INTRODUCTION

Oral route of drug administration is the most important and widely used method of administering drugs for systemic effects, solid oral dosage forms represent the preferred class of product [Lachman et al 1990]. The pharmaceutical industry and the medical profession are today prepared to accept, and to introduce controlled-release drug dosage form through oral administration. Although significant advances have been made in controlled drug delivery the application of controlled release technology to oral administration has been limited. [Langer and Wise, 1984a; Langer and Wise, 1984b; Robinson and Lee, 1987] This is mainly due to the fact that the extent of drug absorption from the gastrointestinal tract is determined by the GI transit time of the dosage irrespective of the controlled release properties of the device.

The transit time in the small intestine ranged from 3 to 4 h under both fasted and fed conditions [Davies et al., 1987; Khosla et al., 1989]. Thus the time for absorption from the GI tract is limited for most drugs.

The frequency of administration or the dosing interval of any drug depends on its half-life [Ansel et al., 2000]. In most cases the dosing interval is shorter than or equal to half-life of the drug resulting in following limitations with such a conventional dosage form:

Conceptually, an ideal drug delivery system should fulfil two prerequisites: The first is to deliver the drug at a rate dictated by the needs of the body over the period of treatment, and the second is spatial targeting to specific site(s) [Chien et al, 1990]. These prerequisites provide a need for controlled-release technologies that can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. Furthermore, the possibility of re-patenting successful drugs, coupled with the increasing expense in bringing new drug entities to market, has been instrumental in generating interest in platform controlled-release drug delivery systems (CRDDS).

Dipyridamole and Carvedilol Phosphate are drugs belonging to the class of cardiovascular drugs used in treatment of various disease conditions. For an effective therapy for these chronic indications, drugs have to be delivered at a constant or modified rate with minimal fluctuations in the plasma concentration for longer duration. Various technologies can be
developed to achieve this; focus of this research work is to develop a platform drug delivery technology for delivery of drugs having pH dependant solubility.

An attempt of developing a novel formulation drug delivery technique shall be done by using Dipyridamole as a model drug from cardiovascular category and the application of this technology with suitable modifications shall be tested for carvedilol phosphate to confirm the delivery mechanism for the formulation.

The market for oral controlled drug delivery alone is expected to grow at 9% or more every year through 2007 [Nandita and Sudeep et al, 2003]

**Oral Controlled Release systems vs. conventional systems**

Over the years there has been an enormous amount of work put into designing drug delivery systems that can eliminate or reduce the fluctuating plasma concentrations seen after conventional drug delivery systems are administered to a patient according to a specified dosage regimen.

One of the first commercially available products to provide controlled release of a drug was Dexedrine Spansules®, made by Smith Kline & French in 1952. After this many more controlled release systems came to the market, some successful, others potentially lethal. A variety of terms were used to describe these systems:

*Delayed release dosage form* indicates that the drug is not being released in the acidic environment and will get released in the basic environment in the GIT. e.g. enteric coated tablets.

*Repeat action dosage form* indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

*Prolonged release dosage form* indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

*Sustained release* indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.
Extended release (ER) dosage form release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 24 hours).

Controlled release (CR) dosage form release drug at a constant rate and provide plasma concentrations that remain invariant with time.

Modified release (MR) dosage form is defined by USP as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms, whereas an extended-release (ER) dosage form allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance. It is interesting to note that the USP considers that the terms controlled release; prolonged release and sustained release are interchangeable with extended release [John Colet and Chris et al, 2002].

Oral CRDDS have many advantages over traditional, immediate release products.

![Figure 1](image)

**Figure 1:** Hypothetical drug concentration profiles in the systemic circulation resulting from the consecutive administration of multiple doses of an immediate release drug delivery system (A1, A2,) compared to the ideal drug concentration profile (B) required for the treatment

The advantages of a controlled delivery system over a conventional system are: [Anaoui and Vergnaud, 2000; Devane, 2003; Nandita and Sudip, 2003]

**Improved therapeutic efficacy** - Reduction in drug plasma level fluctuations; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug. Also having a chance of increased bioavailability.
**Reduced side effects** - Drug plasma levels are maintained and improvement in tolerability within a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms. This greatly reduces the possibility of side effects.

**Patient comfort and compliance** - Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

**Reduced health care cost** - The total cost of therapy of the controlled release product could be comparable or lower than the immediate-release product. With reduction in side effects, the overall expense in disease management also would be reduced.

**Limitations of Oral CRDDS**

On the other hand oral CRDDS suffer from a number of potential disadvantages:

- **Dose dumping**
- Reduced potential for dose change or withdrawal in the event of toxicity
- Loss of effect due to diarrhoea (too fast transit time)
- Not suitable for drugs having instability in the GI environment

**FDA regulation of Oral CRDDS**

In the 1980s, FDA introduced rigorous regulations governing bioequivalence and in vitro–in vivo correlations for controlled-release products. Required Pharmacokinetic evaluations involve: relative bioavailability following single dose; relative bioavailability following multiple doses; effect of food; dose proportionality unit dosage strength proportionality; single-dose bioequivalence study (at various strengths) ;in vivo–in vitro correlation ;pharmacokinetic/pharmacodynamic (PK/PD) relationship. [Nandita and Sudeep, 2003]

The concept of developing a non infringing formulation technology consisting of a Solubliser in the core coated with rate modulating polymers in such a way that the product meets the desired attributes, this concept is based on pelletization technique in which the drug is layered on the pellets. These pellets are coated with polymeric coating systems in such a way that it will ensure release of active from the formulation. Hence it’s imperative to understand the basic of Wurster technology. The following literature review will help in understanding the
concept, providing direction in development and optimisation of the pellet drug delivery system.

AIR SUSPENSION COATING

In 1959, Dr. Dale Wurster, then at the University of Wisconsin, introduced an air suspension technique known as Wurster System [Wurster et al., 1959]. Originally designed to coat tablets, the process is widely used for substrates as small as 100 microns. The technique is principally enumerated in below figure No.1 [Jones et al. 1988] enumerates the major components of the Wurster technology.

![Wurster bottom spry technique diagram](image)

*Fig. 2 Wurster bottom spry technique*

[Jones et al. 1988] enumerates in his article that in pharmaceutical dosage form development, many products require coating to provide the desired release characteristic. Recent advances in film coating equipment have made it possible to coat particles ranging from crystals to tablets reproducibly. Films may be applied to provide sustained, controlled release, delayed release, improved stability; Application of film to a solid is indeed complex. A layer of coating doesn’t occur in single pass through the coating zone, but relies on many of such passes to produce complete coverage of the surface. Droplet formation, contact, spreading, coalescence, and evaporation as shown below in fig. are occurring almost simultaneously during the process.
Process variables, product variables have significant impact on development of robust reproducible formulation; hence a interaction of each variable and its impact on the product performance is critical for understanding

[Jones & Mehta et al 1985] have explained in their research article that Pellets are coated with rate controlling polymers to modify the release of active, the process and composition used to coat the polymers have significant impact on the desired release such as film porosity, film adhesion and permeation of film, the investigation of film properties can effectively be done using SEM scanning electron microscopy, because morphology of the film coating plays significant role in release of drug from pellets, SEM evaluation can provide important direction on process parameters and direction to control the release

[Mehta, Valazza, Abele et al 1986] have explained that Top spray, bottom spray & tangential spray coating system are possible for enteric coating. Bottom spray and tangential spray systems are better for non aqueous system, while top spray is better for aqueous system. Hence its critical based on type of coating dispersion selection of type of process shall be done, critically aqueous enteric coating shall be done in Wurster

Essentially there are 4 different mechanism of controlled drug delivery 1) diffusion / and or dissolution control 2) Ion exchange 3) repeat action and 4) osmotic pressure. Each method has advantages and disadvantages. The physicochemical and pharmacokinetic properties of the particular drug, the volume to be administered and the economic, marketing, patent situations may dictate the method to be used. Products based on diffusion and or dissolution control

[Jones et al 1985] have identified critical factors in fluid bed processing as size, shape, porosity, & friability of the particles. He also exemplified critical factors as friability, bulk
density, and moisture content of starting core being critical. He enumerates that in Wurster nozzle is immersed in the air flow in order to spray concurrently into fluidised particles, the solution droplets travel only a small distance before they contact substrate. Spray rate and required fluidising air volume is critical to consider for scale up.

[Mehta et al 1988] enumerates that Process variable should be optimised in the scale up of fluid bed processes. Such variables include the spray rate, atomisation air, inlet air, air volume, batch size, type of equipment because these parameters can easily alter the end product performance. In addition to method of spraying almost 20 other variable are involved in fluid bed coating process for controlled release products.

[Hall et al 2004] indicate in his article that the Wurster Process (fluid bed coating) is widely used and has become a primary method for the microencapsulating of particles. The original patents were filed in 1953 and, over time, the process has evolved into one of the most adaptable means of coating small particles.

Scale up is a critical factor in any development to take product from small scale development to commercial scale level, as work targeted for this development is directed for USFDA / MHRA submission, it is expected to develop an understanding on scale up, carry out required scale up of the formulations and support product filing at USFDA/MHRA. Below information provides insight on scale up factors of Wurster technology.

It is recognised that scaling up from a one-litre chamber size to a 90-litre chamber size using a single nozzle is fairly easy and predictable. A single nozzle distributes the coating material efficiently to the particles, as evidenced by the proportional relationship between plate area, air volume and spray rate observed routinely up to a coating chamber diameter of 18” to 19” (46cm to 49cm). The primary factors over this range are nozzle function and plate design.

As process scale is increased using a single nozzle, it is essential that the nozzle used is capable of atomising the coating formulation efficiently, even as the rate of liquid delivery increases. At the smaller scale, liquid flow rates are modest, perhaps 5g/min to 20g/min, and many commercially available nozzles work well. As the scale and flow rates increase, the nozzle must still atomise effectively. At higher flow rates (300g/min to 800g/min), only a few well-designed nozzles are capable of delivering a uniformly atomised mist of small droplet size (10µ to 30µ).
Nozzle delivering 500gr/min of coating has a median droplet size of 15µ (80psi) and will include droplets as large as 35µ. Reducing the spray rate to 300gr/min with the same nozzle will reduce the median only to 13µ, but will reduce the maximum to 26µ.

When air volume and spray rate are proportional, and base plate, chamber design and air balance are designed correctly and under control, scale-up from single to multiple nozzle units is quite simple. Load size, plate area, air volume, number of nozzles and total spray rate are all a direct multiple of the parameters developed in a single nozzle unit. Such a unit is equivalent to (n) single nozzle coating units operating side by side.

[Christensen & Bertelsen et.al 1997] exemplifies that the coating process consists of three major phases start up phase, coating phase and drying/cooling phase. The typical coating cycle is of 50-60 sec even for 200 L Wurster. Key factors are substrate, coating solution, fluidization air volume, spray rate & atomisation, Wurster has well defined product movement in the coating zone. The up bade fluid velocity should be above minimum slugging velocity but not so high as to cause attrition to the product in question. Expansion chamber and down bed velocity should be below minimum fluidization velocity.

Spray rate should be adjusted to drying capacity, product movement, droplet in the mist should have sufficient slow drying of coating solution before hitting the substrate to secure proper film formation and avoid spray drying.


[Costa, Sousa & Formosinho et al 2003] indicates that In vitro dissolution has been recognized for the past four decades as an important element both in drug development and
quality assessment especially in controlled release formulations. Release and further dissolution of the drug from the solid dosage forms often constitute a determining step in the in vivo absorption process and is thus used in conjunction with in vivo / in vitro correlations to establish quality control parameters. Couple of drugs are being formulated as platform drug delivery technologies such as chronotherapeutic, where drug delivery is based on time of disease occurrence this concept is well reviewed by [Shan Lin & Yoshiaki K et al 2011]. The aim of my research also is focused on development of platform drug delivery in which drugs from cardiovascular category can be incorporated to achieve desired drug release pattern

[Shan Lin & Yoshiaki K et al 2011] During the past several decades, conventional drug dosage forms have been widely used for treatment of various conditions. These drug dosage forms typically provide an immediate or rapid medication release, and supply a given concentration or quantity of the drug to the body's systemic circulatory system without any rate control. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, frequency of administration and patient compliance of these conventional drug preparations, many traditional drug dosage forms are undergoing replacement by second-generation, modified drug-release dosage forms. Treatments of numerous diseases using traditional drug products are often inconvenient and impractical if disease symptoms occur during the night or early morning. During the early 1990s, second-generation modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration “peak and valley” levels in the blood, so promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second-generation modified-release dosage forms include slowed-release, delayed-release, prolonged-release extended-release, repeated-release, sustained-release, and controlled-release drug preparations [shargel et al 2005] & [Allen, Popovich, Ansel et al 2010]. Several controlled-release preparations present numerous problems such as resistance and drug tolerance, and activation of the physiological system due to long-term constant drug concentrations in the blood and tissues. The idea of chrono controlled is to have maximum therapeutic concentration of the drug in specific hours/ time when disease condition is at critical stage or at accelerated stage as depicted below
Fig. 4 Chronotherapeutic disease modulation

As these systems are time controlled following drug delivery systems can be utilised to achieve the desired drug release.

Fig. 5 Schematic presentation of time-controlled release technologies

Following picture [Litinski, Scheer & Shea et al. 2009] depicts the disease condition and its severity at specific time and as it comes cyclic at specific time interval, it’s ideal to have drug release specific at that time to have better control on the disease.

Fig. 6 Influence of circadian system on disease

Following picture [S. Ohdo et al. 2010] depicts the 24 hr cycle and probability of disease attack; this can be used to develop a technology to deliver the drug at specific time interval or
target hours depending upon disease, e.g. most of cardiovascular disease have occurrence or severity at night time, hence a formulation can be designed to achieve required extent of release in night time using specific controlled release or delayed release with specific lag time

Fig7. 24 hr cycle and probability of disease attack

The number of poorly soluble drug candidates has risen sharply over the last two decades due to the developments in identification strategies (Amidon et al., 1995). The selected drug molecules are from BCS class II and would require detail understanding on the invitro dissolution, selection of type of polymers / solublisers to control and modulate the release accordingly, hence following detail research on related topics was carried out and is being captured below for information. [Ulrich, Florian, Wagner et al, 2010] indicated in their research article that the conventional dissolution testing of MR formulations of pH dependent poorly soluble drugs revealed limited in vivo predictability. For a comprehensive characterization of in vitro drug release, the Implementation of a pH-gradient turned out to be crucial. By the combination of a pH-gradient simulating physiological pH along the GI tract and a distribution step to maintain sink conditions in the dissolution medium, the pH-adjusted biphasic dissolution model enabled an improved characterization of MR formulations of different technologies. [Muschert, Siepmann Siepmann et al 2009] studied drug release from ethyl cellulose: PVA-PEG graft copolymer coated pellets is primarily controlled by diffusion through the intact polymeric membranes, irrespective of the type of starter core and type of release medium. Appropriate analytical solutions of Fick's law can be used to quantitatively predict the resulting drug release kinetics as a function of the major formulation parameters. Importantly, the apparent diffusion coefficients determined with thin free films can be used to predict drug
release from coated pellets. Thus, the optimization of this type of controlled drug delivery systems can be significantly facilitated.

Cupkoko et al. 2011 have exemplified in his article that Polymeric film coatings are highly suitable to control drug release from pharmaceutical dosage forms (Ghebre-Sellassie, 1994; McGinity and Felton, 2008). Several types of polymers used for this purpose are commercially available and well known, e.g. Eudragit L (methacrylic acid copolymer), Eudragit RS (acrylate: methacrylate copolymer), Kollicoat SR (polyvinyl acetate), Aquacoat ECD (an aqueous dispersion of ethyl cellulose). In order to adjust a specific, desired drug release profile for a given application, different formulation parameters can be varied, including the coating level as well as the addition of varying amounts and types of plasticizers (Frohoff-Huelsmann et al., 1999; Struebing et al., 2007; Ye et al., 2007; Ho et al., 2009). However, too thin or too thick, too brittle or too sticky film coatings must be avoided. Thus, it is eventually highly challenging to provide a specific release profile for a given drug and drug dose. The synthesis of novel types of polymers exhibiting new properties (e.g., a specific permeability for a given drug) might help overcoming this restriction. However, in these cases time- and cost-intensive studies are required, including toxicity tests. An interesting alternative option is to use blends of different types of well-known polymers: by simply varying the polymer: polymer blend ratio very different film coating properties can eventually be obtained, allowing to provide broad spectra of drug release patterns (Amighi and Moes, 1995; Lecomte et al., 2003; Siepmann et al., 2008; Ensslin et al., 2008, 2009a). However, yet relatively little is known on how these systems work and the underlying drug release mechanisms are still poorly understood for many of these more complex film coatings (Siepmann and Siepmann, 2008; Ensslin et al., 2009b). [Siahboomi et al 2000] have explained the benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability.

The United States Pharmacopoeia definition of an MR system is that: “the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms...”

This includes technologies that modify the site of drug delivery. The successful formulation of an MR device requires the successful formulation of an MR device requires a
comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions. Multiparticulate dosage forms have been shown to be less prone to food effects than monolithic forms and are often the preferred formulation for extended and/or delayed release. Film coating is an ideal process for the production of extended release multiparticulate dosage forms. For application in extended release delivery systems, film coats with well-characterised permeability properties are essential. Ethyl cellulose is the most widely used water insoluble polymer in extended release coating applications. The advantageous properties of this polymer are that it is tasteless, odourless and has the ability to form tough, flexible coatings.

K. Srinath Reddy and Salim Yusuf et al; 1998 Cardiovascular disease (CVD) is the leading cause of death worldwide and in most countries outside sub-Saharan Africa. The root causes of this modern epidemic are sedentary stressful urban lifestyles and high-calorie diets rich in saturated fats, salt, and simple sugars. Although the mortality from CVD has long peaked in most developed countries, its prevalence continues to rise because of improved survival and aging of the populations, placing tremendous strains on health care financing in some of these countries. In most Asian and Middle Eastern countries, outside East Asia, prevalence of CVD and its risk factors are high and still rising, while the rising mortality is among the highest in the world. As the predominantly young populations of these countries age, they face inadequate health care systems without assured financial coverage. Effective measures are therefore urgently needed to combat the epidemic of CVD. Comprehensive preventive measures are essential to curb the spread of this epidemic, while health care systems should be structured on the basis of locally derived data to provide adequate affordable care to the ever increasing pools of patients with CVD.

Advanced drug delivery technologies can improve a product's clinical and commercial value, differentiate a product, and serve as an effective resource to outdo competitors. Clinically, they improve the pharmacoeconomics of drugs by reducing adverse effects, identifying new indications, and improving therapy, safety, efficacy, convenience, and compliance. Drug delivery technologies make medicines more convenient and acceptable to patients by simplifying the dosing regimen and improving administration. These improvements, in turn, bolster compliance, which helps improve patient outcomes and quality of life and reduce costs. By reducing dosing frequency, these improved medications reduce the frequency of
caregiver interactions. Fewer visits from doctors and nurses save administration costs and time and reduce inconvenience for patients and caregivers.

With medications for chronic diseases that display time-dependent symptoms, such as ulcers or asthma, drug delivery systems can control the formulation release according to the timing of symptoms. For example, they can enable a drug to release when asthma attacks occur, generally in the middle of the night. This chronotherapeutic technology can provide valuable and clinically proven therapeutic benefits and another means for marketers to differentiate their product. Commercially, delivery technologies give new life to drugs, repositioning them with a new or improved therapeutic benefit and a competitive edge. By extending the product's life cycle with a line extension, they sustain the drug's market value. Using drug delivery systems to extend product life cycle a) To give a product a competitive edge b) To enable or accelerate market entry c) Novel drug delivery systems can protect or prolong a product's patent exclusivity d) develop an improved product.

Against this background, pharmaceutical companies are recognizing that drug delivery technologies are a powerful strategic marketing tool to differentiate products and extend product life cycles, thereby overcoming many marketplace challenges. They are pursuing stronger alliances with drug delivery companies, including acquisitions, to enable them to develop superior drugs and remain competitive. The market for advanced drug delivery systems is expected to mushroom from $16.28 billion in 2000 (according to a report from Business Communications Company) to $27.35 billion in 2005-2010

The application of drug delivery is a valuable, cost-effective life-cycle management resource. By infusing drugs with new and innovative therapeutic benefits, drug delivery systems extend products' profitable life cycle, giving pharmaceutical companies competitive and financial advantages and providing patients with improved medications.

The cardiovascular market, historically one of the mainstays of the pharmaceutical industry, is set to be hit by a 'patent cliff', with six of the current top 10 brands due to lose protection between 2010 and 2013. Due to lack of new molecules there is a scope for extension of product life cycle by introducing new better formulations of existing molecules. Hence it is an intention of this research to hold on the opportunity to address the clinical need in area of cardiovascular diseases by tapping potentially good drug molecules for their benefits in respective disease conditions by providing novel controlled release formulations.
Many cardiovascular diseases now have an array of generic drugs that provide effective treatment without the need to resort to expensive branded products. This provides a major challenge to pharmaceutical companies as any new drug must be able to demonstrate significant clinical benefit to meet the cost effectiveness criteria determined by healthcare providers. As a consequence, future blockbusters will not be of the same scale as the current crop. When selecting drug candidates for the application of drug delivery technologies, the following factors should be considered:

**Clinical:** Identify clearly defined unmet medical needs. Choose therapeutically relevant products that can be altered by drug delivery technology to provide significant clinical advantages, such as reduced side effects, improved efficacy, or delivery of the active based on circadian rhythm.

**Technical:** Weigh the ease of achieving the clinical end-point, the ease of formulation, and the cost of negative evidence against the magnitude of the clinical benefit.

**Commercial:** Consider peak year sales, development costs, and the competitive dynamics. Will the enhanced product have a significantly distinctive benefit over products of current or anticipated competitors? Will the product yield maximum return on investment?

Abhinav Goyal & Salim Yusuf; et al. 2006 Ischemic heart disease and stroke are the two most common causes of death worldwide. Over 80 per cent of deaths and 85 per cent of disability from cardiovascular disease (CVD) occur in low- and middle-income countries. The Indian subcontinent (including India, Pakistan, Bangladesh, Sri Lanka, and Nepal) is home to 20 per cent of the world’s population and may be one of the regions with the highest burden of CVD in the world. Although studies have documented that immigrant from the Indian subcontinent (South Asians) living in Western countries has a higher burden of cardiovascular disease than other ethnicities.

**The estimated burden of CVD the Indian subcontinent**

The absence of reliable mortality data in the Indian subcontinent has necessitated estimates of the CVD burden based on cross-sectional studies that have been well described previously. In 2003, the prevalence of CHD in India was estimated to be 3-4 per cent in rural areas (two-fold higher compared with 40 yr ago), and 8-10 per cent in urban areas (six-fold higher compared with 40 yr ago), with a total of 29.8 million affected (14.1 million in urban areas, and 15.7
According to population-based cross-sectional surveys, there are approximately 31.8 million individuals affected by CHD in rural areas. This estimate is comparable to the figure of 31.8 million derived from the Global Burden of Diseases study, which extrapolates data. These numbers are likely underestimates as they do not account for those with silent myocardial infarction or otherwise asymptomatic CHD. In 1990, there were an estimated 1.17 million deaths from CHD in India, and this number is expected to almost double to 2.03 million by 2010. In addition to the high rate of CHD mortality in the Indian subcontinent, CHD manifests almost 10 years earlier on average in this region compared with the rest of the world, resulting in a substantial number of CHD deaths occurring in the working age group. In Western countries where CVD is considered a disease of the aged, 23 per cent of CVD deaths occur below the age of 70; this compares with 52 per cent of CVD deaths occurring among people under 70 years of age in India. As a result, the Indian subcontinent suffers from a tremendous loss of productive working years due to CVD deaths: an estimated 9.2 million productive years of life were lost in India in 2000, with an expected increase to 17.9 million years in 2030 (almost ten times the projected loss of productive life in the United States). The health and economic implications of this staggering rise in early CVD deaths in South Asian countries are profound and warrant prompt attention from governing bodies and policy makers.

It is the intention of this research proposal to satisfy the unmet need of the cardiovascular disease area to provide better patient compliance by selecting molecules which have significant effect. Cardiovascular disease area is a vast area encompassing numerous diseases. In this research proposal, I have selected the major area to focus on, which is treatment of Stroke/Myocardial Infarction / Angina Pectoris (Ant-platelet aggregating agents). From the vast area of research work, this project is focused on development of generic cost effective modified release formulation of Dipyridamole by non-infringing formulation technique.