CHAPTER I

INTRODUCTION
A century ago, pioneer women gathered and dried herbs for ‘doctoring’; a housewife zealously guarded her bag of herbs when her family moved west. Bonset tea reduced fevers, peppermint relieved an aching tooth or a colicky baby and foxglove revived a falling heart. Even, 50 years ago, drug materials were derived only from natural products, such as menthol from peppermint for treating coughs and colds. More recently chemical research on the isolation, identification and synthesis of the drugs has yielded many important drug substances which are both effective and specific. Until World War I, most synthetic drugs and chemicals used in US were discovered and produced in Europe. Discovery and development of sulphonamides, antibiotics and other antiinfective agents dramatically reduced the death rate from a number of infectious diseases. Compounds that control pain are illustrative. The development of reliable oral contraceptive therapy has made intelligent family planning possible. Tranquillizers and other drugs acting on central nervous system have made an important contribution to patients for their normal activities. Diuretics and drugs which alleviate arthritis also have improved the quality of life. Similarly antihypertension and hypotensive drugs play an important role in the treatment of cardiac diseases. Therefore, it can be said that since World War II and in the decades following the war, especially in the last four or five decades, the contribution of drug therapy by antibiotics, anti infective agents, steroids, psychotherapeutic agents, important cardiovascular agents, antineoplastic agents, many new immunizing and biotechnological agents increased the quality and expectancy of life.

Although drugs were dispensed as such in powder papers as recently as several decades ago, this practice is virtually unknown in today pharmacy practice. With possible exception of the anesthetic gases, all drugs in legitimate commerce are now presented to the patients as drug products. It is now well recognized that the therapeutic efficacy and therapeutic index [ratio of LD$_{50}$ (lethal dose in 50% of the subjects) to ED$_{50}$ (effective dose in 50% of the subjects)] of a drug product is not totally defined by the chemical constituent of the drug and its inherent pharmacokinetic profile. The actual performance of many drugs in clinical practice is now known to be greatly affected by the method of presentation of the drug to the patients. Factors affecting the presentation include:
• The portal of drug entry in the body
• The physical form of drug product
• The design and formation of the product
• The method of manufacture of the drug product
• Various physical properties of the drugs and excipients
• Physicochemical properties of the drug product
• Control and maintenance of the location of the drug product at the absorption site(s)
• Control of the release rate of the drug from the drug product

Until late 1940s, tablet, capsule and liquid were the major classes of dosage forms for drug delivery. In the late 1940s and early 1950s, sustained release products appeared as a new class of pharmaceutical product in which product design was intended to modify and improve drug performance by increasing the drug action and reducing the frequency of dosing. In the middle-to late-1960s, the term ‘Controlled drug delivery’ emerged to describe a new concept of dosage form design, but with additional or alternative objective to sustain drug action. The controlled release dosage forms cover a wide range of prolonged action preparations that provide continued release of active ingredients at a predetermined rate, and for a specific period of time. This mode of administration also has certain features that have an important impact on the pharmacological response.

The vast majority of traditional dosage forms can be described as a dump system which deliver their active ingredients in a first-order fashion that is, release occurs at rates that are highest initially and thereafter decline steadily requiring subsequent dosing. Frequent administration gives effective therapeutic level. Clinically, this peak and valley pattern results in a time-dependent mix therapy. Drugs’ side effects tend to predominate at high peak concentration in the blood, whereas an inadequate therapeutic effect may prevail at the valley level (Anon 1985: Madan 1985: Banker 1984: Fara 1983). Use of sustained release systems provides an excellent tool to achieve precise control of the drug release mechanism, not only from a rate standpoint, but also at a particular site. The constant rate of release can optimize drug therapy by cutting blood level spikes and guarding against reaching an unreliable low drug concentration. This is extremely
beneficial for drugs with low therapeutic index, such as theophylline, where blood levels must remain within a narrow range in order to protect asthma patients from attacks, and to prevent toxic side effects.

Aside from the biological benefits incurred from prolonged and predictable drug levels, sustained release systems can allow for significant reduction in the frequency of drug administration and better patient compliance. This is important in developing pharmaceutical market where the main system of drug therapy is shifting from short term use for traditional acute disease to long term use necessary for current, more predominant chronic ailments such as hypertension, arthritis, asthma and diabetes. Several studies indicated that the most common reasons for noncompliance are patient confusion and forgetfulness, inconvenient dosage frequency and symptoms improvement. An inverse relationship was found between the number of dosages per day and compliance rate. When one or two doses were required daily, patients were less forgetful and complied with the dosage regimen more consistently.

There are also good commercial reasons for the increasing trend toward sustained release systems. In the next few years, drug patents on the majority of today’s most used drugs will expire. Formulation of these drugs in the sustained release system is one means to extend the proprietary protection against generic products, particularly if the sustained release drug delivery is patented.

Historically, the oral route of administration has been preferred for both the conventional and novel drug delivery system. There are more obvious reasons for this, not the least of which would include acceptance by the patient, ease of administration, greater flexibility in dosage design as constraints, such as sterility and potential damage at the site of administration, are minimized. The potential advantages of sustained release have been enumerated as follows:

- Minimize or eliminate systemic side effects
- Minimize or eliminate local side effects
- Reduce fluctuation of drug levels
- Improve bioavailability of some drugs
- Minimize the drug accumulation with chronic dosing
- Obtain less potentiation or reduction in drug activity with chronic use
• Improve efficiency of treatment
• Cure or control the conditions more promptly
• Avoid patient compliance problems
• Employ less total drug
• Economy

Specific attributes of drug candidates for sustained release system

(A) Biological properties:

(i) Elimination and biological half-life:

The usual goal of an oral sustained release product is to maintain the therapeutic blood levels over an extended period. To achieve this, drugs must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitively described by half life ($t_{1/2}$) of the drug. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all other processes that permanently remove drug. Therapeutic compounds with short half lives are excellent for sustained release preparation. Since this can reduce dosing frequency. However, too short half lives are ineligible for sustained release as the drugs may require excessively large amount of drug in each dosage unit to maintain the sustained effect, forcing the dosage form itself to become limitingly large. In general, drugs with half lives shorter than two hours such as furosemide or levodopa (Lee and Robinson 1978), are poor candidates for sustained release preparations. Drugs with half lives more than 8 hours are also generally not used in sustained release forms, since this type of drugs have inherent sustained profiles. Digoxin, warfarin and phenytoin are examples of few of such drugs (Lee and Robinson 1978). Furthermore, transit time of most dosage forms in the G.I. tract (ie mouth to eileocecal) is 8 to 12 hours. This makes difficult to increase the absorptive phase of administration beyond the time frame. Occasionally absorption from the colon may allow continued drug delivery for upto 24 hours.

(ii) Absorption: The characteristics of absorption of a drug can greatly affect its suitability as sustained release product. Since the purpose of forming sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs
and devices in the absorptive areas of G.I. tract is about 8 to 12 hours, the maximum half life for absorption should be approximately 3 to 4 hours; otherwise the device will pass out of the potential absorptive region before drug release is completed. Therefore, compounds those demonstrate true lower absorption rate constants will probably be poor candidates for sustaining systems. If a drug is absorbed by active transport or facilitated transport is limited to a specific region of the intestine, sustained release preparations may be disadvantageous.

(iii) Distribution: The apparent volume of distribution, a proportionality constant which relates the drug concentration in the blood or plasma to the total amount of drug in the body is an important factor for the distribution of a drug into vascular and extra vascular spaces in the body and hence plays an important role in its overall elimination kinetics. This, in turn, influences the formulation of that drug into a sustained system, primarily by restricting the magnitude of the release rate and dose size which can be employed (Reigelman et al., 1968).

(iv) Metabolism: Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine can show decreased bioavailability from the slower-releasing dosage forms. Most enzyme systems of intestinal wall are saturable. As the drug is released at a slower rate to these regions, lesser amount of drug is presented to the enzymatic process during a specific period allowing more complete conversion of the drug to its metabolite.

(v) Side effects and safety consideration: The most widely used measure of the margin of safety of a drug is its therapeutic index, TI. Which is equal to

$$\frac{TD_{50}}{ED_{50}}$$

where, TD$_{50}$ is the median toxic dose and ED$_{50}$ is the median effective dose. For very “potent” drugs, whose therapeutic concentration range is narrow, the values of TI are small. In general, the larger the value of TI, the safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into sustained products primarily due to technological limitation of precise control over release rates.
(B) Physiochemical Factors:

(i) Dose size: For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.09 is considered maximal for a conventional dosage form (Eriksen 1970). Since a sustained release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional dosage form. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable, depending on route of administration.

(ii) Ionization, pKa and Aqueous solubility: Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation which under sink conditions, is

$$\frac{dc}{dt} = K_D A C_S$$

where $dc/dt$ is the dissolution rate, $K_D$ is the dissolution rate constant, $A$ is the total surface area of the drug particles and $C_S$ is the aqueous saturation solubility of the drug. The initial rate is proportional directly to aqueous solubility $C_S$ when $A$ is constant. Therefore, aqueous solubility of a drug can be used as a first approximation of the dissolution rate. In general, extremes in the aqueous solubility of a drug are undesirable for formulation into a sustained release product. A drug with a low solubility and a slow dissolution rate will exhibit dissolution limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into a sustained release system is redundant.

For weak acids,

$$S_t = S_0 (1 + Ka [H^+]) = S_0 (1 + 10^{pH-pKa})$$

where $S_t$ is the total solubility (both the ionized and unionized forms) of weak acid and base, $S_0$ is the solubility of the unionized form, Ka is the acid dissociation constant and $[H^+]$ is the hydrogen ion concentration of the medium. Equation 1 predicts that the total solubility, $S_0$ of a weak acid with a given pka can be affected by the pH of the medium.

For weak bases,

$$S_t = S_0 (1 + [H^+]/ Ka) = S_0 (1 + 10^{pKa - pH})$$

where $S_t$ is the total solubility (both conjugate acid and free base forms) of weak base, $S_0$ is the solubility free base form, Ka is the acid dissociation constant of the conjugate acid. Analogous to Eq. 1, Eq. 2 predicts that the total solubility, $S_0$ of a weak base whose
conjugate acid has a given pka can be affected by the pH of the medium. The pH-partition hypothesis simply states that the unionized form of a drug will be absorbed preferentially in a passive manner through membrane. The absorption of weakly acidic drugs will be favored in the stomach (pH = 1 to 2) in their unionized form and at the same site the absorption of weakly basic drug will be poor due to their ionized form (conjugate acid). In the upper portion of the small intestine, the pH is less acidic (pH = 5 to 7) and the reverse will be expected for weak acids and bases. The ratio of Eq. 1 and Eq. 2 written for either the pH of the gastric or intestine fluid or the pH of blood is indicative of the driving force for absorption based on pH gradient. Ideally the release of an ionizable drug from a sustained release system should be ‘programmed’ in accordance with the variation in pH of different segment of the gastrointestinal tract so that the amount of preferentially absorbed species, and thus the plasma level of drug will be approximately constant throughout the time course of drug action.

**(iii) Partition coefficient:** When a drug is administered to the G.I. tract it must cross a variety of biological membrane to produce a therapeutic effect affecting another area of the body. It is common to consider these membranes are lipid in nature, therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier permeation. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominately lipid soluble and, consequently, have very low aqueous solubility. Furthermore, these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. Phenothiaznes are representatives of this type of compound (Salzman and Brodie 1956). Similarly, compounds with very low partition coefficients will have difficulty in penetrating membranes, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion membranes must largely depends on the partitioning characteristics of the drug.

**(iv) Stability:** Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the G.I. tract are
beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propanthelin (Beerman et al., 1972) and probanthine (Bachrach, 1958) are representative examples of such drugs.

**Terminology**

Several terms have been utilized to describe the different types and mode of action intended to furnish long duration of drug activity. These can be described under the major categories as discussed below.

(i) **Delayed release preparation:** A drug which is released from a dosage form at later time after administration is known as delayed release formulation. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as formaldehyde treatment of soft and hard gelatin capsules. The purpose of such preparations are to prevent side effects related to the presence of drug in the stomach, to protect the drug from degradation in the high acidic pH of the gastric fluid or simply for patient comfort to avoid awaking during the night for drug administration.

(ii) **Repeat-Action preparation:** In such preparations, a dose of the drug is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparations, a third single dose is released after a certain time has elapsed, following the second dose. Again, delayed action is achieved by the presence of a special coating between the various layers of the dosage form. Although this type of preparations offer some kind of continued action therapy, it has the disadvantage that the blood levels still exhibit the “peak and valley” characteristics of conventional, intermittent drug therapy. The main advantage, however, is that it provides the convenience of supplying additional dose(s) without the need of readministration.

(iii) **Sustained-Release dosage forms:** These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time (usually between 8-12 hour). The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides levels
that are devoid of the peak and valley effect, characteristic of the conventional intermittent dosage regimen. Sustained-release products are probably the first long-acting dosage forms purposely designed to deliver the drug at different times of release.

(iv) Controlled-release formulations: Although this term has been interchanged widely with sustained release preparations in the past, recently it became customary to restrict the latter term to oral formulations where the mechanism of prolonged action is dependent and invariably sensitive to one or more of the environmental factors in the gastrointestinal tract such as pH, a specific enzyme or gastric motility. On the other hand, the term controlled release dosage forms, is usually restricted to the preparation that are designed for all routes of administration and where the mechanism of prolonged action is inherent and determined totally by the delivery system itself (Madan 1985; Anderson and Olanoff 1974). Consequently, this category offers the current state-of-art preparation where the drug release profile is controlled accurately and often can be targeted to a specific body site or a particular organ(s).

**Design of sustained release drug delivery system**

Because of the above limitations, until today, the residence time of sustained release dosage forms can’t be extended beyond 10-12 hour. Nonetheless, the oral route is the still most convenient and common mode of administration of sustained release systems. The following summarizes the major types of sustained release systems intended for oral use.

(1) Slow-Erosion core with loading dose:

The drug release starts by surface erosion from the intact tablet of drug and insoluble materials. Initial dose is given in outer shell or separate layer.

(2) Erosion core with loading dose:

Uniform release occurs by the erosion of core and there is no initial dose. So the device maintains its geometric shape practically intact during travel. Release rate is maintained almost constant as the surface area and drug solubility remain constant.

(3) Coated pellets:

This is a dissolution based system where the drug is incorporated into many nucli composed of the confectioner’s nonpareil (sugar) seeds in the 20-40 µ range and coated with slowly dissolving material like waxes (Khalil and EI Gamal, 1971), polymeric
substances (Fites et al., 1970) or a mixture of both (Khan et al., 1984). The rate of release is controlled by the thickness of coating layer along with its composition. Usually certain portion of the pellets is left uncoated to deliver an immediate dose, while the rest is subdivided into three or four groups. Each of which is covered with a specific number layers of the coating material. As the drug release rate is dependent on the coat thickness and because there is overlapping within each group, as well as between the different groups, the overall release pattern of drug from the dosage form approaches a steady level. Sustained release coated pellets preparations were probably the first purposefully designed long-acting preparations.

(4) Mixed-release granules:

This is another type of sustained release product containing granules in place of pellets. A part of granules are uncoated to give the desired immediate response of the drug. The rest of the granules are coated with a slowly dissolving waxy or polymeric substance, or mixed with solution-retarding additives. Usually different sets of granules are used to give a continuous sustained release pattern (Kssem et al., 1973).

(5) Mixed tablets:

In this preparation, the drug is suspended in an inert nondissolving polymer matrix, mixed with appropriate excipients and compressed into tablets. The release rate limiting process is the speed by which the drug leaches out by diffusion through the polymer and into the GIT fluids. The insoluble cell is excreted after it has delivered its drug content, usually still intact with little change in its geometrical shape. The drug delivery rate is independent of pH, GI motility or enzymatic actions, but largely can be influenced (Desai et al., 1965; Banita et al., 1984) by the type and concentration of the polymer, the compacting pressure (affects the matrix porosity) and the geometry of the pellet.

(6) Altered density microparticles:

Drugs can be coated on light empty shells with an apparent density lower than that of GIT fluid to provide sustained release effects. The product floats on the gastric juice for an extended time while slowly releasing the drug. Another system which utilizes an appropriate mechanism is based on the high density cores. An increase in density from 1.0 to 1.6 was reported to have increased the transit time in the GIT from 7-25h (density
of GIT fluid is about 1.4). This is because the subunits of the multiunit formulation are distributed throughout the GIT and their passage is not influenced significantly by the transit time of food (Bechgard and Ladefoged 1978).

(7) Osmotically controlled oral preparation (The OROS® system):

In this system, the drug which is compressed into a core tablet exits from a small orifice introduced in the membrane by a lesser beam. The mechanism of action is based on the principle of osmotic pressure which develops between the inside of the device and the outside GIT fluid. As these fluids reach the core, the drug dissolves and is then pumped out through the orifice by osmotic force. Therefore, the oral osmotic pump can provide a prolonged zero-order release characteristic.

(8) Ion exchange and complexation methods:

In this method the drug is bound with sulfonated cross-linked polystyrene resin of varying divinyl-benzene content. The resulting resin salt exchanges the drug for the ions, such as sodium and potassium, as it pass through the GIT. As the concentration of these ions is about constant in GIT it can be assumed that the release rate of the drug will be constant.

Similarly, complexation techniques also have been used to extend the release of drugs in the GIT. Amines drugs can be reacted with the tannic acid to form insoluble complexes that, when incorporated in tablets, exhibit a long acting release profiles.

(9) Microencapsulation:

This technology offered a system having a well defined core and a well defined envelop made of a continuous, porous or nonporous polymeric phase for entrapping solids, liquids or gases. The microcapsules can be prepared following different processes like coacervation, spray drying, phase separation, solvent evaporation etc.

Multi-unit microparticulate dosage forms have several advantages over single-unit sustained release tablets. They pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates (Beckett, 1980), spreads over a large area of absorbing mucosa preventing the exposure to high drug concentration (Davis et al., 1984) and release drugs in a more predictable manner (Follonier & Doelkar, 1992). Moreover, microparticles can be formulated as a liquid suspension allowing ease of swallowing and flexibility of dosing. Microencapsulation is one of the most intriguing fields in the area of
multi-unit microparticulate dosage forms. Among the various methods for the preparation of microcapsule or microsphere dosage forms of drugs, emulsion-solvent evaporation method appears to be more popular because of its simplicity, reproducibility and feasibility of tailoring the process parameters. The oil in oil emulsion-solvent evaporation method utilizes the emulsification of a polymer solution containing dissolved or dispersed drug in liquid paraffin or mineral oil. Continuous stirring of this emulsion allows the solvent from the dispersed droplets to diffuse out into the dispersion medium and to evaporate. After a suitable period of time, the microcapsules/microspheres are rigidized by washing with petroleum either or n-hexane. Several synthetic polymers like ethylcellulose (Sa et al., 1996; Lin and Wu 1999), polyvinylacetate (Sa, 1991), eudragits (Bentia et al., 1988; Kim et al., 2002) have been used to prepare microspheres of various drugs by this method. Although the entrapment efficiency of both water soluble and insoluble drugs in the resulting microspheres have been reported to be high, release of drugs having appreciable aqueous solubility is quit rapid. Moreover, this method requires large volume of organic solvents making the method uneconomical, and leads to the possibility of toxic effects due to the presence of even traces of organic solvent in the dosage form, explosion hazards and environmental pollution. With a view to eliminate the above hazards, the oil in oil emulsion solvent evaporation method has been modified. In the modified oil in water emulsion solvent evaporation method, a solution of polymer containing dissolved or dispersed drug is emulsified in water containing suitable stabilizer. The emulsion is agitated for sufficient time during which the organic solvent from the disperse phase diffuse out from the disperse droplets into the dispersion medium and evaporates. The resulting microcapsules are washed with sufficient water and dried. Several polymers like polystyrene (Tamilvanan and Sa 2000), polymethylmethacrylate (Sa et al., 1996), poly (d,l-lactide) (Benita et al.,1984), ethylcellulose(Yang et al., 2000) have been used to prepare microcapsules/ microspheres by this method. Although the use of organic solvents was minimized, but not eliminated, the method is unsuitable for water soluble drugs. Drugs having appreciable aqueous solubility are partitioned from the dispersed phase into the aqueous dispersion medium. This results in a considerable decrease in the drug content of the microspheres. Moreover, the release of drug could not be prolonged for sufficient period. In order to avoid the use of organic solvent
completely, considerable attention has been drawn towards the use of natural polymers for the formulation of microcapsules dosage forms. Sodium alginate appears to be a highly promising natural polymer in this regard. When an aqueous solution of sodium alginate containing dissolved or dispersed drug is dropped in aqueous solution containing divalent ions like Ca$^{+2}$ ion, water insoluble calcium alginate beads are formed instantaneously through ionotropic gelation between the alginate and Ca$^{+2}$ ions. This method is not only simple but also eliminates the use of organic solvents completely and the microcapsules are prepared in a completely ecofriendly condition. The major disadvantages of sodium alginate beads are low drug entrapment efficiency and rapid release of the embedded drug especially in the simulated intestinal fluid (Tomida et al., 1993; El-kamel et al., 2003). Although ion-exchange resin complexes have been used traditionally for sustained release of drugs, the release of the drugs depends on the equilibrium constant and selectivity coefficient of the resin. The drug having high selectivity constant is discharged rapidly and resins having low selectivity constant are constraint for both drug entrapment and prolonged release.

Several workers have proposed that coating of drug resin complex with synthetic polymers can modify the release of drugs. Various synthetic polymers like ethylcellulose, polymethylmethacrylate (Sriwongjanya and Bodmeier 1997), cellulose acetate butyrate (Torres et al. 1998), eudragits (Cunna et al. 2000) have been used to encapsulate resinates to provide sustained release of drugs. However, sodium alginate has not been used as a coating material for drug resin complex. In this investigation attempt has been made to coat drug-resin complex with synthetic and natural polymers and to compare the efficacy of the polymers to achieve prolonged release of drug. Diltiazem-HCl and propranolol-HCl have been selected as water soluble drugs.

**Rationale of selection of drugs:**

Diltiazem-HCl, a calcium channel antagonist, is used in the treatment of hypertension, arrhythmia and angina pectoris. However, the plasma elimination half-life of diltiazem is approximately 3 to 4.5 h and needs frequent dosing. It is usually administered in a dose of 30 mg initially 2-5 times daily to a maximum 240 mg in 3-4 divided doses. Moreover, diltiazem produces dose-related adverse effect like oedema, bradycardia, high-degree A-V block, dozziness and hypotension. Clinical studies have
shown that rapid release formulations of diltiazem determine an abrupt liberation of the active principle with a peak-effect after 1 to 1.5 h from the administration (Juneau and Theroux 1992; Morselli et al., 1979). Therefore, at least three daily administrations are necessary to maintain the plasmatic concentration in effective levels because of short plasma half-life and low bioavailability of the drug (Brighley et al., 1980; Koiwaya et al., 1981; Zelis and Kinney 1982). However, this system may result large ‘peaks’ and ‘valleys’ in the drug-blood level which, in turn, increases patient non-compliance and dose-related adverse effects. Conversely, the oral administration of sustained release formulation of diltiazem determines a reduced plasmatic peak (7 to 8 h versus 1 to 1.5 h respectively) and slower elimination from the plasma (midlife of elimination ranging from 5-8 h) (Gordin et al., 1986). Consequently, this method of administration can provide a therapeutically effective steady-state concentration with only two daily administrations (Campistron et al., 1987). Further, with sustained release formulation, the interdose variation of both plasmatic levels, and emergence of peak plasma concentration as well severity of the side effects are reduced.

Propranolol-HCl, a non-selective β-blocker, has been widely used in the treatment of angina pectoris, cardiac arrhythmias and hypertension (Boakes and Prichard 1973). It has a plasma half-life of 3.4 to 6 h. Among the common adverse effects, confusion, changes in heart beat, difficulty in breathing, discoloration of finger-nails/palms, loss of conciousness, sleepiness or seizures are dose related. Multiple dosing may also increase the dose related side effects and patient non-compliance. On the other hand, sustained release formulations may reduce the frequency of dosing (Doughlas et al., 1978; Halkin et al., 1979; Floras et al., 1982) which results in the reduction of dose-related side-effects as well as patient non-compliance.