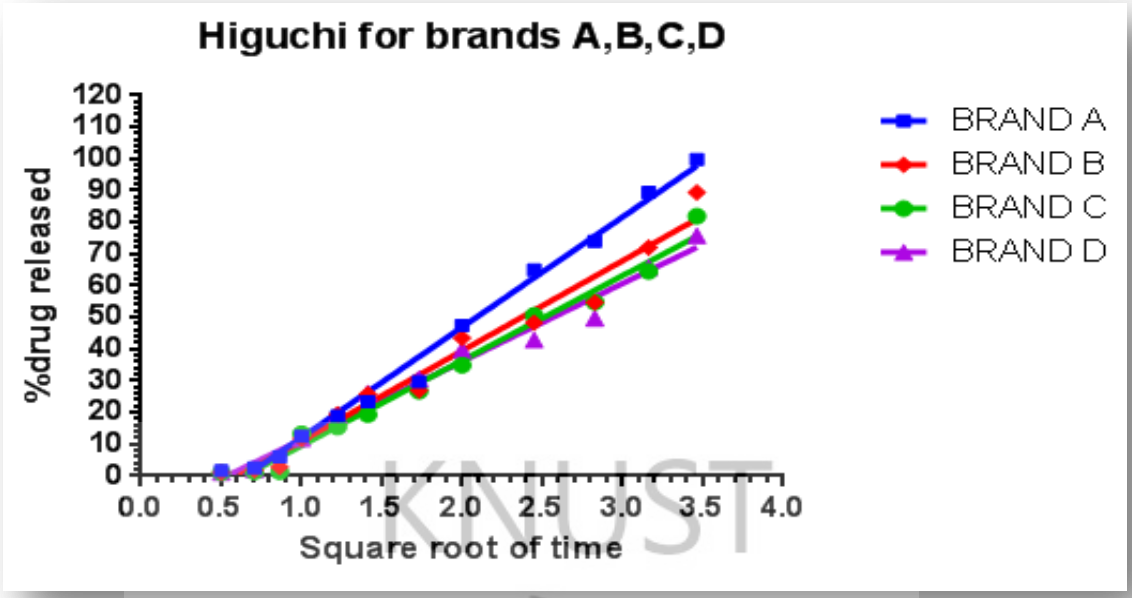

Figure 4.13 Higuchi kinetic plot for brands A, B, C, D

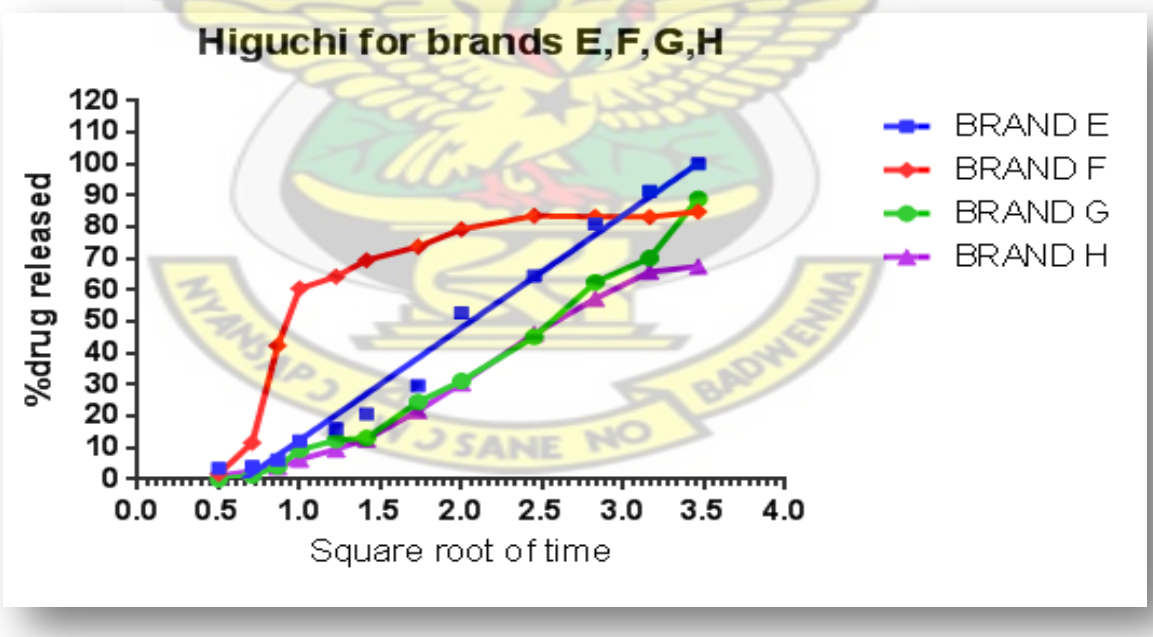

Figure 4.14 Higuchi kinetic plot for brands E, F, G, and H

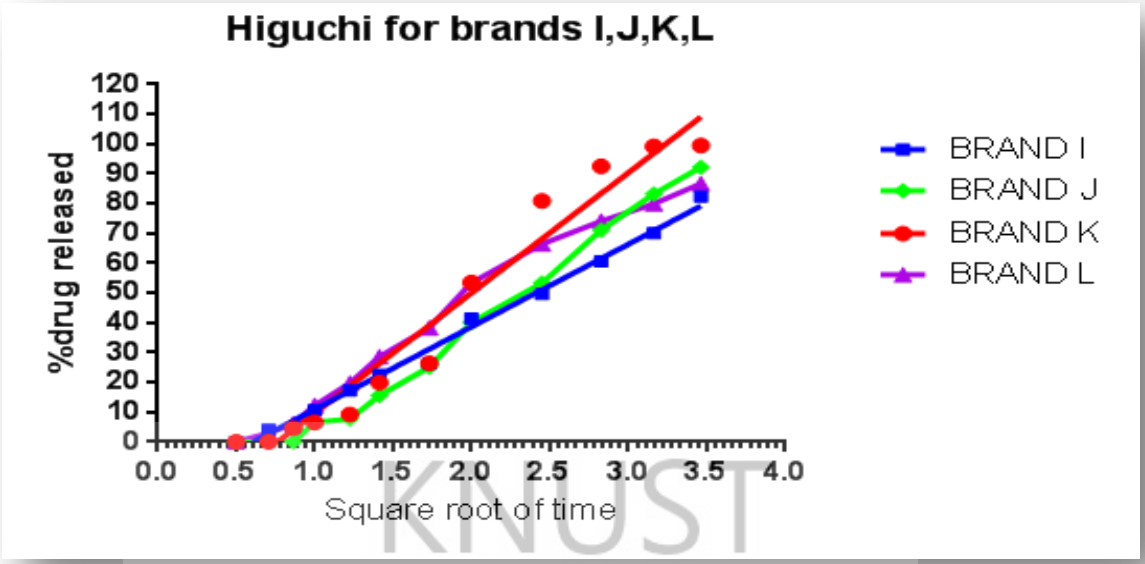

Figure 4.15 Higuchi kinetic plot for brands I, J, K and L

4.7.4 Hixson- Crowell cube root law

(1-Ft) 1/3 = 1-Kt

Where,

Ft= Amount of drug release in time t

K = release constant

t = Release time

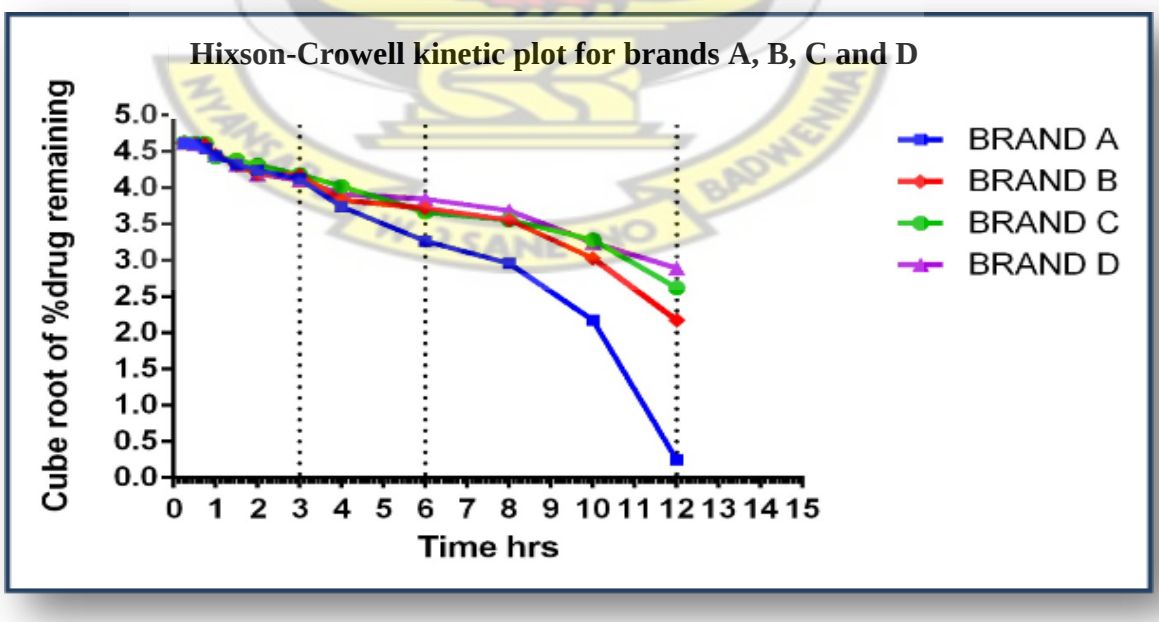

Figure 4.16 Hixson-Crowell kinetic plot for brands A, B, C and D

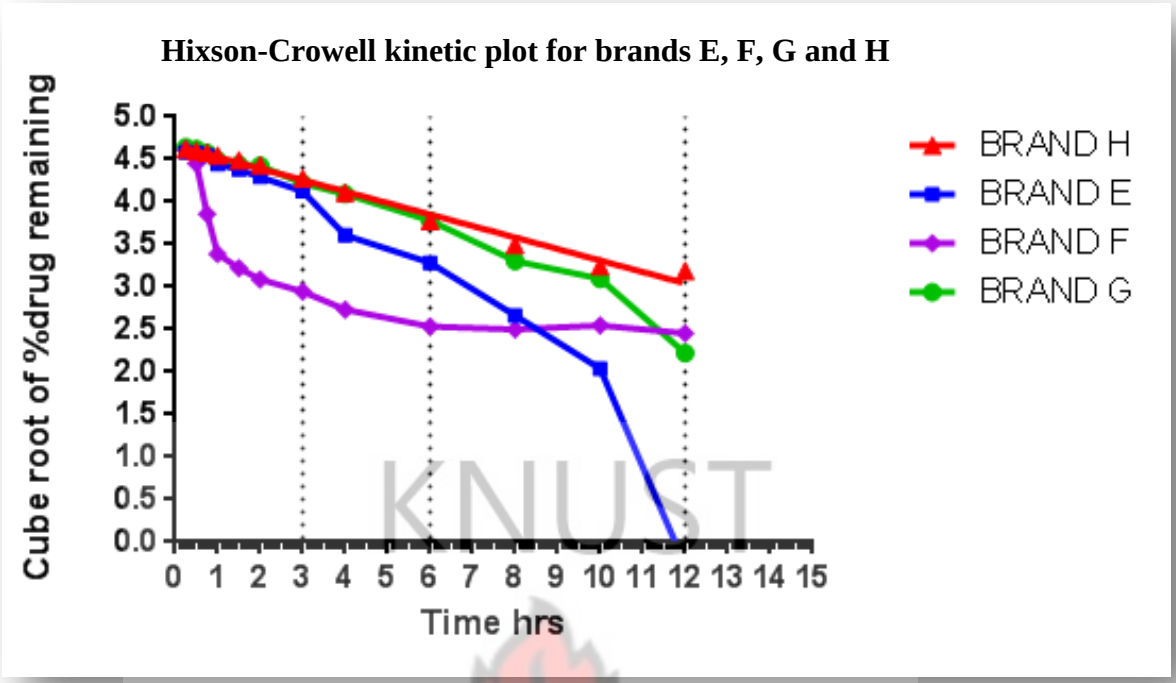

Figure 4.17 Hixson-Crowell kinetic plot for brands E, F, G and H

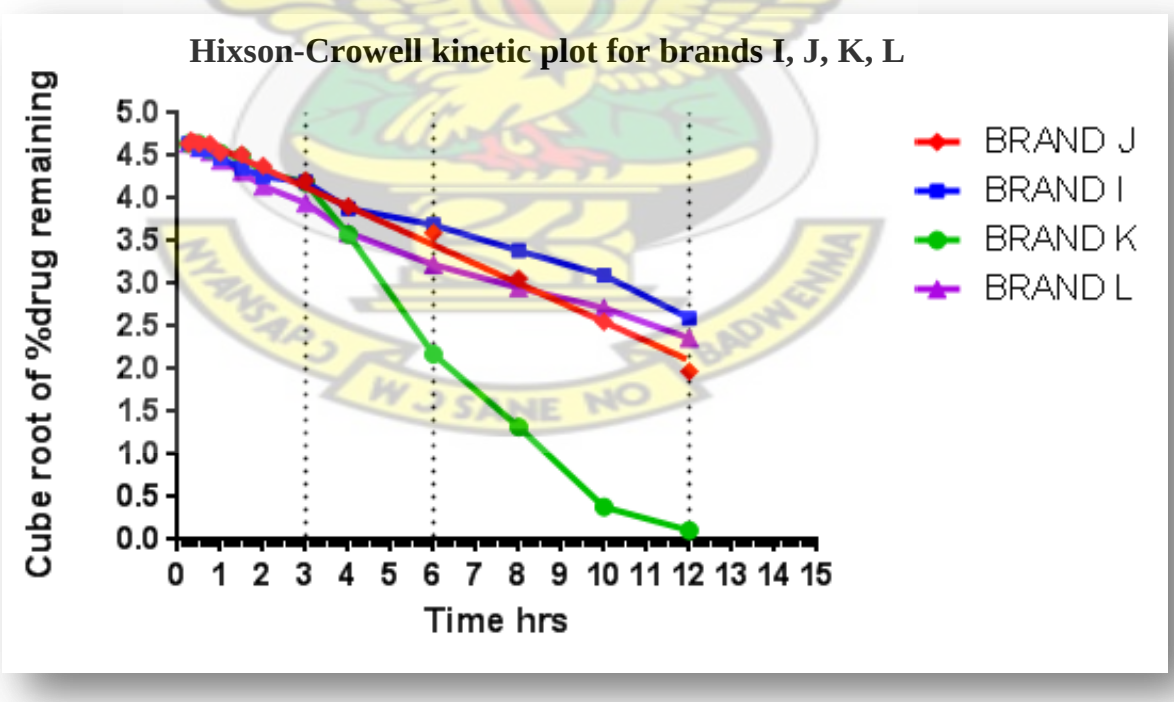

Figure 4.18 Hixson-Crowell kinetic plot for brands I, J, K and L

4.7.5 Korsmeyer-Peppas model

$Mt / M\infty = Kt^{n}$

Where,

Mt = amount of drug released at time t

M∞ = amount of drug released after infinite time

Mt /M∞ = fraction solute release

t = release time

K = kinetic constant incorporating structural and geometric characteristics of the polymer system

n = diffusional exponent that characterizes the mechanism of the release of drug

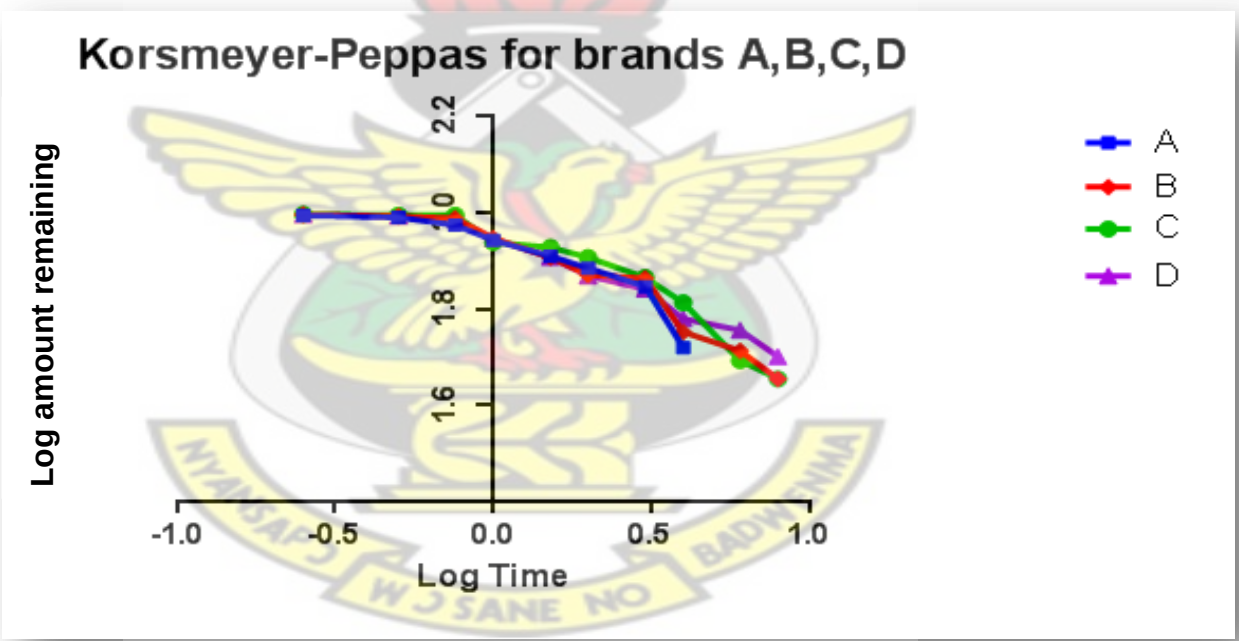

Figure 4.19 Korsmeyer-Peppas kinetic plot for brands A, B, C, D

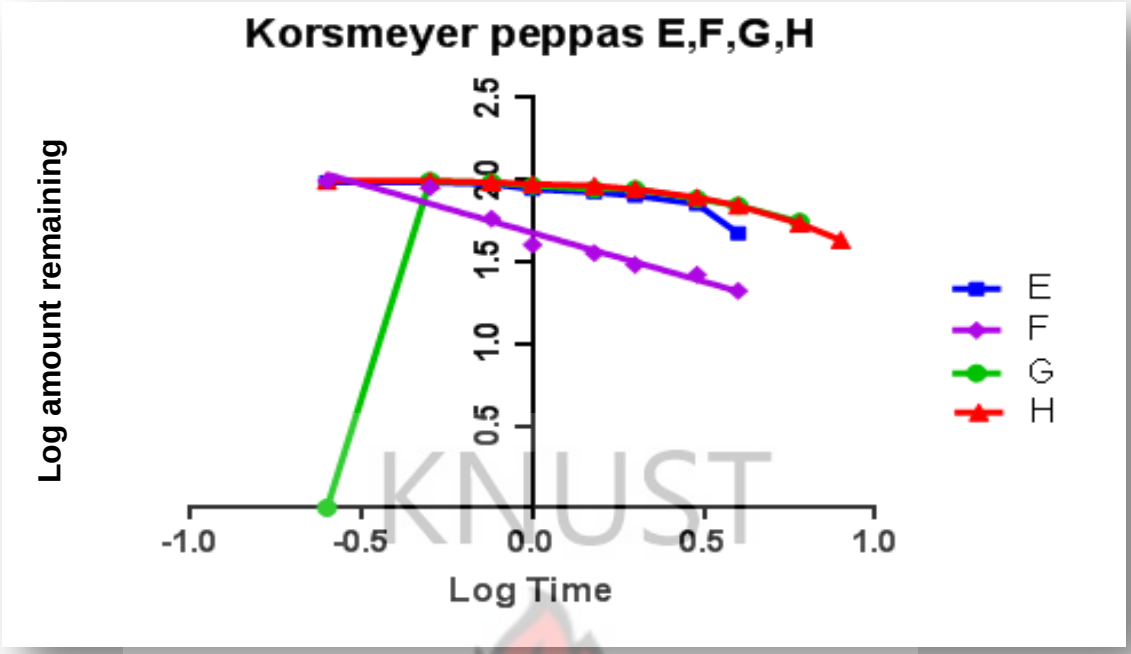

Figure 4.20 Korsmeyer-Peppas kinetic plot for brands E, F, G and H

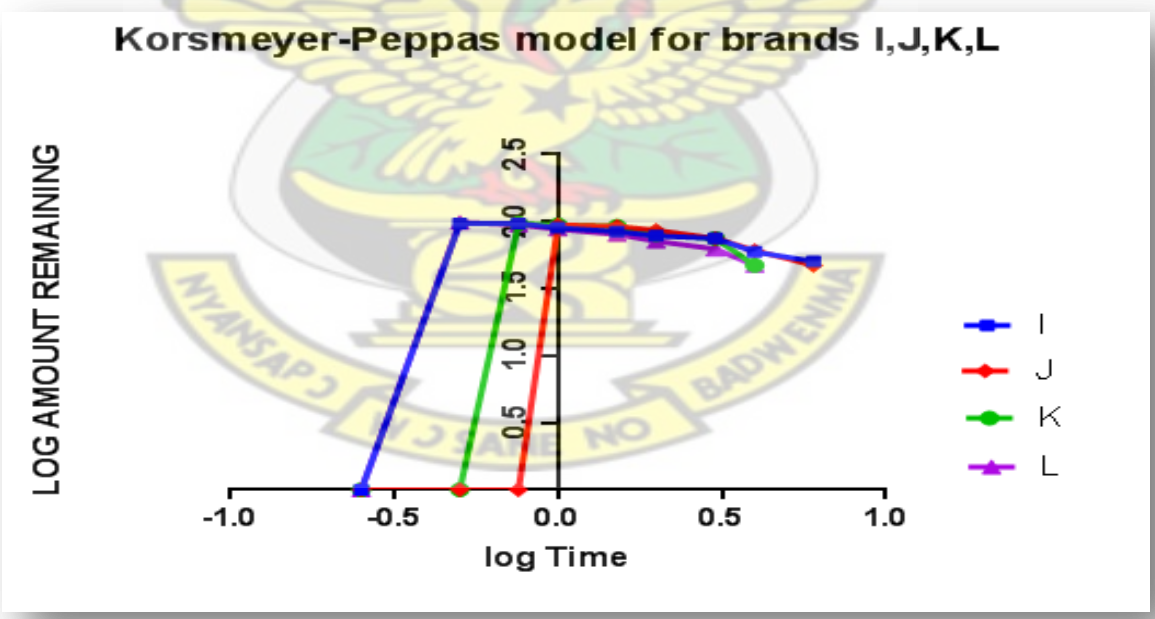

Figure 4.21 Korsmeyer-Peppas kinetic plot for brands I, J, K and L

Table 4.16 Release kinetic parameters for brands A, B, C and D

Kinetics Model	Coefficient of determination, R^2			
	Brand A	Brand B	Brand C	Brand D
Zero Order	0.9759	0.9598	0.9694	0.9387
First Order	0.7723	0.8877	0.9559	0.9619
Higuchi	**0.9885**	**0.9716**	**0.9822**	**0.974**
Hixson-Crowell	0.8963	0.942	0.9756	0.9642
Korsmeyer- Peppas	0.8017	0.8899	0.8493	0.9276

Table 4.17 Release kinetic parameters for brands E, F, G, H, I, J, K and L

Kinetics Model	Coefficient of determination, R^2							
	E	F	G	H	I	J	K	L
Zero Order	0.9694	0.4584	**0.9594**	0.9691	0.9646	0.9822	0.907	0.9179
First Order	0.9365	0.4593	0.9478	0.9579	0.9807	0.9826	0.6573	**0.9862**
Higuchi	**0.9811**	0.6182	0.9386	0.9772	**0.985**	0.9785	**0.9339**	0.9848
Hixson-Crowell	0.8639	0.5523	0.9356	**0.9837**	0.9814	**0.9909**	0.8292	0.979
Korsmeyer-Peppas	0.6695	**0.9561** **n = 1.76**	0.2846	0.7522	0.2614	0.5871	0.5334	0.3013

CHAPTER FIVE

DISCUSSION

5.1 Survey discussion

5.1.1 SR antihypertensive drug mostly marketed in the Kumasi Metropolis

With the identification of the SR drugs commonly marketed in Kumasi, an initial survey was conducted to enquire from various community pharmacies, clinics and hospitals the SR antihypertensive drugs in their stock. Results from Table 4.1 indicated that nifedipine SR drug was the mostly stocked and sold SR drug out of three other SR brands (Indapamide, atenolol and diltiazen hydrochloride). Nifedipine SR ranked first in each of the health centres visited, whereas indapamide, atenolol and diltiazem hydrochloride, respectively ranked 2nd, 3rd and 4th, respectively.

5.1.2 SR brands preferred by doctors and patients and their reasons for preference

Before achieving this objective, basic information was extracted from both respondents. Major findings have been indicated below:

- **Number of hypertensive cases received by respondent doctors per day**

From figure 4.1, it is evident that approximately 50 out of 66 respondent doctors receive more than 30 hypertension cases daily indicating prevalence of hypertension in the Kumasi Metropolis. This confirms the findings from earlier studies on the expected upsurge of hypertensive prevalence in Ghana (urban areas) in the absence of broad and preventive measures (Chobanian *et al.,* 2003). This implies that hypertension is still a public health challenge in Ghana, which is an economically developing country (Kearney *et al*., 2004).

- **Patients knowledge on SR brands**

Patients were initially assessed on their ability to identify/distinguish between the various brands they had ever used before their opinions were sought on brand preference and interchangeability.

Table 4.2 shows that 74% of the patients could identify SR brands they use. This confirmed that majority of patients have knowledge generally about the appearance and physical attributes of their medication and are able to detect differences as was detected in a focus group study by Toverud *et al*., (2011). However, 60% (67 out of the 111 patients who could identify their brands) complained they did not receive same brand every time they visited their respective health centres. Therefore 96% (64 out of the 67 in the above) were worried about the situation.

Ranking their concerns about not receiving the same brand in order of importance from Table 4.3 showed that issues with side-effects when certain brands were changed (such as headache and pedal edema), perceived efficacy, availability and affordability were worrisome. This finding relates to the hypothesis by Toverud *et al*., (2011) about the confusion and discontent that arise due to differences in drug name and physical attributes when brands changed among patients. Although some of the patients usually accepted substitution by the pharmacy, they considered the inexpensive generics to be of poorer quality than the brand-name products. A patient expressed view as:

"We are given these generic brands because they are cheap but they are not as powerful as the more expensive ones not served under NHIS''.

From figures 4.2 and 4.3, the top 2 brands preferred by doctors and patients were nifecard XL and caredin 30 which were both 30 mg brands. For doctors however, three 20 mg brands (caredin 20, nifin 20 and nepine) were ranked as 3rd, 4th and 5th, respectively

whereas patients ranked nifin 20, nepine SR and cordipin 20 mg as their 3rd, 4th and 5th most preferred brands, respectively. Therefore, there was a slight contrast in preference of SR brands between the two categories of respondents.

From Table 4.5, the main reasons (ranked as 1 and 2, respectively) influencing doctor's decision for the preferred brands were based on factors such as perceived efficacy of product and compliance. According to majority of the doctors, brand B for example which was their rank 1(most preferred) brand had always been a product which patients exhibited better clinical outcomes (obtained improved BP readings) and compliance due to relatively better tolerability compared to other brands in the group. Some prescribers, however, admitted that their constant choice for some particular brands like brand B as preference is simply out of habit, probably due to culture developed right from their training as they understudied specialists in their field. Their reason is a confirmation of Hellerstein's (1998) assertion on the effect of habit influencing prescribers" consistent choice of the same version of a given drug.

Other reasons considered by doctors for preferring particular SR brands in order of importance were the concepts of tolerability, availability and insurance coverage which were ranked as 3, 4 and 5, respectively. Alday *et al*., (2013) has also opined in his study that medical histories, drug insurance and personal preferences may also influence doctor's decision for a particular brand of product.

According to Table 4.5, on the part of the patients, the most important factor (rank 1) influencing their choice of a particular brand was affordability. This finding supports Buabeng *et al*., (2004) and Harries *et al.,* (2005) who found cost as a major contributing factor to patients' " non- compliance and subsequently low control rate of the hypertension disease. According to the majority of these patients, although they usually accepted substitution by the pharmacy as the NHIS list allowed, they considered the

inexpensive generics supplied to be of poorer quality than the brand-name products but they had to accept the offer because of economic reasons. This view of inferiority in the quality of substituted generics was similar to that by Himmel *et al*., (2005), who in a study to assess the opinions of primary care patients in Germany on generic drug use revealed that one-third of the participants considered inexpensive generics to be inferior to, or different from, more expensive brand-name drugs because of their lower price. Other considerations informing patients‟ preferences were availability (rank 2), NHIS coverage (rank 3), tolerability (rank 4), efficacy (rank 5) and compliance (rank 6).

On the basis of availability and NHIS coverage, most patients preferred particular brands since as NHIS holders these brands were always available at their respective hypertension clinics. They expressed dissatisfaction when their usual brands were not available. Across various disease states, the feeling of dissatisfaction (such as confusion, anxiety, and misconceptions) reported among patients whenever there were differences in name, appearance and packaging between brands of drugs has also been reported in a study by Roman (2009). This consequently leads to non-adherence since patients do not have faith in the effect of other brands and decide not to take them at all. Findings from an earlier study in the Ashanti region by Agyemang *et al*., (2013) revealed that only 6.2% of hypertension patients on treatment had their BP adequately controlled. Definitely, such intentional attitude of non-adherence to therapy could account for low control rates noted in the metropolis and high rates of hypertension in Ghana as indicated in earlier studies by Cappucio *et al*., (2004) and Amoah, (2003).

One major contributor to the low control rate of hypertension according to Munger *et al*., 2007 in his study is the issue of non-adherence as a result of side effects (poor tolerance) associated with certain antihypertensive drugs. In this study, patients ranked issues of tolerability and efficacy as their 4th and 5th reasons for preferring particular brands with

respect to others in the group. Issues about side-effects and tolerability have also been mentioned in a Norwegian survey by Kjønniksen *et al*., (2006), in which one-third of the participants reported one or more negative experience with generics substitution, e.g. more side effects or a poorer effect, and 21% reported an overall negative experience with the change.

5.1.3 Doctors and patients' attitude on interchangeability of SR Nifedipine brand

It has been reported in some previous studies that negative attitudes and experiences with generics substitution were associated with intentional non-adherence (Briesacher *et al*., 2009). In this regard the opinions of doctors and patients were sought on the issue of interchanging or brand switching of SR Nifedipine brands.

Table 4.6 shows a summary of doctors and patients views on brand interchangeability with reasons. According to prescribers, 60% were of the view that Nifedipine SR brands were interchangeable, whereas 40% were of opposing view.

Generally, 41% of patients were of the opinion that Nifedipine SR brands are interchangeable whereas 59% thought they were not interchangeable. A curious patient also expressed concerns on why he thought brands were not interchangeable as follows:

"I am doing well on my favourite brand but sometimes when i come to the pharmacy and they give me another brand, I feel insecure because I know my new tablets won't be as effective as the old one."

Moreover, patients (41%) who believed that brands were interchangeable claimed that because all brands had the same active ingredients and were all covered by the NHIS as substitutable brands of the drug, they were interchangeable. For the 59% of patients who believed that brands were not interchangeable, their reasons were that different physical attributes of the brands, such as the packaging and different specifications or manufacturing variables among producers of the brands made them not interchangeable.

The opinions of the 40% of doctors who believed that brands were not interchangeable were based on the fact that different tolerability/side effects and efficacy among the various brands did not make them therapeutically equivalent, thus they were not interchangeable. Additionally psychological factors could at times determine a patient's level of adherence and affected the outcome of the treatment, and contributed to it being a decisive factor on possible brand interchangeability or otherwise. This view has been supported by a similar quote in a study by Paveliu *et al*., (2011) which was;

"Psycological factors could have effect on how patients saw general tolerability and anticipated effect of substituted brands given them",

However for the 60% who believed in possible interchangeability, they were of the opinion that brands of SR drugs like other groups of drugs could be interchanged, as their training allowed for generic prescribing, which works in most cases. In addition, the existence of many generic medicines list in western countries like Canada which allowed for drugs in the medicine list to be prescribed by their generic name attested to the fact that interchangeability was possible. Furthermore, they based their stance on interchangeability with reference to the definition of interchangeable drug as defined in the drug interchangeability update, 2004 of Canada as a drug that contains the same amount of the same active ingredients, possesses comparable pharmacokinetic properties, has the same clinically significant formulation characteristics and is to be administered in the same way as the drug prescribed." Therefore since the various SR brands bear these properties, they were interchangeable. The two contrasting opinions of doctors on brand interchangeability confirms Paveliu *et al*., (2011) quote that "Concerns over the therapeutic equivalence of branded products and generics are common amongst physicians too".

The views of the respondent doctors in this study confirm that variability of effect of generic substitution, although accepted by clinicians as possible, is little discussed or even understood by them as (Paveliu *et al.,* 2011) postulated in his study on generic substitution.

5.2 General assessment and information gathered on brands

Following a research finding that has indicated the influence of tablet appearance on the effectiveness of drugs (de Craen *et al.,* 1996) and the general confusion and misunderstanding that substitution may cause due to changes in physical attributes and name, it was considered vital to assess the physical attributes of the selected brands to distinguish them appropriately in the study.

Tables 4.7 shows the information gathered on the 12 selected brands regarding their physical characteristics such as shape, colour, nature of surface and type of cavity profiles. Each brand exhibited unique characteristics that made it different from another. All the brands were imported products from four major countries worldwide, namely: England, Slovenia, India and Germany. This suggests the wide prevalence of hypertension and the extent of SR Nifedipine use (Addo *et al*., 2007).

5.3 Characterization of nifedipine standard

The Nifedipine reference standard (powder) was subjected to specific tests as required by the British Pharmacopoeia 2011 such as tests for identification (appearance, solubility and colour), assay and loss on drying. It complied with all specifications and was therefore considered suitable for use as reference standard, RS for the dissolution study.

5.4 Tests for weight variation

Table 4.8 shows the results of the weight variation test carried out on the twelve brands. Weight variation range for all the brands: A, B, C, D, E, F, G, H, I, J, K, L fell within the

BP specification on weight variation for coated tablets (BP, 2011). The variations in weights for the various brands indicate the differences in the degree of uniformity in the amount of the nifedipine drug substance among the various brands during manufacture by their respective manufacturers.

Differing manufacturing variables such as different tablet compressors, punch dies, and so on. among the various manufacturing companies could account for the varying weights obtained for the various brands. Results of the standard deviation which gives a measure of the variability or dispersion around the mean weight of 20 tablets of each of the 12 brands showed that brand A which had the least standard deviation value of 0.00135 had the best uniformity of weight variation which was most clustered around the mean weight value. Brand L however with the highest standard deviation value of 0.01481 indicated a higher dispersion /least clustering of tablet weight from the mean weight making the tablet weights least uniformed.

5.5 Assay of brands

Table 4.9 shows the results for assays of the various brands. All the brands exhibited assay profile within the prescribed limit 90% to 110% (USP, 2007) except tablets of brands B, H, and K which showed relatively high assay values of 113.97%, 111.45% and 115.47% , respectively. For brand B, which had the 1st rank as the most preferred brand by patients and doctors, its high active content might have contributed to its known efficacy among the respondents, however, it could be related to the periodic headaches associated with its use as disclosed by some patients during the survey. However, further analysis of brand B would be necessary to confirm this relationship.

5.6 In *vitro* dissolution studies

Dissolution profiles for the 30 mg and 20 mg brands are shown in fig 4.5 and fig 4.6, respectively. According to Shah *et al*., (1998), dissolution profile enables the characterization of products more precisely than a single point dissolution test under appropriate conditions. Based on evidence from literature which suggests that no single approach is widely accepted to determine if dissolution profiles are similar (Yuksel *et al*., 2000), two main approaches to compare dissolution profiles were applied in this study. These were the model dependent approach (Shah *et al*., 1998) and model independent (fit factor) approach by Moore and Flanner, 1996.

5.6.1 Assessment of dissolution results according to USP Test 2, (2007 specification)

The USP Test 2 method for dissolution of sustained-release Nifedipine requires that the drug release tests be carried out at three (3) specific time points namely 3, 6 and 12 hours, respectively), and gives an acceptance criteria of the percentage drug release at these times as 10% to 30% (at 3 hours), 40 % to 65% (at 6 hours) and more than 80% release (at 12 hours). Figures 4.5 and 4.6 represent the summarized dissolution profiles obtained for the 12 selected brands of SR Nifedipine, namely; brands A, B, C, D (which were 30 mg Tablets) and E, F, G, H, I, J, K and L (20 mg tablets) at all the 18 time-points selected. They are represented as the cumulative percentage (%) drug dissolved versus time (hrs.).

Table 4.12 shows a summary of the percentage drug release of the 12 brands obtained using USP pharmacopoeial standard at 3, 6 and 12 hours. At 3 hours, brands A, B, C, E, G, H, I, J and K passed the USP acceptance criteria of having less than 30% of their percentage drug release.Brands D, F and L however failed at 3 hours with values of 30.62%, 73.83% and 38.40%.

At 6 hours, all the 30 mg brands A, B, C and D passed the requirement of having their percentage drug release values to be 64.98%, 48.35%, 50.66% and 42.94%, respectively. The 20 mg brands which passed dissolution at 6 hours were E, G, H, I and J.

Brands A, B, C, E, F, G, I, J, K, L at 12 hours had their percentage drug release values greater than 80% and thereby showed compliance to the USP requirement.

According to USP (2007) test 2 dissolution requirements, a good formulation of an SR nifedipine considered suitable for use must satisfy the acceptance criteria of percentage drug release at all the 3 time-points stated (USP, 2007). According to this specification, 3 brands (A, B and C) out of the 4 Nifedipine SR (30 mg) formulations could be considered interchangeable by USP standard and suitable SR Nifedipine formulations. Brand D failed two of the three time- points specification.

Four brands (E, G, I and J) out of the eight 20 mg brands complied with the USP specification on percentage drug release at all the 3 time points suggested. However brands F, H, K and L failed the USP (2007) dissolution test by not showing compliance at all the 3 time-points specified. They could be considered as sub-standard for their intended purpose as effective SR formulations. Brands A and E which were innovator brands gave the highest percentage release at 3, 6 and 12 hours for the 30 mg and 20 mg formulations.

According to Salomon and Doelker (1980) and El-Arini and Leuenberger (1995), variations noticed among dissolution profiles for the various brands could be as a result of varying factors relating to the physicochemical properties of the drug, the drug product formulation, the dissolution testing device and factors related to dissolution test parameters. This implies that factors such as choice of drug, its polymorphic form, concentration of the polymer, crystalline nature, particle size, solubility hydration rate and influence of ionic strengths could account for the different release profiles and kinetics

obtained. Furthermore, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates of SR formulations (Bravo *et al.*, 2002).

5.6.2 Model-independent methods

The dissolution profiles of all possible pairs of pharmaceutical equivalents were compared by similarity factor (f2) and difference factor (f1). Tables 4.14 and 4.15 show the f1 and f2 values for the two sets of brands (30 mg and 20 mg). Shah *et al.*, (1998) proposed that f2 value of 50-100 and an f1 value of 0-15 indicate similarity/equivalence in dissolution profiles.

The calculation of f1 was based on the modified formula by Costa, who proposed a modification of the difference factor, f1 formula to avoid the problem of obtaining different f1 values depending on the formulation chosen as the reference (Costa and Lobo, 2001). Application of the modified formula (which depicted the divisor as the sum of the average values of two formulations for each dissolution sampling point and not the sum of the reference formula values) was used to obtain the various f1 values.

The paired brands (30 mg) that were considered similar and therefore interchangeable included: B&C, B&D, C&B, C&D, D&B and D&C. They were considered similar/interchangeable by virtue of their f1 and f2 values which fell within the ranges given: f1= 0-15 and f2= 50-100. Hence brands B, C and D out of the four (30 mg) could be considered to be similar and interchangeable. The dissimilar (non- interchangeable) 30 mg brands included brands A&B, A&D, C&A and D&A whose (f2, f1) values fell outside the range specified.

From Table 4.15, paired brands of the 20 mg which were similar and therefore interchangeable include: E&K, E&L, G&H, G&I, G&J. Similar f2 and f1 values were obtained for the same pairs H&G, I&G, J&G, K&E and L&E, notwithstanding when the

reference and sample brands were interchanged in the calculation. Therefore the results obtained confirmed that the formula for the analysis by fit factors as proposed by Costa was sound (Costa and Lobo, 2001).

5.6.3 Model-dependent methods

In order to describe the release kinetics and the mechanism of drug release, the dissolution data were fitted into various kinetic models which included zero order, first order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas Model. The following plots were made: Cumulative % drug release versus time (zero order kinetic model); log cumulative of % drug remaining versus time (first order kinetic model); cumulative % drug release versus square root of time (Higuchi model), cube root of drug % remaining in matrix versus time (Hixson-Crowell cube root law). Representative kinetic plots for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas for brands A, B, C and D. are shown in figures 4.7, 4.10, 4.13, 4.16, and 4.19, respectively.

For brands E, F, G, H their zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-peppas plots are shown in figures 4.8, 4.11, 4.14, 4.17 and 4.20, respectively. Figures 4.9, 4.12, 4.15, 4.18, 4.21 represent the zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas plots for brands I, J, K and L, respectively.

The results of the coefficient of determination (R^2) for the 30 mg and 20 mg brands are shown in tables 4.16 and 4.17, respectively. The R^2 value as a statistic gives some information about the goodness of fit of a model. In regression, the R^2 (coefficient of determination) is a statistical measure of how well the regression line approximates the real data points and an R^2 of 1 indicates that the regression line perfectly fits the data (Steel and Torrie, 1960). From Table 4.17, brands G and L followed zero order and first order kinetics, respectively by virtue of having their coefficient of determination (R^2 as 0.9594 and 0.9862, respectively) as highest for these models compared to all the other

models. For brand G, zero order implied that its drug release rate is independent of the drug concentration (Hadjiioannou *et al*., 1993). For brand G, its first order release kinetic indicates that the velocity of solution of the brand in a liquid is expressed as a function of the concentration at the surface (Bravo *et al.,* 2002).

From the results, Higuchi model was the most represented kinetic model for majority of the brands. Thus for brands A, B, C, D, E, I and K the best linearity of their curvilinear plotted data was found for Higuchi's equation plot. This model signified that the release of drug of these brands from their matrix was a square root of time dependent process based on Fickian diffusion. This further implied that their drug was embedded in an insoluble matrix and its release from the matrix was a square root of time dependent process based on Fickian diffusion (Higuchi, 1963).

Brands H and J had the best linearity of their plots for the Hixson-Crowell kinetic model. Their R^2 values were 0.9837 and 0.9909, respectively, signifying that their dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (Dash *et al.,* 2010).

The first 60% drug release data for all the brands was fitted in Korsmeyer–Peppas model equation which helped to describe the drug release mechanism of each brand from a polymeric system. The brand that best fitted Korsmeyer-Peppas model was brand F which had an R^2 value of 0.9561 which signified that the diffusional release mechanism of brand F was from a polymeric film (Peppas, 1985).

According to Siepmann *et al.,* (2001), the n value (diffusional coefficient) is used to characterize different release for cylindrical shaped matrices and its value characterizes the release mechanism of drug. In the case of cylindrical tablets, when n is greater than or equal to 0.45, it corresponds to a Fickian diffusion mechanism,whereas when n is greater

than 0.45 but less than 0.89 (that is, $0.45 < n < 0.89$), it is referred to as non-Fickian transport.when n is equal 0.89,it is described as a Case II (relaxational) transport. An n value greater than 0.89 is known as super case II transport.

From Table 4.17, the exponent n value obtained for brand F which followed Korsmeyer-Peppas model was 1.76 indicating that its mechanism of drug release follows Super case II transport mechanism.

The various R^2 values obtained could be as are result of different assumptions made by each model which restricts the applicability of each model to the different unknown drug-polymer systems used for each brand. From the results data, various brands followed different kinetic models by virtue of their varying formulation factors, particularly their type of polymer/matrix controlling their sustained-release mechanism (Siepmann *et al*., 2000).

The results of the above mathematical modeling and kinetics of drug release on the selected 12 brands depict that the switchover from one brand to another is not advisable since different polymers used for the brand formulations could account for the different release patterns. Similarity of brands based on their drug release kinetics can be determined for brands which follow one type of kinetic model.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Results from the survey revealed that Nifedipine SR drug was the most prescribed and used SR antihypertensive drug within the Kumasi metropolis.

- The top five brands preferred by doctors were in the order nifecard xl (30 mg), caredin 30 (30 mg), caredin 20 (20 mg), nifin-20 (20 mg) and nepine (20 mg). Reasons for such preference in order of importance were based on perceived efficacy, compliance, tolerability, availability and insurance coverage, respectively.
- The top five brands preferred by patients by ranking were nifecard xl (30 mg), caredin 30 (30 mg), nifin (20 mg), nepine (20 mg), and cordipin (20 mg). The main factors influencing their preference in order of importance were affordability, availability, NHIS coverage, tolerability, efficacy and compliance.
- On the subject of interchangeability of SR brands of nifedipine, 60% of prescribers and 41% of patients were of the opinion that brands of SR nifedipine brands are interchangeable.
- Brands A, C, D, E, F, G, I, J and L passed the USP test for assay (determination of active content). Brands B, H and K however failed this parameter.
- For the *in vitro* USP dissolution test conducted,7 out of the 12 brands passed at all the 3 time-points specified (3, 6 and 12 hours). These comprised 3 of the 30 mg brands (brands A, B and C) and 4 of the 20 mg brands (E, G, I and J).
- Similar brands by fit factors analysis were B, C and D (30 mg) and for the 20 mg brands: E and K, E and L, G and H, G and I and G and J.

- Based on release kinetics, brands A, B, C, D, E, I and K were considered similar because their drug release kinetic followed Higuchi's model. Brands H and J were considered similar because their drug release kinetics followed Hixson-Crowell kinetic model. Similarity of brands based on their drug release kinetics can be determined for brands which follow one type of kinetic model.

From the results of this analysis, it may be suggested that confirmation for similarity of brand for brand interchangeability should be based on compendia method e.g. USP and at least one of these applied models: fit factors or kinetic models.

6.2 Recommendations

Further *in vivo* correlation studies could be performed on the selected brands since the drug release performance obtained *in vitro* is a likely prediction but does not necessarily mean that formulations will perform similarly *in vivo*.

6.2.1 Recommendations to various bodies

On the basis of the results from the survey and experiment, some recommendations can be made to various bodies as listed below:

6.2.1.1 Drug manufacturers

Complete emphasis on total quality management for SR Nifedipine production should encompass proper storage of the raw material (Nifedipine) from source, during manufacturing, distribution and during the entire shelf-life of the finished-product due to the photosensitive nature of Nifedipine.

• Proper validation and authentication of varying manufacturing variables will help minimize the effect of variations in the manufacturing process and will help attain consistent high product quality for SR Nifedipine.

• Research and development could study and validate the various polymers and their particular release patterns to furnish manufacturers on the best formulations involving particular selection of polymers in appropriate concentrations.

6.2.1.2 Drug selection committees

They should communicate directly with patients and get informed about their opinions (experience) on various SR Nifedipine brands and their effectiveness. Information accrued could be communicated with appropriate regulatory bodies and manufacturers for further analysis and rectification of crucial issues.

6.2.1.3 Regulatory agencies

- They should intensify post market inspection and surveillance on various SR Nifedipine brands introduced on the market to confirm their quality as affected by various storage conditions and disseminate the appropriate information regularly to drug selection committees on effective/qualified brands to stock/prescribe.
- They could adopt and implement a national legislative guide like the ″″drug interchangeability update" as practiced in countries like Canada to guide all decisions about drug brand interchangeability of SR Nifedipine. In effect only legalized and acceptable equivalents of SR Nifedipine should be served to patients.

6.2.1.4 Patients

Patients need to be constantly educated by health professionals and government bodies about the concepts of therapeutic equivalence and brand substitution in order to accept brands given them by substitution as equally effective and consequently show better adherence to drug regimens prescribed.

They should be encouraged to visit their healthcare providers regularly to update them on any negative experiences associated with SR Nifedipine brand substitution.

6.2.1.5 Prescribers

Concerns over the therapeutic equivalence of branded products and generics as well as confusion over brand names will be minimized when prescribers seek for regular updated report on equivalent SR Nifedipine brands to prescribe from regulatory agencies or drug-selection committees in hospitals.

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APPENDICES

APPENDIX 1: Sample preparation for dissolution

A. Buffer concentrates preparation:

Dibasic sodium phosphate, 330.9 g and 38 g of citric acid, respectively were transferred into a 1L volumetric flask. Distilled water was added to dissolve the powders and 10 ml of phosphoric acid was added. The resulting solution was further diluted with water and mixed to obtain a volume of 1L.

B. Dissolution medium preparation:

A volume of buffer concentrate, 125 ml from the stock of buffer concentrate was added to 1L of the prepared 10% sodium lauryl sulfate solution and mixed thoroughly. (The 10% sodium lauryl sulphate solution was prepared by dissolving 100 g of sodium lauryl sulphate powder in sufficient distilled water to 1L solution in a volumetric flask with the aid of a magnetic stirrer The resulting solution was further diluted to 10L with distilled water. The pH of the resulting mixture was adjusted to 6.8.

APPENDIX 2: Interview guide for initial survey

AIM: To establish the most prescribed or most used SR antihypertensive drug used in the Kumasi Metropolis

Respondents- doctors/pharmacists in: community pharmacies, Government/Quasi government hospitals and Private hospitals.

Category of health Centre. Please indicate.

( ) Community pharmacies

( ) Government/Quasi government hospitals

( ) Private hospitals

Do you stock /dispense SR antihypertensives for your hypertensive patients?

YES ( ) NO ( )

What are the types of sustained-release antihypertensives you usually prescribe/serve to patients?.....

.....

Can you list the various brands of your most stocked SR drug?

……

……

APPENDIX 3: Questionnaire for respondent doctors who handle hypertension cases

How many hypertension cases do you handle during your clinic days?

Less than 10 ( )

10 to 20 ( )

20 to 30 ( )

More than 30 ( )

Do you prescribe Sustained-release (SR) nifedipine for your patients? Please tick.

YES ( )

NO ( )

3. If your answer in question (2) above is yes,do indicate below the class of hypertension patients you usually prescribe SR Nifedipine brands.

Code	Class of hypertension	Systolic	Diastolic	Tick where appropriate
1	Mild	140-159	90-99	
2	Moderate	160-179	100-109	
3	Severe	>180	110	

4. Do indicate in the table below the brands of SR Nifedipine you mostly prescribe.

Code	Brand name	Strength/mg	Please tick if prescribed
1	Nepine	20	
2	Cordipin	20	
3	Nifedi-denk	20	
4	Caredin	30	
5	Caredin	20	
6	Adalat	30	
7	Adalat	20	
8	Procardia	30	
9	Nifecard	30	

10	Niflex	20	
11	Retardine	30	
12	Nifedose	20	
13	Nifin	20	
14	Cardovasc	30	
15			
16			

********please specify brand(s) if not indicated in last three rows provided.

What is your most preferred brand of SR antihypertensive drug?

.....

Why is that your preferred brand?

a) Better efficacy ( ) b) better tolerability ( ) c) availability ( )

d) Less expensive ( ) e) better compliance ( ) f) NHIS coverage ( )

e) Other reasons.....

.....

In your opinion, do you think that all SR brands of nifedipine are interchangeable?

YES ( ) NO ( )

9) What reasons do you have to support your answer in question 8 above?

.....

.....

APPENDIX 4: Questionnaire for respondent patients

Do you know the name(s) of your antihypertensive drug(s)?

YES ( ) NO ( )

Can you identify your SR drug from the displayed brands (samples) as shown?

YES ( ) NO ( )

Code	Brand name	Strength/mg	Please tick if ever prescribed/used
1	Nepine	20	
2	Cordipin	20	
3	Nifedi-denk	20	
4	Caredin	30	
5	Caredin	20	
6	Adalat	30	
7	Adalat	20	
8	Procardia	30	
9	Nifecard	30	
10	Niflex	20	
11	Retardine	30	
12	Nifedose	20	
13	Nifin	20	
14	Cardovasc	30	
15			
16			
17			

********please specify brand(s) if not indicated in last three rows provided.

What is your preferred brand of SR antihypertensive drug?

.....

.....

.....

Why is that your preferred brand?

a) Better efficacy ( ) b) better tolerability ( ) c) availability ( )

d) Less expensive ( ) e) better compliance ( ) f) NHIS coverage ( )

g) Other reasons.....

.....

Do you always receive your preferred brand whenever you visit your hospital or pharmacy?

YES ( ) NO ( )

If your answer is no in question ( ) above, do you worry about not receiving the same brand of your preferred SR drug upon every visit to your hospital/pharmacy?

YES ( ) NO ( )

What are some of your concerns when you are not given the same brand you prefer when you go for re-fill

Efficacy ( ) b) Side-effects ( ) c) Availability ( ) d) Cost ( ) e) Other reasons ……

…….....

Do you think that all SR brands are interchangeable?

YES ( ) NO ( )

9) What reasons do you have to support your answer in question 8 above?

.....

.....

APPENDIX 5: Tables of some results

A: CALCULATION OF STANDARD DEVIATION OF WEIGHT FOR BRAND A

BRAND A				
Tablet number	**weight of tablet (g) X**	**Average weight (g) $\bar{X}$**	$\mathbf{X - \bar{X}}$	$\mathbf{(X - \bar{X})^2}$
1	0.3011	0.29886	0.002240	0.0000050176
2	0.2965	0.29886	-0.002360	0.0000055696
3	0.2998	0.29886	0.000940	0.0000008836
4	0.3005	0.29886	0.001640	0.0000026896
5	0.3001	0.29886	0.001240	0.0000015376
6	0.2972	0.29886	-0.001660	0.0000027556
7	0.2984	0.29886	-0.000460	0.0000002116
8	0.2969	0.29886	-0.001960	0.0000038416
9	0.2985	0.29886	-0.000360	0.0000001296
10	0.2989	0.29886	0.000040	0.0000000016
11	0.2985	0.29886	-0.000360	0.0000001296
12	0.2989	0.29886	0.000040	0.0000000016
13	0.2989	0.29886	0.000040	0.0000000016
14	0.2984	0.29886	-0.000460	0.0000002116
15	0.2988	0.29886	-0.000060	0.0000000036
16	0.2998	0.29886	0.000940	0.0000008836
17	0.2974	0.29886	-0.001460	0.0000021316
18	0.2975	0.29886	-0.001360	0.0000018496
19	0.2999	0.29886	0.001040	0.0000010816
20	0.3012	0.29886	0.002340	0.0000054756

Standard Deviation = $\sqrt{\frac{\sum(X-\bar{X})^2}{n-1}}$

$\sum(X - \bar{X})^2$ = 0.0000344080

n = 20

n – 1 = 20 – 1 = 19

Standard deviation = $\sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.0000344080}{19}} = \sqrt{0.000001811}$ = 0.001345714

B: RAW DISSOLUTION DATA FOR BRAND A USING HPLC

BRAND	TIME HRS	AREA UNDER THE CURVE (AUC)						AVERAGE
		1	2	3	4	5	6	
A	0.25	6.30	5.86	5.25	5.99	6.12	4.60	5.69
A	0.5	8.90	9.07	9.00	9.50	8.99	8.59	9.01
A	0.75	22.00	20.89	21.06	20.78	22.00	21.56	21.38
A	1	45.12	44.65	42.15	43.67	43.00	45.89	44.08
A	1.5	67.90	67.70	66.20	65.90	66.70	64.54	66.49
A	2	82.34	80.99	81.35	83.00	83.45	83.56	82.45
A	3	105.66	101.22	110.00	105.55	100.11	105.23	104.63
A	4	169.88	165.55	166.70	165.45	164.98	169.99	167.09
A	6	230.95	223.54	231.60	238.89	225.23	220.00	228.37
A	8	258.99	256.00	265.00	259.50	260.10	259.50	259.85
A	10	310.00	290.00	320.00	321.00	322.00	321.00	314.00
A	12	350.07	352.24	352.22	349.98	348.99	349.10	350.43
A	14	353.00	351.40	349.99	350.29	348.99	349.99	350.61
A	16	350.11	348.99	353.29	349.85	351.00	350.89	350.69
A	18	350.00	348.90	354.00	348.89	349.95	352.18	350.65
A	20	352.00	351.90	349.98	347.88	349.70	352.50	350.66
A	22	352.11	349.56	350.45	351.67	350.78	351.16	350.96
A	24	354.40	349.45	350.09	349.98	349.99	351.89	350.97

C: RAW DISSOLUTION DATA FOR BRAND E USING HPLC

BRAND	TIME HRS	AREA UNDER THE CURVE (AUC)						AVERAGE
		1	2	3	4	5	6	
E	0.25	8.00	7.90	8.23	7.93	8.45	8.00	8.09
E	0.5	8.80	10.11	8.98	9.54	8.58	9.10	9.19
E	0.75	13.90	14.10	14.00	13.80	14.30	15.00	14.18
E	1	28.60	27.90	28.00	28.00	27.89	27.90	28.05
E	1.5	36.67	39.00	37.55	37.00	35.95	33.99	36.69
E	2	49.96	47.89	48.00	45.95	48.00	45.96	47.63
E	3	68.50	68.85	69.95	67.50	65.90	68.54	68.21
E	4	119.98	121.50	122.00	123.10	121.90	119.56	121.34
E	6	149.58	146.75	147.55	150.00	147.55	145.00	147.74
E	8	189.00	184.77	186.32	179.99	183.55	189.54	185.53
E	10	211.50	209.00	208.95	210.00	208.65	207.77	209.31
E	12	230.43	235.56	231.20	229.95	221.00	225.50	228.94
E	14	229.23	229.90	228.00	227.50	227.00	229.50	228.52
E	16	229.56	229.43	232.45	230.00	224.60	225.00	228.51
E	18	226.00	234.23	221.00	222.80	235.58	232.65	228.71
E	20	231.10	230.56	221.40	226.80	231.11	230.55	228.59
E	22	227.20	233.56	223.20	230.10	232.65	225.00	228.62
E	24	225.56	224.60	232.10	227.20	231.23	230.78	228.58

D: MEAN CUMULATIVE DRUG DISSOLVED FOR 30 mg

NIFEDIPINE BRANDS

	Mean cumulative drug dissolved, cAUC			
TIME/hrs	BRAND A	BRAND B	BRAND C	BRAND D
0.25	5.69 ±0.26	3.98 ± 0.39	3.57 ± 0.27	4.08 ± 0.13
0.5	9.06± 0.12	6.68 ±0.14	4.63 ± 0.26	6.82 ± 0.07
0.75	21.46± 0.22	10.14 ± 0.13	4.87 ± 0.08	10.04 ± 0.08
1	44.27± 0.57	41.52 ± 1.01	47.28 ± 2.39	41.66 ± 0.67
1.5	66.88 ±0.51	68.80 ± 1.01	54.54 ± 0.65	68.27 ± 0.70
2	83.05 ± 0.44	91.48 ± 0.87	68.54 ± 1.79	92.46 ± 1.43
3	105.37 ± 1.45	95.82 ± 0.20	94.61 ± 0.27	108.34 ± 3.92
4	168.03 ± 0.93	154.02 ± 1.01	123.54 ± 2.02	140.96 ± 4.38
6	229.86 ±2.77	171.04 ± 0.21	179.22 ± 0.75	151.92 ± 1.57
8	261.89 ± 1.20	193.85 ± 1.20	193.91 ± 0.12	175.85 ± 3.80
10	316.33 ± 5.14	255.06 ± 3.34	228.22 ± 0.99	232.73 ± 0.57
12	353.25 ± 0.57	316.27 ± 5.13	290.03 ± 0.04	267.87 ± 0.32
14	353.75 ± 0.57	328.64 ± 3.62	290.56 ± 0.73	302.88 ± 0.99
16	353.83 ± 0.60	330.92 ± 1.42	302.08 ± 2.79	316.86 ± 0.71
18	353.80 ± 0.84	347.78 ±3.79	308.19 ± 1.40	320.98 ± 0.75
20	353.81 ± 0.73	348.09 ± 1.29	311.57 ± 1.99	318.69 ± 3.51
22	354.10 ± 0.37	348.09 ± 2.24	314.77 ± 3.31	323.83 ± 0.58
24	354.12 ± 0.77	346.43 ± 1.66	314.47 ± 1.10	321.71 ± 2.16

E: MEAN CUMULATIVE DRUG DISSOLVED FOR 20 mg NIFEDIPINE BRANDS E, F, G, and H

	Mean cumulated drug dissolved, Cauc			
TIME/hrs	BRAND E	BRAND F	BRAND G	BRAND H
0.25	8.09 ± 0.09	4.05 ± 1.98	0.00 ± 0.00	2.70 ± 0.89
0.5	9.26 ± 0.23	26.80 ± 2.56	2.92 ± 1.09	6.21 ± 0.25
0.75	14.27 ± 0.18	97.80 ± 5.13	9.23 ± 0.86	9.16 ± 0.22
1	28.18 ± 0.11	139.64 ± 8.02	21.62 ± 3.66	14.55 ± 0.24
1.5	36.95 ± 0.68	148.42 ± 15.07	28.76 ± 3.91	22.10 ± 0.55
2	47.96 ± 0.62	160.39 ± 9.81	30.27 ± 1.51	29.71 ± 0.70
3	68.63 ± 0.56	170.26 ± 6.76	56.70 ± 7.64	50.12 ± 1.05
4	121.95 ± 0.54	182.91 ± 3.27	71.99 ± 6.03	70.36 ± 2.56
6	148.82 ± 0.76	192.93 ± 0.29	104.29 ± 11.05	106.43 ± 2.35
8	186.85 ± 1.46	192.18 ± 7.62	144.28 ±11.51	132.18 ± 2.25
10	210.97 ± 0.53	191.89 ± 3.48	162.02 ± 0.65	151.86 ± 0.37
12	230.82 ± 2.06	195.86 ± 3.51	205.29 ± 0.34	155.77 ±0.36
14	230.57 ± 0.49	189.39 ± 0.47	212.84 ± 0.40	163.49 ± 0.00
16	230.56 ± 1.26	190.08 ± 0.72	214.74 ± 0.51	166.73 ± 1.07
18	230.76 ± 2.54	190.08 ± 0.72	214.41 ± 0.17	167.78 ± 0.01
20	230.64 ± 1.60	188.81 ±0.59	214.47 ± 0.18	169.09 ± 0.00
22	230.67 ± 1.71	188.83 ± 0.59	214.22 ± 0.33	168.97 ± 1.17
24	230.63 ± 1.30	193.91 ±0.94	214.79 ± 0.06	169.20 ± 0.11

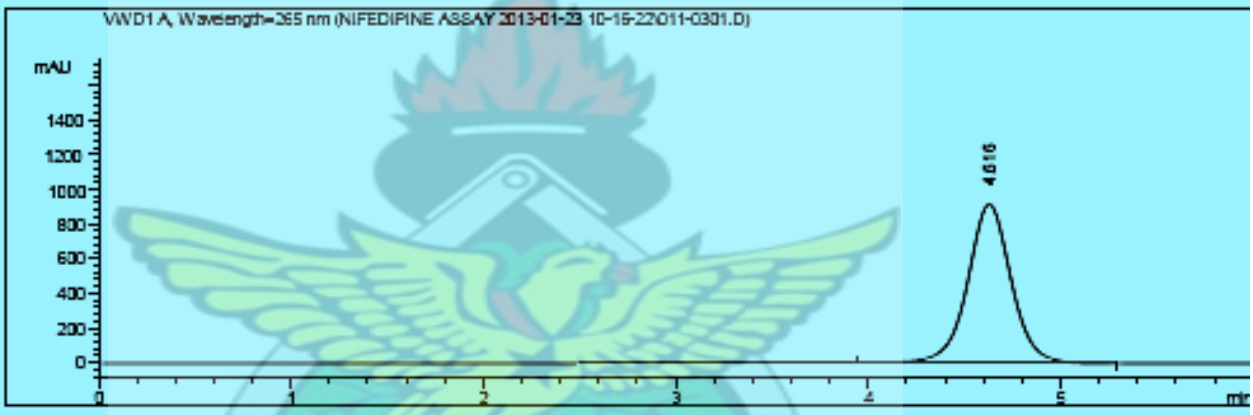
F: MEAN CUMULATIVE DRUG DISSOLVED FOR 20 mg NIFEDIPINE BRANDS I, J, K, L

	Mean cumulated drug dissolved, cAUC			
TIME/hrs.	BRAND I	BRAND J	BRAND K	BRAND L
0.25	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.5	9.67 ± 0.16	0.00 ± 0.00	0.00 ± 0.00	7.10 ± 1.07
0.75	11.16 ± 0.30	0.00 ± 0.00	10.83 ± 0.31	14.25 ± 0.18
1	24.57 ± 0.27	15.12 ± 0.32	15.22 ± 0.32	28.17 ± 0.11
1.5	40.09 ± 1.35	17.88 ± 3.56	21.24 ± 0.30	45.54 ± 1.11
2	52.09 ± 0.57	36.05 ± 1.02	45.96 ± 0.59	66.06 ± 0.32
3	60.43 ± 1.62	58.07 ± 1.50	60.99 ± 0.22	88.55 ± 0.05
4	95.54 ± 0.17	92.68 ± 0.92	123.48 ± 9.45	123.24 ± 0.30
6	114.40 ± 2.97	123.12 ± 2.11	186.75 ± 18.48	153.18 ± 0.80
8	139.87 ± 7.48	164.13 ± 1.14	213.41 ± 9.23	171.09 ± 0.17
10	161.73 ± 0.49	191.98 ± 0.63	228.93 ± 2.62	184.30 ± 0.50
12	190.15 ± 0.64	212.77 ± 0.87	229.58 ± 2.25	200.12 ± 0.40
14	191.87 ± 0.18	212.34 ± 0.35	229.91 ± 2.79	213.78 ± 0.52
16	191.80 ± 0.67	212.12 ± 0.32	230.23 ± 1.67	229.52 ± 1.87
18	191.97 ± 0.57	213.72 ± 1.05	230.26 ± 3.08	231.66 ± 3.97
20	192.49 ± 0.48	212.48 ± 0.21	230.46 ± 1.19	231.06 ± 1.92
22	192.41 ± 0.33	214.72 ± 1.96	230.13 ± 0.31	231.42 ± 2.12
24	192.68 ± 0.43	212.84 ± 0.84	230.54 ± 2.25	231.26 ± 2.01

APPENDIX 6: Sample Chromatograms

A: Sample chromatogram for assay of 30 mg nifedipine brand A

```
Data File C:\CHEM32\1\DATA\NIFEDIPINE ASSAY 2013-01-23 10-16-22\011-0301.D
Sample Name: BRAND A

================================================================
Acq. Operator   : OSEI-ASARE CHRISTINA          Seq. Line :   3
Acq. Instrument : ERNEST CHEMISTS                Location : Vial 11
Injection Date  : 1/23/2013 10:32:41 AM               Inj :   1
                                                Inj Volume : 25 µl
Acq. Method     : C:\Chem32\1\DATA\NIFEDIPINE ASSAY 2013-01-23 10-16-22\NIFEDIPINE ASSAY.M
Last changed    : 1/15/2013 6:42:55 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE
Last changed    : 4/9/2013 7:45:33 AM by OSEI-ASARE
Method Info    CHRISTINA  : ANALYSIS OF NIFEDIPINE
                 Mobile Phase:::::: 250 ml distilled water; 125 ml
                acetonitrile and 125 ml methanol
                Flowrate::::: 1.5ml/min
                 Temp.............30 deg C
                 Agilent Prep C18 Scalar 4.6X250mm
```

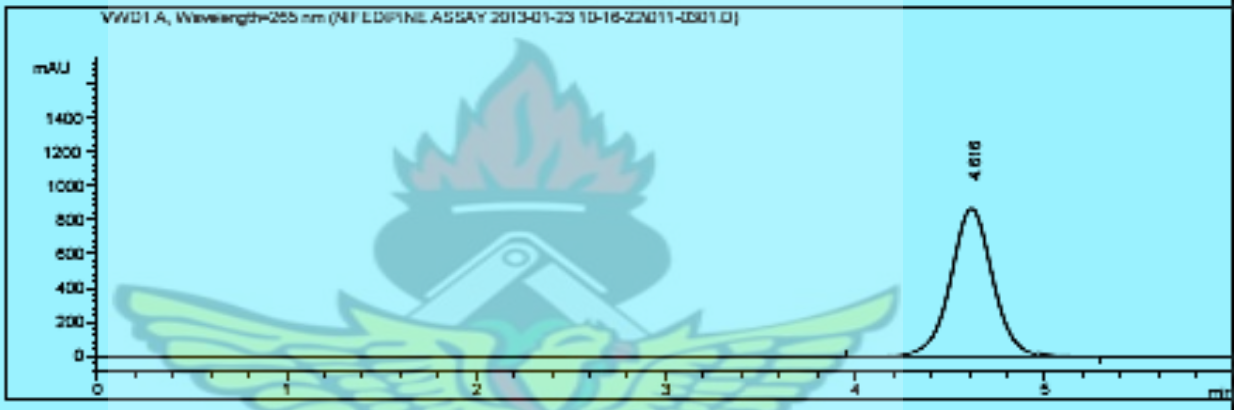



```
================================================================
                Area Percent Report with Performance
================================================================

Multiplier              :      1.0000
Dilution                :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=265 nm


RetTime    k'      Area       Height   Symm.  Width    Plates Resol Select
 [min]          mAU   *s    [mAU   ]          [min]           ution ivity
-------|------|----------|----------|-----|-------|--------|-----|------
  4.616    -  1.40520e4   906.8839    0.97  0.2305    4221     -      -


================================================================
                          *** End of Report ***
```

B: Sample chromatogram for assay of 20 mg nifedipine brand E

Data File C:\CHEM32\1\DATA\NIFEDIPINE ASSAY 2013-01-23 10-16-22\011-0301.D
Sample Name: BRAND E

Acq. Operator : OSEI-ASARE CHRISTINA Seq. Line : 3
Acq. Instrument : ERNEST CHEMISTS Location : Vial 11
Injection Date : 1/23/2013 11:13:31 Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE ASSAY 2013-01-23 10-16-22\NIFEDIPINE ASSAY.M
Last changed : 1/15/2013 6:42:55 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE
Last changed : 4/9/2013 7:45:33 AM by OSEI-ASARE
Method Info CHRISTINA : ANALYSIS OF NIFEDIPINE
Mobile Phase:::::: 250 ml distilled water; 125 ml acetonitrile and 125 ml methanol
Flowrate:::: 1.5ml/min
Temp.....30 deg C
Agilent Prep C18 Scalar 4.6X250mm



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=265 nm

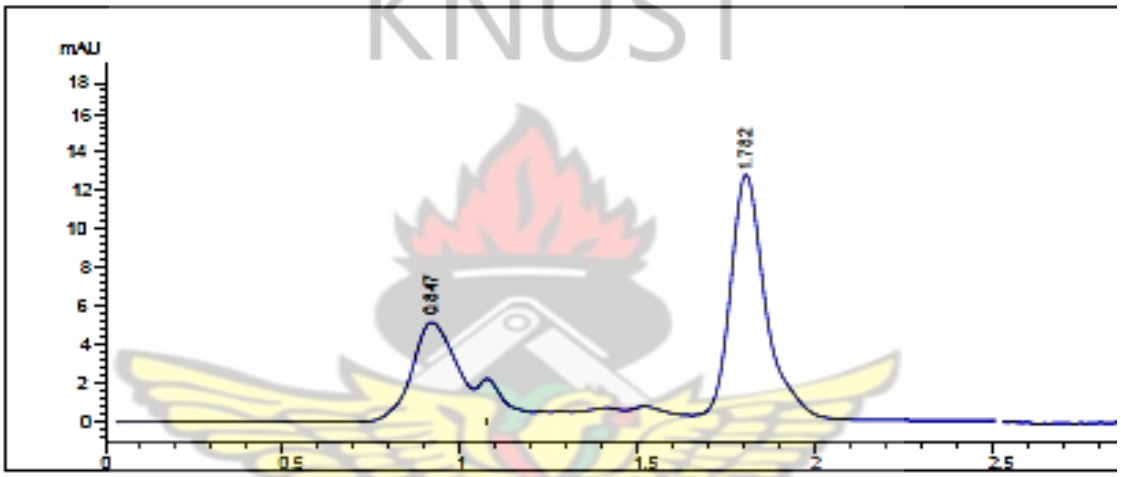
RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
4.616	-	1.32260e4	852.5211	0.97	0.2305	4221	-	-

*** End of Report ***

C: Sample chromatogram for dissolution of 30 mg nifedipine brand A at 3hrs

Sample Name: A-3 HRS

```
Acq. Operator    : CHRISTINA OSEI-ASARE          Seq. Line :   1
Acq. Instrument : ERNEST CHEMISTS                Location : Vial 1
Injection Date  : 3/14/2013 10:18:00 AM             Inj :   1
                                                 Inj Volume : 25 µl
Acq. Method     : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed    : 3/13/2013 7:47:02 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M
                  Mobile Phase::::: Acetonitrile and water (70:30)
                  Flowrate::::: 1.5ml/min
                  Wavelength::::: 350nm
                  Temp.............40 deg C
                  Agilent Prep C18 Scalar 4.00mm x 125mm
```




```
                Area Percent Report with Performance

Multiplier              :      1.0000
Dilution                :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=350 nm
```

RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
0.847	-	58.7709	7.74906	0.63	0.31474	281	-	-
1.782	-	105.6596	12.8906	0.58	0.27333	2647	5.01	2.13

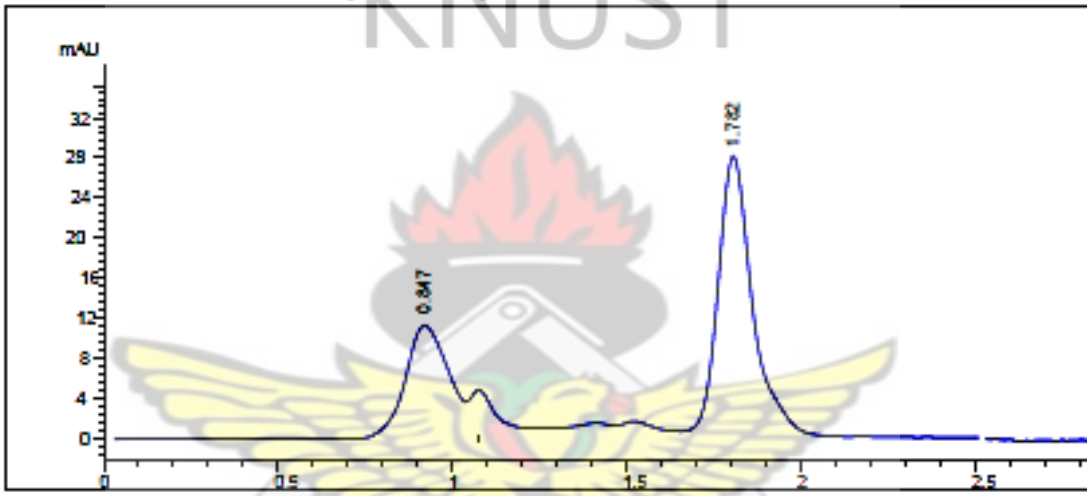
```
                      *** End of Report ***
```

D: S**a**mple chromatogram for dissolution of 30 mg nifedipine brand A at 6hrs

Sample Name: A-6 HRS

Acq. Operator : CHRISTINA OSEI-ASARE Seq. Line : 1
Acq. Instrument : ERNEST CHEMISTS Location : Vial 1
Injection Date : 3/14/2013 1:19:20 PM Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed : 3/13/2013 7:47:02 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M

Mobile Phase::::: Acetonitrile and water (70:30)
Flowrate::::: 1.5ml/min
Wavelength::::: 350nm
Temp.....40 deg C
Agilent Prep C18 Scalar 4.00mm x 125mm



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=350 nm

RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
0.847	-	128.3017	16.1496	0.63	0.60474	281	-	-
1.782	-	230.9506	28.6090	0.58	0.50333	2647	5.01	2.13

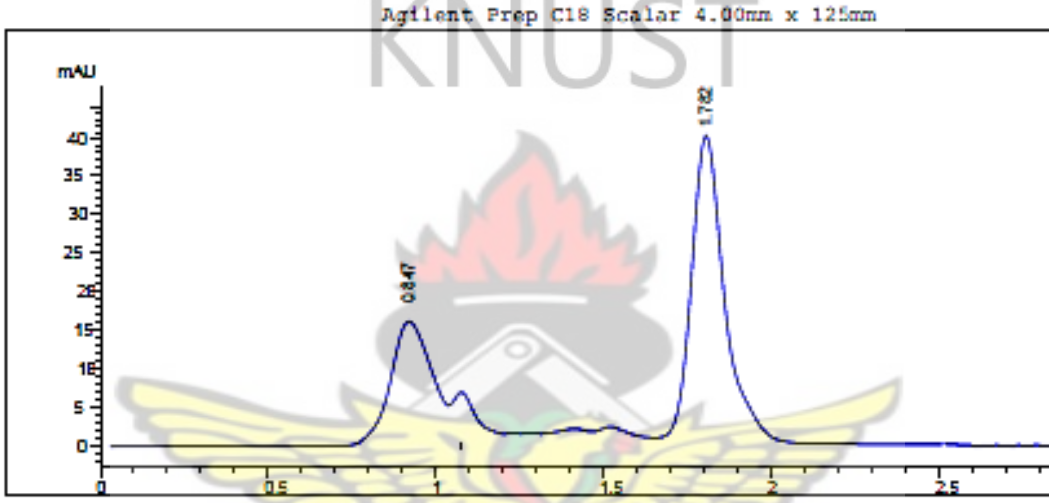
*** End of Report ***

E: Sample chromatogram for dissolution of 30 mg nifedipine brand A at12hrs

Sample Name: A-12 HRS

Acq. Operator : CHRISTINA OSEI-ASARE Seq. Line : 1
Acq. Instrument : ERNEST CHEMISTS Location : Vial 1
Injection Date : 3/14/2013 7:18:50 PM Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed : 3/13/2013 7:47:02 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M

Mobile Phase::::: Acetonitrile and water (70:30)
Flowrate::::: 1.5ml/min
Wavelength::::: 350nm
Temp.....40 deg C
Agilent Prep C18 Scalar 4.00nm x 125mm



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=350 nm

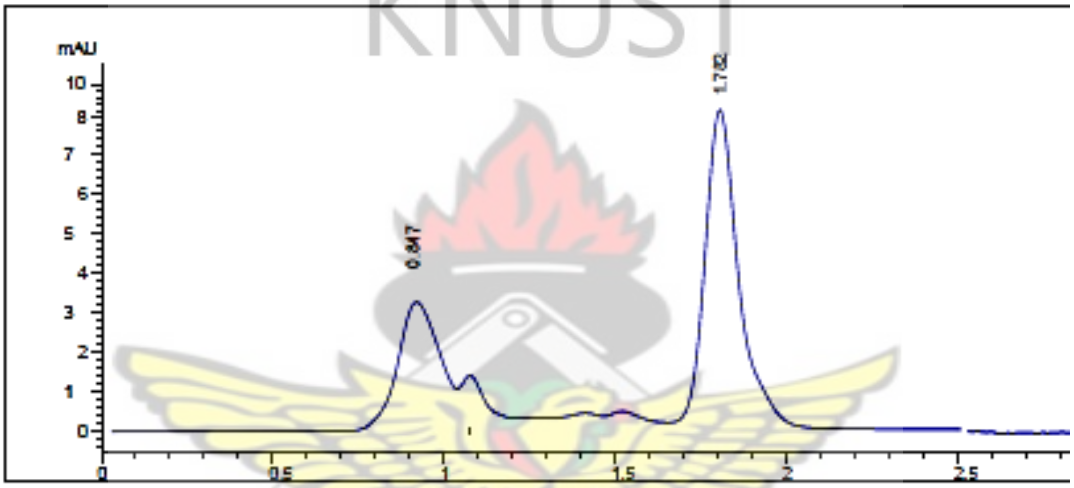
RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
0.847	-	194.2117	24.6246	0.63	1.49274	281	-	-
1.782	-	350.0706	42.4990	0.58	1.28123	2647	5.01	2.13

*** End of Report ***

F: Sample chromatogram for dissolution of 20 mg nifedipine brand E at 3hrs

Sample Name: E-3 HRS

Acq. Operator : CHRISTINA OSEI-ASARE Seq. Line : 1
Acq. Instrument : ERNEST CHEMISTS Location : Vial 1
Injection Date : 3/23/2013 9:18:35 AM Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed : 3/18/2013 6:15:02 AM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=350 nm

RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
0.847	-	38.0509	4.8906	0.63	0.19474	281	-	-
1.782	-	68.5001	8.3184	0.58	0.27433	2647	5.01	2.13

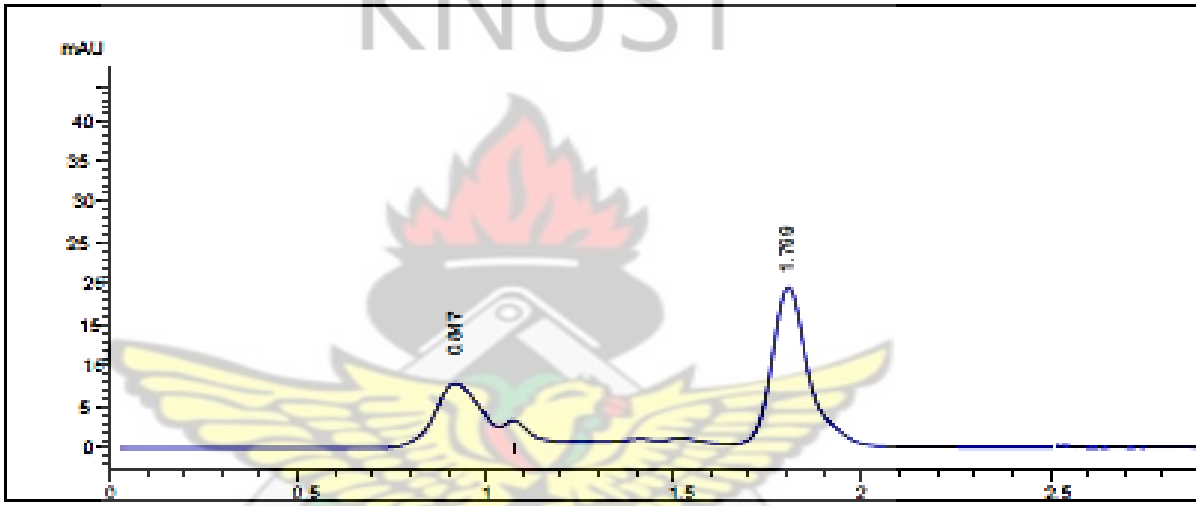
*** End of Report ***

Figure G: Sample chromatogram for dissolution of 20 mg nifedipine brand E at 6hrs

Sample Name: E-6 HRS

Acq. Operator : CHRISTINA OSEI-ASARE Seq. Line : 1
Acq. Instrument : ERNEST CHEMISTS Location : Vial 1
Injection Date : 3/23/2013 12:17:32 PM Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed : 3/13/2013 7:47:02 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M

Mobile Phase::::: Acetonitrile and water (70:30)
Flowrate::::: 1.5ml/min
Wavelength::::: 350nm
Temp.....40 deg C
Agilent Prep C18 Scalar 4.00mm x 125mm



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=350 nm

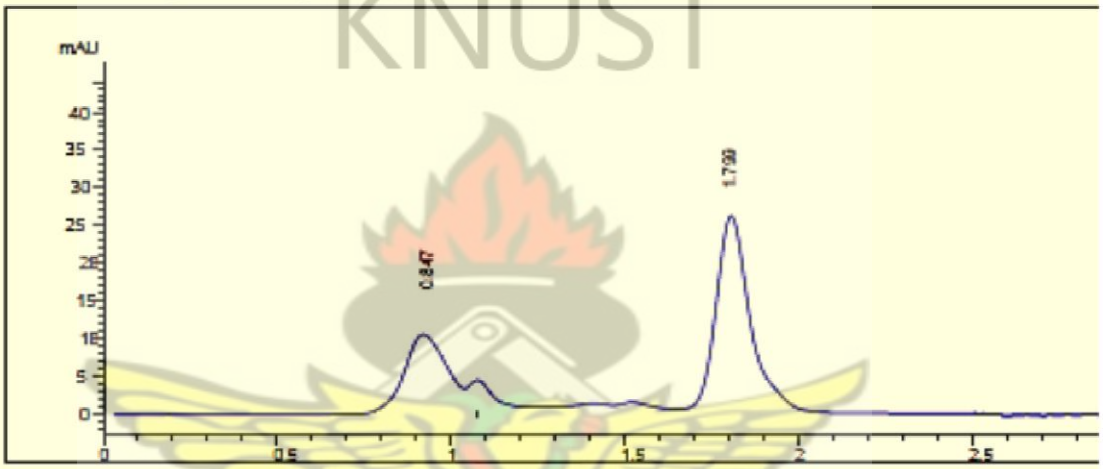
RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
0.847	-	83.0211	10.5626	0.63	0.58274	281	-	-
1.782	-	149.5812	18.1390	0.58	0.42123	2647	5.01	2.13

*** End of Report ***

Figure H: Sample chromatogram for dissolution of 20 mg nifedipine brand E at 6hrs

Sample Name: E-12 HRS

Acq. Operator : CHRISTINA OSEI-ASARE Seq. Line : 1
Acq. Instrument : ERNEST CHEMISTS Location : Vial 1
Injection Date : 3/23/2013 5:17:32 PM Inj : 1
Inj Volume : 25 µl
Acq. Method : C:\Chem32\1\DATA\NIFEDIPINE 2013-03-14 07-01-08\NIFEDIPINE.M
Last changed : 3/13/2013 7:47:02 PM by CHRISTINA OSEI-ASARE
Analysis Method : C:\CHEM32\1\METHODS\NIFEDIPINE.M
Mobile Phase::::: Acetonitrile and water (70:30)
Flowrate::::: 1.5ml/min
Wavelength::::: 350nm
Temp.....40 deg C
Agilent Prep C18 Scalar 4.00mm x 125mm



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=350 nm

RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
0.847	-	128.4911	16.2226	0.63	0.58274	281	-	-
1.782	-	230.4301	27.9790	0.58	0.42123	2647	5.01	2.13

*** End of Report ***