INTRODUCTION
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Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods, and generally improved shelf-life of the product. For many drugs and therapeutic agents. Conventional, multiple dosing of immediate release formulations provides satisfactory clinical performance with an appropriate balance of efficacy and safety. The rationale for development of an extended-release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition. Besides its clinical advantages, an innovative extended-release formulation provides an opportunity for a pharmaceutical company to manage its product life-cycle. The dearth of new chemical entities is forcing many pharmaceutical companies to reformulate an existing conventional formulation to an extended-release product as a strategy of life-cycle management and retaining market share.

To imagine the ideal drug-delivery system, two prerequisites would be required.

1. It would be a single dose for the duration of treatment.

2. It should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects.

Thus the goal of sustained/controlled release dosage form is to maintain therapeutic blood or tissue levels of the drug over an extended period of time.
Figure 1 shows comparative blood drug level profiles obtained from administration of conventional, controlled as well as sustained release dosage forms. Thus, the conventional tablet provides only a single and transient burst of drug. A Pharmacological affect is seen as long as the amount of drug is within the therapeutic range. Pharmacological effect is altered when the peak concentration is above or below the therapeutic range. The main purposes of controlled release is to improve safety and minimize side effects of the drug by reducing fluctuation in drug level.

1.1 Advantages and Disadvantages of Controlled Release Systems:

1.1.1 Advantages:

1. Decreased incidence and/or intensity of adverse effects and toxicity.
3. Controlled rate of release.
4. More uniform blood concentrations.
5. Improved patient compliance.
6. Reduced dosing frequency.
7. More consistent and prolonged therapeutic effect.
8. A greater selectivity of pharmacological activity.
1.1.2 Disadvantages:

1. Increased variability among dosage units.
2. Stability problems.
3. Toxicity due to dose dumping.
4. Increased cost.
5. More rapid development of tolerance.
6. Need for additional patient education and counseling.

1.1.3 Characteristics Of Drugs Suitable For Controlled Release:

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract (GIT).
3. Administered in relatively small doses.
4. Possess a good margin of safety.
5. For the treatment of chronic therapy.

1.1.4 Characteristics Of Drugs Unsuitable For Controlled Release:

1. Not effectively absorbed in the lower intestine (riboflavin).
2. Absorbed and excreted rapidly; short biological half lives, <1 hr (penicillin G, furosemide).
3. Long biological half-lives > 12 hr (diazepam, phenytoin).
4. Large doses required. 1g (sulfonamides).
5. Drugs with low therapeutic index (Phenobarbital, digoxin).
6. Precise dosage titrated to individuals required (anticoagulants, cardiac glycosides).
7. No clear advantage for sustained release formulation (griseofulvin).
2. FACTORS GOVERNING THE DESIGN OF CONTROLLED RELEASE DOSAGE FORMS

2.1 Physico-Chemical Properties

2.1.1 Molecular Size and Diffusivity:

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The ability of a drug to diffuse in polymers and its so-called diffusivity (diffusion coefficient D), is a function of its molecular size (or molecular weight). For most polymers, it is possible to relate \( \log D \) empirically to some function of molecular size as

\[
\log D = -sv \log u + kv = -sM \log M + km
\]

Where, \( v \) is molecular volume, \( M \) is molecular weight, \( sv, sM, kv \) and \( km \) are constants. For drugs with a molecular weight greater than 500 daltons, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify (ie, less than 10-12 cm\(^2\)/sec). Thus, high molecular weight drugs should be expected to display very slow release kinetics in extended release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

2.1.2 Aqueous Solubility:

For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence, the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility, as shown by the Noyes-Whitney equation under sink conditions as

\[
\frac{dC}{dt} = kD A Cs
\]

where \( dc/dt \) is the dissolution rate, \( kD \) is the dissolution rate constant, \( A \) is the total surface area of the drug particles, and \( Cs \) is the aqueous saturation solubility of the drug.
Drugs with low aqueous solubility have low dissolution rates and usually suffer from oral bioavailability problems. Considering the pH partition hypothesis, basic drugs exist primarily in the ionized form (conjugate acid) at the same site, and their absorption will be poor. In the upper portion of the small intestine, the pH is more basic (pH = 5 to 7) and the reverse will be expected for weak acids and bases. Ideally, the release of an ionizable drug from an extended release system should be programmed in accordance with the variation in pH of the different segments of the gastrointestinal tract so that the amount of preferentially absorbed forms and thus the plasma level of the drug will be approximately constant throughout the time course of drug action (Alfonso.R., 2002). Some of the drugs which are poor candidates for Controled Release systems are Digoxin, Warfarin, Griseofulvin, Diazepam, and Chlorpheniramine.

2.1.3 pKa-Ionization Constant:

The pKa is a measure of the strength of an acid or a base. The pKa allows us to determine the charge on a drug molecule at any given pH. The amount of drug that exists in unionized form is a function of dissociation constant of a drug and pH of fluid at absorption site. For a drug to be absorbed, it must be in unionized form at the absorption site. Drugs which exist in ionized form at the absorption site are poor candidates for sustained/controlled release dosage forms (James Swarbrick., 2007).

2.1.4 Partition Coefficient:

Partition coefficient influences not only the permeation of drug across the biological membranes but also diffusion across the rate controlling membrane or matrix. The ability of a drug to penetrate lipid membranes (i.e., its membrane permeability) in its apparent oil/water partition coefficient is defined as

$$K = \frac{C_O}{C_W}$$

Where $C_O$ is the equilibrium concentration of all forms of the drug in an organic phase at equilibrium, and $C_W$ is the equilibrium concentration of all forms in an aqueous phase. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poor candidates for formulation as extended release dosage forms.
2.1.4 Stability:

One important factor for the loss of drug is through acid hydrolysis and/or metabolism in the GIT when administered orally. It is possible to significantly improve the relative bioavailability of a drug that is unstable in G.I. by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach the most appropriate controlling unit would be one that releases its contents only in the intestine. The release of these drugs that are unstable in the environment of the intestine, the most appropriate controlling such as in this case would be one that releases its contents, only in the stomach. So, drugs with significant stability problems in any particular area of the G.I. tract are less suitable for formulation into controlled release systems that deliver the contents uniformly over the length of GIT (Venkataraman Daar.S N., 2000).

2.2 Biological Factors

2.2.1 Absorption:

The rate, extent, and uniformity of absorption of a drug are important factors when considering its formulation into an extended release system (Gilberts., 2001). For a drug with a very slow rate of absorption results in poor bioavailability in many patients. Therefore slowly absorbed drug will be difficult to be formulated as extended release systems (Rudnic E., 2000).

If the drugs were erratically absorbed because of variable absorptive surface of gastrointestinal tract, design of controlled release product would be more difficult. For example, the oral anticoagulant – Dicoumarol, Iron.

2.2.2 Protein Binding:

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action (Ahmad., 1984). Since blood proteins are for the most part recirculated and not eliminated, drug protein binding can serve as a depot for the drug producing a prolonged release profile, especially if a high degree
of drug binding occurs. The elimination half-life of a drug generally increases when the percentage of bound drug to plasma increases. Such drugs need not be formulated into controlled release formulations.

2.2.3 Distribution:

The distribution of drugs into tissues can be an important factor in overall drug elimination kinetics, since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extracellular fluid.

The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, with in the body. The total apparent volume of distribution for a drug at steady state can be calculated from

\[ V_{dss} = \frac{(K_{12} + K_{21})}{K_{21}} V_p \]

Where \( V_{dss} \) is apparent volume of distribution at steady state. \( V_p \) is the constant for distribution of drug from the central to peripheral compartment, and \( K_{21} \) is that from the peripheral to central compartment and \( K_{12} \) is that from the central to peripheral compartment.

2.2.3 Metabolism:

The metabolism of a drug can either inactivate an active drug or convert an inactive drug to active metabolite. Complex metabolic patterns would make the Controlled Release design much more difficult particularly when biological activity is wholly or partly due to a metabolite. If a drug upon chronic administration is capable of either inducing or inhibiting enzyme synthesis, it will be a poor candidate for a Sustained Release/ Controlled Release product because of the difficulty of maintaining uniform blood levels of a drug. If there is a variable blood level of a drug through either intestinal (or tissue) metabolism or through first pass effect, this also will make formulation of SR dosage form difficult, since most of the process are saturable, the fraction of the drug loss would be dose dependent and that would result in significant reduction in bioavailability, if the drug is slowly released over a extended period of time (Joseph Robinson., 2002).
2.2.5 Elimination Half Life:

Half life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half and is determined by both clearance (Cl) and volume of distribution (Vd)

\[ t_{1/2} = \frac{0.693 \, V_d}{Cl} \]

Drug with short half lives (<1hrs) and high dose impose a constraint on formulation into controlled release systems because of the necessary dose size and drugs with long half-lives (>8hr) are inherently sustained (Birkett.D.J., 1996).

2.2.6 Therapeutic Index:

Among the indices used to describe the margin of safety of a drug, the therapeutic index is the most widely used.

Therapeutic index (TI) = median toxic dose (TD50)/ medium effective dose (ED50)

\[ TI = \frac{TD_{50}}{ED_{50}} \]

The longer the value of TI, the safer the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products.

2.3 Formulation Aspects Influencing the Design of Oral Controlled Release Drug Delivery Systems

2.3.1 Drug Properties:

1. Drug solubility and dose are the most important factors to consider in the design of ER matrices. In general, extended-release formulation of extreme drug solubilities coupled with a high dose is challenging. Drugs with very low solubility (e.g. < 0.01 mg/ml) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix. Therefore, the main mechanism of release would be through erosion of the surface of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent extended release throughout the GI tract is critical. For drugs with very high water solubility, the drug dissolves within the gel layer (even
with small amounts of free water) and diffuses out into the media. Therefore, it is important to control the factors that affect drug diffusivity (e.g. pH, gel strength and availability of free water) within the gel layer and parameters that ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. For poorly soluble drugs, particle size of the drug has a major influence on its release profile (Hogan., 1989., Velasco, M.V., 1999., Mitchell, K., 1993). A decrease in particle size of the drug causes increase in solubility and hence faster drug release rate.

2.3.2 Polymer Considerations:

Depending on dosage size and desired release rate, the typical use level can vary from 20 to 50% (w/w) (Rajabi – Siahboomi., 2000). For drugs with high water solubility, there is a threshold level of polymer for achieving controlled release, and further increase in polymer level may not decrease the drug release rate. However, for obtaining a robust formulation with consistent performance and insensitivity to minor variations in raw materials or manufacturing processes, a usage level of ≥30% (w/w) has been recommended ( Ford, J.L., 1985., Levina, M., 2006).

Particle size of the polymer is also another important factor. The finer the particle size, the faster the rate of hydration of the polymer and hence better the control of drug release (Alderman., 1984). Coarser polymer particles used in a direct compression formulation have been reported to result in faster drug release than finer particles (Shah, N., 1996). The coarser the particle size, the slower the hydration rate and gel layer formation.

2.3.3 Presence of Other Excipients:

2.3.3.1 Fillers:

Soluble fillers (e.g. lactose), insoluble fillers (e.g. microcrystalline cellulose, dicalcium phosphate) and/or partially soluble (e.g. partially pregelatinized starch) fillers are generally used in hydrophilic matrices to enhance pharmaco technical
properties of tablets (improve compressibility, flow and mechanical strength) or to modify the drug release profile. The inclusion of fillers affects the dissolution performance of a matrix by a "dilution effect" on the polymer. The magnitude of the effect on the performance of matrices is dependent on the drug, the polymer level and the level of excipient itself. The presence of water-soluble fillers in high concentrations in the matrix leads to faster and greater water uptake by the matrix, resulting in weaker gel strength, higher erosion of the gel layer and therefore faster drug release. Insoluble but weakly swellable fillers such as microcrystalline cellulose remain within the gel structure and generally result in decreased release rate. The presence of partially pregelatinized starch such as Starch 1500® in HPMC matrices has been reported to decrease the drug release rate (Levina M., 2004). For a highly soluble or sparingly soluble drug, the rank order of release rate was as follows: lactose > microcrystalline cellulose > partially pregelatinized starch.

2.3.3.2 Release Modifiers and Stabilizers:

Drugs with pH-dependent aqueous solubility (weak acids or bases) are formulated in HPMC matrices, they may exhibit pH-dependent drug release. Formulating CR matrices of such drugs may lead to lower drug release due to exposure of the dosage form to increasing pH media of the GI tract (from pH 1.2 to 7) (Hotter, D., 1997). Formulating pH-independent CR matrices for such drugs would not only ensure adequate release throughout the physiological pH, but also lower intra- and inter-patient variability (Vashi, V.I., 1988, Kohri, N., 1992). Development of such pH-independent matrices for weakly basic drugs has been shown with the incorporation of acidic excipients (weak acids or salts of strong acids) that lower the micro-environmental pH within the gel layer and thus maintain high local solubility of the drug independent of the external release media (Tatavarti, A.S., 2006, Siepe, S., 2006, Tatavarti, A.S., 2004, Siepe, S., 2006, Streubel, A., 2000, Gabr, K., 1992, Varma, M.V.S., 2005).
2.3.3.3 Effect of Salts and Electrolytes:

In general, as the concentration of ions in a polymer solution increases, polymer hydration or solubility decreases (A. Abhirami. et al., 2010). The amount of water available to hydrate the polymer is reduced because more water molecules are required to keep the ions in solution. Moreover, the types of ions in solution affect polymer hydration to varying degrees. The susceptibility of cellulose ethers to ionic effects follows the lyotropic series of the ions (chloride < tartarate < phosphates and potassium < sodium) (Mitchell, K., 1990). Changes in the hydration state of a polymer in solution are manifested primarily by changes in solution viscosity and turbidity or cloud point (Sarkar, N., 1979). At low ionic strengths, the polymer hydration is unaffected, but higher ionic strengths may lead to a loss of gel integrity of the matrix. The extent of this influence depends on the polymer type and lyotropic series of the ions. The effect of electrolytes or salts is important only in cases where high concentrations of salts or electrolytes are present as tablet components or as constituents of dissolution media. In-vivo conditions, however, have fairly low ionic strength (ionic strength of gastrointestinal fluids, (0.01–0.15)) to affect the polymer hydration and have significant impact on release rate (Johnson, J.L., 1993).

2.3.3.4 Characteristics of Dosage Form:

Variation in tablet shape and size may cause changes in surface area available for drug release and hence influences drug release profiles from HPMC matrices. A constant surface area to volume ratio (S/V) of different size and shape tablets for a HPMC formulation would lead to similar drug release profiles (Reynolds, T.D., 2002). The size of the tablet may also dictate the polymer level requirement. Smaller tablets have been reported to require higher polymer content because of their higher surface area to volume ratio and thus shorter diffusion pathways (Siepmann, J., 2000). One technology proposed for modifying the matrix surface area to volume ratio was by physical restriction of the swelling of hydrophilic matrix by partially coating the matrix with insoluble polymers or multi-layered tablets (Geomatrix® technology) (Colombo, P., 1990), Colombo, P., 1992).
2.3.5 Presence of Coating:

Application of film coatings to tablet formulations is a common practice in the pharmaceutical industry. Tablets are coated for a variety of reasons such as improving the stability of the formulation, taste masking, enhancing the aesthetic appearance, identification and branding, improving the packaging process or modifying drug release profile. Coating of hydrophilic matrices with water-soluble polymers such as Opadry® or low-viscosity HPMC generally does not alter drug release profiles (Levina, M., 2003., Vuong, H., 2006). Coating with water-insoluble polymers such as ethyl cellulose with or without permeability modifiers (e.g., low viscosity grades of HPMC or Opadry) may be used for modulating the drug release profile from HPMC matrices (Tiwari, S.B., 2003., Dias, V.D., 2006)

2. Classification of Oral Controlled Drug Delivery System:

1. Dissolution controlled systems
2. Diffusional systems
   a) Reservoir devices
   b) Matrix devices
3. Bioerodible and combination of diffusion and dissolution systems
4. Osmatically controlled systems
5. Ion-exchange systems
6. pH-independent formulations
7. Altered density formulations
   a) High density approach
   b) Low density approach

The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract.
3.1 Dissolution-Controlled Systems:

Controlled release preparations of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include, preparation of appropriate salts or derivatives, coating the drug with a slowly dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

Dissolution controlled systems can be made in several different ways. By alternating layers of drug with rate controlling coats, a pulsed delivery can be achieved. If the outer layer is a quickly releasing bolus of drug, initial levels of drug in the body can be quickly established with pulsed intervals following. An alternative method is to administer the drug as a group of beads that have coatings of different thicknesses. Since the beads have different coating thicknesses, their release will occur in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later times will be achieved from those with thicker coatings. This is the principle of the spansule technology or microencapsulation.

3.2. Diffusional Systems:

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types of diffusional systems are recognized. They are reservoir device and matrix devices.

a) Reservoir Devices:

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system.

The advantages of reservoir diffusional systems are zero-order delivery are possible and release rate variable with polymer type. The disadvantages of reservoir diffusional systems are system must be physically plant sites, difficult to deliver high-molecular weight compounds, generally increase as post per dosage unit and potential toxicity if the system fails.
b) Matrix Devices:

A matrix device consists of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. Obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

3.3 Bioerodible And Combination Of Diffusion And Dissolution Systems:

These systems can combine diffusion and dissolution of both the matrix material and the drug. Drug not only can diffuse out of the dosage form, as with some previously described matrix systems but the matrix itself undergoes a dissolution process. The complexity of the system varies from the fact that, as the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release can occur only if surface erosion occurs and surface area does not change with time. The inherent advantage of such a system is that the bioerodible property of the matrix does not result in a ghost matrix and removal from implant sites is not necessary. The disadvantages of this system include, difficulty to control kinetics owing to multiple processes of release, potential toxicity of degraded polymer must be considered.

Another method of bioerodible systems is to attach the drug directly to the polymer by a chemical bond (Goldberg, E., 1978). Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. A third type, which in this case utilizes a combination of diffusion and dissolution, is that of a swelling-controlled matrix (Hopefenberg, H.B., 1978). Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer, as in previous systems, swelling of the polymer occurs. This allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate, drug solubility and the amount of soluble fraction in the matrix (Nakagami, H., 1991). This system usually minimizes burst effects, since polymer swelling must occur before drug release.
3.4 Osmotically Controlled Systems:

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. Consider a semi permeable membrane that is permeable to water, but not to drug. A tablet containing a core of drug surrounded by such a membrane and when this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference.

These systems generally appear in two different forms. The first one contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device. The electrolyte surrounds the bag. Both systems have single or multiple holes bored through the membrane to allow drug release. In the first example, high osmotic pressure can be relieved only by pumping solution, containing drug, out of the hole. Similarly in the second example, the high osmotic pressure causes compression of the inner membrane and drug is pumped out through the hole.

The advantages of osmotically controlled devices are, zero-order release is obtainable. Reformulation is not required for different drugs and release of drug independent of the environment of the system. The disadvantages of these systems include, systems can be much more expensive than conventional counterparts, quality control is more extensive than conventional tablets.

3.5 Ion-Exchange Systems:

Ion-exchange systems generally use resins composed of water-insoluble, cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

\[
\text{Resin}^+ - \text{drug}^- + X^- \rightarrow \text{resin}^+ - X^- + \text{drug}^-
\]

Conversely,

\[
\text{Resin}^- - \text{drug}^+ + Y^+ \rightarrow \text{resin}^- - Y^+ + \text{drug}^+
\]
where $X'$ and $Y^+$ are ions in the GI tract. The free drug then diffuses out of the resin. The drug-resin complex is either by repeated exposure of the resin to the drug in a chromatography column or by prolonged contact in solution.

The date of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin.

This system is advantageous for drugs that are highly susceptible to degradation by enzymatic processes, since it offers a protective mechanism by temporarily altering the substrate. This approach to controlled release, however, has the limitation that the release rate is proportional to the concentration of the ions present in the area of administration. Although the ionic concentration of the GI tract remains rather constant with limits, the release rate of the drug can be affected by variability in diet, water intake and individual intestinal content.

An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethyl cellulose or waxes (Motyeka, S., 1978). These systems rely on the polymer coat to govern the rate of drug availability.

### 3.6 pH – Independent Formulation Systems:

The granules are designed for the oral controlled release of basic or acidic drugs at a rate that is independent of the pH in the GI tract. They are prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and finally coating with a gastrointestinal fluid permeable film-forming polymer. When the GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to a suitable constant pH, thereby rendering a constant rate of drug release.

### 3.7 Altered Density Formulation Systems:

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. At this end, several approaches have been developed to prolong the
residence time of drug delivery systems in the GI tract. One such approach is the bioadhesion approach (Park, K., 1984) which is based on the adherence of bioadhesive polymers to the mucin / epithelial surface of the GI tract. The other approach is to alter the formulation’s density by using high or low density pellets.

a) **High – Density Approach:**

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4 (Bechgaard, H., 1980). In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder and zinc oxide. The weighed pellet can then be covered with a diffusion controlled membrane.

b) **Low-density Approach:**

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for controlled release purposes. Polystyrol, poprice and even popgive are all candidates as carriers. The surface of these empty shells is undercoated with sugar or with a polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by a mixture of drug with polymers such as ethyl cellulose and hydroxylpropylcellulose. The final product floats on the gastric fluid for a prolonged period, while slowly releasing drug.
AIM AND OBJECTIVES OF THE INVESTIGATION

Controlled release drug delivery systems have received much attention in the past few decades with numerous technologically sophisticate products on the market. Much advancement have come about by the simultaneous convergence of many factors, including the discovery of novel polymers, formulation optimization better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities and the introduction of biotechnology and biopharmaceutics in the drug product design. The major benefits of these products lie in the optimization of drug input rate in to the systemic circulation in order to achieve an appropriate pharmacodynamic response. This in turn should add to product safety and reduce the extent and incidence of major adverse drug reactions due to a more strict control of blood levels. Furthermore, with less frequent dosing, it is speculated that this should improve patient compliance and possibly maximize drug product efficiency in therapeutics.

Recently numerous hydrophilic polymers have been investigated and are currently used in the design of complex controlled release systems (Hayashida, T., 1997). In many cases the formulator depends on the inherent rate – controlling mechanisms of the polymer to provide constant rate of drug delivery. Among desirable features, the polymers should posses' inherent physicochemical characteristics which provide for the attainment of high gel state viscosity upon swelling, ability to maintain constant gel layer integrity over a prolonged period and hence low erosion rate, and complete dissolution of polymer upon exhaustion of drug release. The ideal polymers would permit these processes to operate synchronously, i.e. affording a balance between the principle processes of swelling, erosion and dissolution. Among the most widely used polymers, such as the nonionic polyethylene oxide (PEO), hydroxyl propyl methyl cellulose (HPMC) , hydroxyl propyl cellulose(HPC) types. The cationic chitosan types and anionic alginate types, the attainment of high gel state viscosity, maintenance of constant gel layer, in a monolithic sense for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. Since the various dynamic phases in the rate processes of polymer relaxation, disentangled and (or) erosion during dissolution are manifested in a
non constant manner, realization of zero-order drug release from such monolithic devices is difficult.

This limitation of hydrophilic polymers may be circumvented through modification of the polymeric gel system. In the present work a reliable process has been established for inducing in situ reactions between pharmaceutically acceptable electrolytes and drug which influences the intra gel swelling dynamics and relative physical integrity of the swollen matrix structure. Furthermore, this may produce heterogeneous domines with in the swollen gel.

In the past alkaline compounds or buffers have been included in solid oral formulations of several acidic studies dissolution rate limited absorption (Pagay, S.N., 988). The same principle of addition of buffers osmotically active agents, surfactants or combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques (McClelland, G.A., 1992). However no specific strategy has been employed to apply the same principle to design a simple, and then directly compressible, monolithic, control release system with provision of zero order kinetics. In general, the application of buffers and ionisable compounds are essentially been limited to the minimization of localized gastrointestinal tract adverse effect and pH solubility dependency of poorly soluble compounds (Thoma, K., 1990). The drugs such as Verapamil Hydrochloride, Losartan Potassium were selected taking in to consideration of their physicochemical, biopharmaceutical properties and rationale of clinical efficacy.

Verapamil Hydrochloride is a calcium channel blocker and a class IV antiarrythmic drug. It is a white crystalline powder, soluble in water; sparingly soluble in alcohol, freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.5. Verapamil Hydrochloride is approximately 90% absorbed from the GI tract but the bioavailability is only about 20% due to first-pass metabolism in the liver. It has terminal elimination half-life of 2 to 8 hours and prolonged after repeated oral doses. its plasma protein binding is up to 90%.

Losartan Potassium potassium is an angiotensin II receptor antagonist with antihypertensive activity. It is readily absorbed from the GI tract following oral administration but the bioavailability is about 33% due to substantial first-pass
metabolism. Peak plasma concentration occurs at about 1 hr after an oral dose and terminal elimination half-life is about 1.5 to 2 hrs respectively. Losartan Potassium is about 98% bound to plasma proteins. It is given orally as the potassium salt. Maximum hypotensive effect is achieved in about 3 to 6 weeks after initiating the treatment.

Based on the above physical chemical, biopharmaceutical, properties and clinical relevance, Verapamil Hydrochloride and Losartan Potassium were selected as drug candidates for developing matrix tablets as controlled release systems.

The aim of this work was to design and formulate in novel oral controlled release matrix tablet dosage form for the above mentioned drugs that may be tailored to provide steady state drug release over a prolonged period (Pillay, V., 1998). The mechanisms and the electrolytes induced matrix stiffening and their modulation in the integral changes for the possibility of controlled drug release will be elucidated.

The major objectives of the work are as follows:

➢ To design oral controlled release matrix tablets by using polyethylene oxide, PEO-WSR-301 & PEO-WSR-303.

➢ To make the comparative evaluation of the poly ethylene oxide, PEO-WSR-301 & PEO-WSR-303 matrix tablets.

➢ To study the influence of electrolytes on the controlled drug release matrix tablets.

➢ To incorporate Verapamil Hydrochloride and Losartan Potassium in the matrix tablets and to evaluate them for controlled release.

➢ To study the physical parameters of directly compressed matrix tablets by weight uniformity, Hardness, Friability and drug content.

➢ To evaluate the kinetics and mechanism of drug release from the matrix tablet by in vitro dissolution studies.
➢ To characterize *in situ* interaction between drugs and electrolytes if any in the matrix tablets by infrared spectroscopy and X-ray diffraction studies.

➢ To evaluate the *in vivo* pharmacokinetics of Verapamil Hydrochloride and Losartan Potassium from the selected matrix tablets.

➢ To evaluate the stability of the selected matrix tablets as per ICH guidelines.

➢ Extensive investigations, both *in vitro* and *in vivo* studies on various matrix formulations have been carried out to fulfill the objectives of the investigation and the results obtained are presented and discussed in the subsequent chapters.
Oral Controlled Release System Adopted in the Present Investigation

**Bioerodible and Combination Diffusion and Dissolution Systems:**

Therapeutic systems will never be dependent on dissolution only or diffusion only. However, the predominant mechanism allows easy mathematical description. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion controlled. Bioerodible devices, however, constitute a group of systems for which mathematical descriptions of release characteristics can be quite complex.

![Drug Dispersed in Matrix](Figure2)

**Fig 2:** Representation of Bioerodible matrix systems. Drug is dispersed in the matrix before release at time $= 0$. At time $= t$, partial release by drug diffusion or matrix erosion has occurred.

**Advantages of Bioerodible systems:**

1. Easier to produce than reservoir devices.
2. Can deliver high molecular weight compounds.
3. Accidental leakage of the total drug component is less.
4. The bioerodible property of the matrix does not result in a ghost matrix.
Disadvantages of Bioerodible systems:

1. Cannot obtain zero order release.
2. Removal of remaining matrix is necessary for implanted systems.
3. Release Kinetics are often hard to control.

The mechanism of release from simple erodible slabs, cylinders and sphere has been described (Maryadele.J.oneil., 2006). A simple expression describing release from all three of these erodible devices is

\[ \frac{M_t}{M} = 1 - \left( 1 - \frac{K_0 t}{C_0 a} \right)^n \]

Where \( n = 3 \) for a sphere, \( n = 2 \) for a cylinder, and \( n = 1 \) for a slab. The radius of a sphere, or cylinder, or the half-height of a slab is represented by \( a \). \( M_t \) is the mass of a drug release at time \( t \), and \( M \) is the mass released at infinite time. As a further complication, these systems can combine diffusion and dissolution of both the matrix material and the drug. The complexity of the system arises from the fact that, as the polymer dissolves, the diffusional path length for the drug may change. Zero-order release can occur only if surface erosion occurs and surface areas does not change with time. The disadvantages of these matrix systems are that release kinetics are often hard to control, since many factors affecting both the drug and the polymer must be considered.

Another method for the preparation of bioerodible systems is to attach the drug directly to the polymer by a chemical bond (Prajapati, B.G., 2010). Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. This makes control of the rate of release somewhat easier. Another advantage of the system is the ability to achieve very high drug loading, since the amount of drug placed in the system is limited only by the available sites on the carrier.

A third type, which in case utilizes a combination of diffusion and dissolution, is that of a swelling controlled matrix (A. B. Thomas et al., 2010). Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer, as in previous systems. Swelling of the polymer occurs. This allows entrance of water, which causes
dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate, drug solubility and the amount of soluble fraction in the matrix (Nanda, N. et al., 1991). This system usually minimizes burst effects, since polymer swelling must occur before drug release.

Therefore, a plot of amount of drug release versus the square root of time should be linear of drug release from matrix is diffusion controlled. In this instance, one may control drug release from a homogeneous matrix by varying the following parameters.

1. Initial concentration of drug in the matrix.
2. Drug solubility
3. Porosity
4. Tortuosity
5. Leaching solvent composition.
6. Polymer system making up matrix.
DRUGS USED IN THE PRESENT STUDY

VERAPAMIL HYDROCHLORIDE

Chemical Name: Benzene acetonitrile, \([3 - \{(2 - (3, 4 - \text{dimethoxyphenyl}). \text{Ethyl}
\text{ethyl amino}] \text{propyl}] -3, 4 - \text{dimethoxy - \alpha - (1-methyl ethyl) monochloride.}

Structure

\[
\begin{align*}
\text{Molecular Formula: } & C_{27}H_{38}N_{2}O_{4}.HCl \\
\text{Molecular Weight: } & 491.07
\end{align*}
\]

Therapeutic Category:

Calcium ion influx inhibitor (slow-channel blocker (or) calcium antagonist)

Physical Properties:

It is a white or practically white crystalline powder. It is practically odorless and has a bitter taste.

Solubility:

It is soluble in water, methanol and chloroform.

Pharmacokinetics and Metabolism:

More than 90% of the orally administered dose of Verapamil Hydrochloride is absorbed (Muller.F.B., 1986). Because of rapid biotransformation of Verapamil Hydrochloride during its first pass through portal circulation bioavailability ranges from 20% to 35%. Peak plasma concentrations are reached between 1 and 2 hrs after oral administration.
A nonlinear correlation between the Verapamil Hydrochloride dose administered and Verapamil Hydrochloride plasma levels does exist. No relationship has been established between the plasma concentration of Verapamil Hydrochloride and a reduction in blood pressure. In early dose titration with Verapamil Hydrochloride a relationship exists between Verapamil Hydrochloride plasma concentration and prolongation of the PR interval. However, during chronic administration this relationship may disappear.

The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. In these same studies, after repetitive dosing, the half-life increased to a range from 4.5 to 12.0 hours. Half-life of Verapamil Hydrochloride may increase during titration. Aging may effect the pharmacokinetics of Verapamil Hydrochloride. Elimination half-life may be prolonged in the elderly. In healthy men, orally administered Verapamil Hydrochloride undergoes extensive metabolism in the liver.

Twelve metabolites have been identified in plasma, all except nor Verapamil Hydrochloride are present in trace amounts only. NorVerapamil Hydrochloride can reach steady-state plasma concentrations approximately equal to those of Verapamil Hydrochloride itself (Follath.F., 1986). The cardiovascular activity of NorVerapamil Hydrochloride appears to be approximately 20% that of Verapamil Hydrochloride. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3 to 4% is excreted in urine as unchanged drug. Approximately 90% is bound to plasma proteins.

Preparations Available:

Verapamil Hydrochloride is available in the form of tablets, controlled release tablets and in the form of injection.

Therapeutic Uses:

Verapamil Hydrochloride is used widely in the treatment of Angina, Arrhythmias and essential hypertension.
LOSARTAN POTASSIUM

Chemical Name: Losartan Potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1, 1'-biphenyl]-4-yl]methyl]-1H-imidazole -5-methanol monopotassium salt.

Structural Formula

![Structural Formula](image)

Molecular formula: C_{22}H_{22}ClKN_{6}O

Molecular weight: 461.01

Therapeutic Category:

Angiotensin-II (Type-I) receptor blocking agent.

Physical Properties: Losartan Potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01(Michael Weber, M.D.,1997). It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Solubility: Freely soluble in water and methanol and insoluble in chloroform (McIntyre, M. 1997).

PHARMACOKINETICS & METABOLISM

Following oral administration, Losartan Potassium is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of Losartan Potassium tablets is approximately 33%. Mean peak concentrations of Losartan Potassium and its active metabolite are
reached in 1 hour and in 3-4 hours, respectively (Sean C Sweetman; 2005, John B Taylor, 2005, R.G. Mc Allister, 1976, C.K. Lim, 1983). There was no clinically significant effect on the plasma concentration profile of Losartan Potassium when the medicine was administered with a standardised meal.

Both Losartan Potassium and its active metabolite are >99% bound to plasma proteins, primarily albumin. The volume of distribution of Losartan Potassium is 34 litres. Studies in rats indicate that Losartan Potassium crosses the blood-brain barrier poorly, if at all.

About 14% of an intravenously- or orally-administered dose of Losartan Potassium is converted to its active metabolite. Following oral and intravenous administration of 14C-labelled Losartan Potassium, circulating plasma radioactivity primarily is attributed to Losartan Potassium and its active metabolite. Minimal conversion of Losartan Potassium to its active metabolite was seen in about one percent of individuals studied. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Plasma clearance of Losartan Potassium and its active metabolite is about 600mL/min and 50mL/min, respectively. Renal clearance of Losartan Potassium and its active metabolite is about 74mL/min and 26mL/min, respectively. When Losartan Potassium is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of Losartan Potassium and its active metabolite are linear with oral Losartan Potassium doses up to 200 mg. Following oral administration, plasma concentrations of Losartan Potassium and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively.

**Preparations Available:** Losartan Potassium is available in the form of tablets.

**Therapeutic Uses:**

Losartan Potassium is used widely in the treatment of Arrhythmias & essential hypertension.
<table>
<thead>
<tr>
<th>Matrix Characteristics</th>
<th>Materials</th>
</tr>
</thead>
</table>
| Insoluble, inert       | Polyethylene  
                        Polyvinyl chloride  
                        Methyl acrylate-methacrylate copolymer  
                        Ethylcellulose, Cellulose Acetate. |
| Insoluble, erodible    | Carnauba wax  
                        Stearyl alcohol  
                        Stearic acid  
                        Polyethylene glycol  
                        Castor wax  
                        Polyethylene glycol monostearate  
                        Triglycerides |
| Hydrophilic            | Methylcellulose (400 cps, 4000 cps)  
                        Hydroxyethylcellulose  
                        Hydroxypropyl methylcellulose (High viscosity grades) (K₄M, K₁₀₀M etc.)  
                        Sodium carboxymethylcellulose  
                        Carboxypolymethylene  
                        Galactomannose  
                        Sodium alginate  
                        Poly Ethylene Oxide (PEO-WSR N-301 & PEO-WSR N-303) |
In the present study polyethylene oxide (polyox) and microcrystalline cellulose were evaluated for their application in the design of matrix diffusional tablets.

The properties of these cellulose polymers are as follows.

**Polyoxyethylene:**

**Synonym:** polyoxinate, polyoxinrane, polyoxyethylene

**Description:**

Polyethylene oxide is a white to off-white, free flowing powder, slight ammonial odour.

It is available in several grades which vary in these viscosity.

Two different grades of polyox were used in present day study.

They are 1) polyox WSR n-301

2) polyox WSR N-303

**Viscosity:**

1) polyox WSR N-301: 1652-5500 CPC

2) polyox WSR N-303: 7500-10000 CPC

**Solubility:**

Soluble in water and a number of common organic solvents such as acetonitrile, chloroform and methylene chloride. It is in soluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.

**Stability and storage conditions:**

Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.
Incompatibilities:

Polyoxyethylene oxide is incompatible with strong oxidizing agents.

Safety: Animal studies suggest that polyethylene oxide has a low level of toxicity regardless of route of administration. It is poorly absorbed from gastrointestinal tract but appears to be completely rapidly eliminated. The resins are neither skin irritant nor sensitizers, and they do not cause eye irritation.

Applications in pharmaceutical formulation or technology:

Polyethylene oxide can be used as tablet binder at a concentration of 5-8%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach (Dhawan S, Part I 2005, Dhawan S Part II, 2005). Polyethylene oxide also been show to facilitate coarse extrusion for tableting (Pinto JF, 2004) as well as being an aid in hot melt extrusion (Repka MA, 2000, Coppens KA, 2005).

The relationship between swelling capacity and molecular weight a good guide when selecting release matrix formulations mucoadhesive polymer. polyethylene oxide has been shown to be an excellent mucoadhesive polymer (Bottenberg P, 1991). Low level of polyethylene oxide is effective thickness, although alcohol is usually added to water based formulations to provide improved viscosity stability.

Polyethylene oxide film demonstrated good turbidity when wet. This property has been utilized in the development of coating for medical devices.

Polyethylene oxide can be radiation cross linked in solution to produce a hydrogel that can be use in wounded care applications.
MICROCRYSTALLINE CELLULOSE

Synonym: Cellets, celex, cellulose gel, hellulosum microcrystallinum, celphere, ceolus KG, crystalline cellulose, E460, Emocel, Ethispheres, Fibrocel, MCC sanaq, Pharmacel, Tabulose, Vivapur.

Description:
Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility:
Slightly soluble in 5% w/w sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and storage conditions:
Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well closed container in a cool, dry place.

Incompatibilities:
Microcrystalline cellulose is incompatible with strong oxidizing agents.

Safety:
Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively non toxic and non irritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely a problem when cellulose is used as an excipient in pharmaceutical preparations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas (Cooper CB, 1983).
Applications in pharmaceutical formulation or technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes (Enezian GM, 1972, Lerk CF, 1973, Lerk CF, 1974, Lamberson RF, 1976, Lerk CF, 1979, Chilamkurti RN, 1982, Wallace JW, 1983). In addition to its use as a binder/diluent microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.
ELECROLYTES USED IN THE STUDY (Qadry, J.S.-S.Z.Qadry, 2007)

1.10.1 Dried Aluminum Hydroxide Gel:

Chemical Formula: Al(OH)$_3$

It is a white, light amorphous powder, odorless and tasteless. It is not soluble in water and alcohol but is soluble in dilute mineral acids and in large volume of caustic alkali solution. A solution of 40% in water gives pH not more than 10 (approx. 8). It is mainly used as an antacid in the management of peptic ulcer and gastritis. It reacts chemically to neutralize the gastric contents. It is usually taken up to 1g daily in divided doses.

1.10.2 Aluminum Sulphate:

Chemical Formula: Al$_2$(SO$_4$)$_3$, 14 H$_2$O

It is a white, crystalline powder, shining plates or crystalline fragments; odorless with sweet taste at first and then mildly astringent. It is highly soluble in water, giving an acid solution; due to hydrolysis. A 1% w/v solution in water gives pH more than 2.9 (approx. 4.5). It is used as pharmaceutical aid (for mineral carrier for absorbed vaccines) and is also used for water purification.

1.10.3 Calcium Carbonate:

Chemical Formula: CaCO$_3$

It is a fine, white, microcrystalline powder without odor and taste. It is practically insoluble in water and alcohol but dissolves with effervescence in dilute acetic, hydrochloric and nitric acids. A 20% suspension in water gives pH of 9.5. It is mainly used as an antacid. It is usually taken up to 10g daily in divided doses.
1.10.4 Light Magnesium Carbonate:

Chemical Formula: $3 \text{MgCO}_3, \text{Mg(OH)}_2, 3\text{H}_2\text{O}$

It is white granular tasteless powder. It is practically insoluble in water and alcohol but is soluble in dilute mineral acids with effervescence. A 20% w/v suspension in water has pH of approximately 10.0. It is used as an antacid at 0.3 to 0.6 g and as a laxative at 2.0 to 4.0 g daily dose.

1.10.5 Sodium Bicarbonate:

Chemical Formula: $\text{NaHCO}_3$

It is a white crystalline powder with saline taste. It is soluble in 10 parts of water and insoluble in alcohol. A 1% w/v solution in water has a pH of 8.1. It is mainly used as an antacid especially for the treatment of systemic acidosis. It is usually taken up to 4 g daily in divided doses.

1.10.6 Sodium Carbonate:

Chemical Formula: $\text{Na}_2\text{CO}_3, 10\text{H}_2\text{O}$

It is a white colorless crystalline powder which is odorless. It is soluble in water and alcohol. A 1% solution in water gives pH approximately 11.0. It is used as an antacid and as a pharmaceutical aid. It is also used as a mouthwash and as a vaginal douche. It is usually taken up to 2 g daily in divided doses.