REVIEW OF LITERATURE
LITERATURE REVIEW
Past Studies on Polyethylene Oxide Polymers:

Comparision of PEO polymer blends were done, by using a monolithic water swellable and soluble polymers to describe the release behavior of \( \beta \)-hydroxyethyl-theophylline. The water swelling and dissolution characteristics of the polymer blend was analysed, with the permeation test the drug diffusivitives also analysed. The drug release kinetics of diff systems in an aqueous environment at 37\(^{\circ}\)C was also performed. The high M.W poly was shown maximum release than that of dissolution type polymer. Therefore, a decrease in drugs diffusivity conductance in the swollen layer and hence a non constant release induced by diffusive type layer. The achievement of drug release by low M.W polymer in which the rate of swelling equals the rate of dissolution and ensure a constant release (Apicella, A. 1993).

Solid dispersions were prepared with the composition of poly(ethylene oxide) PEO – carbonyvinylpolymer (CP) complex with phenacetin (PHE) by using water/ethanol (1/1, v/v) mixture as a solvent. The release pattern was studied for the above composition and analysed various analytical properties. The degree of PEO CP complex formation was varied based on PEO/CP ratio. Its release was controlled by the degree of the complex formed. It was also observed the effect of pH on the dissolution behavior as the pH is higher. The release from the solid dispersion is increased, it may be the fact that the PEO-CP complex is broken at a higher pH (Tetsuya Ozeki, 1998).

The triblock copolymer matrices were prepared by compression with its swelling characteristics of copolymer matrices, an increase in the thickness of the gel layer around the matrix following ingress of water into matrices. In drug release from the copolymer matrices was predominantly by fickian diffusion mechanism (Mahmoud Ameri, 1998).

This study was conducted as Controlled Release matrix tablets with Ibuprofen & Carbopol resins blend at different ratio’s by direct compression. The release rate of drug from the tablets were studied by using pH 7.2 phosphate buffer solution by diffusion & swelling-controlled mechanisms. The release kinetics were modified when polymer blend is used. The co-exciipients were enhanced the release rate of the drug. The influence co-
excipients order is lactose > microcrystalline cellulose > starch. Lactose demonstrated slower and more linear release behavior as compared to the other two (Gul Majid Khan, 1999).

This study deals with Verapamil Hydrochloride release from tablets based on high molecular weight PEO. The drug release proceeds as a controlled diffusion under the condition of the Half-change test. Drug release ceases after 4h as a result of obtaining low soluble in the water base. The release kinetics also changes as and when the above test is made. The decrease in drug concentration leads not only to retard release of the drug sample but also to changes in the kinetics of the process (Milen Dimitrov, 1999).

This study was tells us about performance of PEO & HPMC polymers when employed to achieve extended release of drugs at a constant rate. Three-layer systems were prepared by using these core & barrier formulations. The release profiles of the above systems obtained were compared to verify the efficiency of PEO over HPMC. The result shows the slower release rate can be obtained from the plain matrices containing HPMC compared to PEO (Maggi L, 2000).

The Ionic conductivity was measured from AC impedance values by using PEO and its derivatives along with natural rubber (NR). At 10% of NR mix with PEO have got improvement in its conductivity values were found. Also it was observed that there is an increase in the conductivity values when simple salt is added. On the other hand, the DSC curve for NR/PEO derivation showed two glass transition temperatures based on the separate components, suggesting phase separation of the PEO derivatives in the NR phase (Yoshizawa M, 2000).

A good attempt was made and succeeded PEOs as retarding polymers in hydrophilic matrix tablets in controlled release of drugs. It explains the hydration behavior of matrix tablets containing a water soluble drug & polymer's of two diff molecular weights: Polyox WSR N 301 ($M_w = 4x10^6$) and Polyox WSR N 1105 ($M_w = 0.9x10^6$). The hydration rate, extent of swelling & erosion rate of matrices with polymer, the drug and other excipients were evaluated in comparison to matrices made of pure polymers. Lower M.W PEO are shown better hydration, a strong gel & more liable to erosion. When compared with higher M.W PEO's. This behavior shows the different efficiencies of the
two polymer in drug release rate of water soluble drugs also observed the presence of other soluble components of the matrices enhances the erosion trend (Maggi L, 2002).

A very good attempt was made to have an alternative for Controlled Release of drug from a simple monolithic system, comprise of a water. Soluble propranolol HCl, hydrophilic polymer and electrolytes such as Al. hydroxide, Al. sulphate, Mg. trisilicate & Zinc sulphate to monitor integral pH changes, swelling and gel properties: The results shows the swelling & gel formation in presence of ionizable species were very good and leads a Controlled Release Drug Delivery System (Vidyadhara S, 2003).

The HPMC was used to form Oral hydrophilic monolithic systems to provide Controlled Release of drugs. The insitu interactions between drug and electrolytes devised to control the release of highly water soluble drop from the oral systems. Diltiazom HCl with some electrolytes was employed in designing of swellable matrix tablets along with HPMC as controlled release hydrophilic polymer. Electrolytes were used to monitor intragel changes, swelling and gel properties. The result shows that the drug release at a controlled rate was due to differential swelling rate, matrix stiffening and a uniform gel layer formation (Viness Pillay, 1999).

The Hydrophilic monolithic systems were used to form oral controlled release of drugs with HPMC as polymer. The polymer may not be released drug for prolonged period of time. To achieve prolonged period; they made an attempt for in situ interaction between drug, electrolytes and polymer for oral hydrophilic monolithic systems. Some of the electrolytes were incorporated in design of swellable tablet formulation with polymer. Electrolytes were used to monitor intragel pH changes, swelling and Gel properties. Results shows controlled release was due to differential swelling rate, uniform gel layer formation and matrix stiffening. In simple monolithic systems hydrophilic matrices shows the attractive, alternative for C.D.D was due to the presence of ions in swelling and gel formation (Vidyadhara S, 2003).

Controlled release matrix tablets were formulated using HPMC with electrolytes along with propranolol HCl. In this work some of the electrolytes were used at diff concentration (5-100 mg/tab) in various formulation, while drug: & polymer concentrations were maintained count at 1:2 level in all formulations. Electrolytes used
were to monitor matrix swelling & gel properties. Controlled release of drug was accounted max at low concentration (5-50 mg/tab) than at high concentration (75-100 mg/tab). Results indicates that the drug release was due to differential swelling rate, matrix stiffening and a uniform layer formation (Vidyadhara S, 2004).

It was a good attempt to develop a new monolithic matrix to release in a zero order manner over an extended period. In this approach they were observed using drug in formulation with swellable (HPMC) and erodible (PEO) polymer. These were prepared using direct compression technique and dissolution was also assessed using modified USP apparatus II. Under the dissolution evaluation the interrelationship b/u matrix hydration, erosion and textural properties were determined. The drug delivery kinetics was directly relates to the synchronization of swelling erosion & fractional release. Comparatively swellable polymer has get significant greater degree of hydrates & swelling and stronger texture property than erodible polymer. Results has shows & understands that drug release heavily depends on the synchronization of erosion & swelling properties of the entire dissolution study (Shahla Jamzad Reza, 2006).

This model is worked on mechanistic approach for simulating the drug release from a swelling and dissolving polymer tablet, and employed to study the sensitivity of the drug diffusion coefficient on the drug solubility. It generates the drug & polymer release profiles, the solid core & the solid-drug interface. The mass transfer for slowly diffusing drugs shows great importance. It also shows that the initial drug release rate is faster than the polymer dissolution rate followed by a slower drug rate release. The saturated drug in the gel layer is not showing significant drug release than polymer dissolution. This was mainly concentrated on the drug release and polymer dissolution of slightly soluble drugs with poly (ethylene oxide) tablets (Per Borgquist, 2006).

The production of Monolithic Matrices by the use of PEO/PCL blends with Carvedilol as API. Matrices were prepared using various extrusion parameters to investigate the effect of screw speed & barrel temp on drug delivery. The extrudate was characterized using steady state parallel plate rheometry, DSC & Dissolution testing. Higher screw speed were showed slightly lower matrices than lower screw speeds but the Dissolution testing showed the incorporation of PCL polymer into a PEO matrix results in a show drug profile (John G. Lyons, 2008).
Past Studies on Anti-Hypertensive Agents:

A large amount of highly water soluble drug (DTZ) was used to evaluate the feasibility of using a counter polymers PEO/PEG matrices for the S.R of for drugs with diff water solubilities were prepared to investigate the effect of drug solubility on the drug release & diffusion properties of matrices. Cross-linked carboxyvinyl polymer (CVP)/PEO/PEG matrices containing a drug were also prepared and there in vitro characteristics were compared with the above. There *invitro* drug release properties were calculated. The drug release was faster for CR-A than CR-B and its rate is also increased to the amount of drug loaded. Extended release of drug was observed upto 6hr with CR-A. To control its faster dissolution & diffusion and made its further extend of drug release up to 24hrs was made with a polymer beaming a opposite charge than the drug consisting charge (Kojima H., 2008).

Polyethylene Glycol (PEG) based biodegradable hydrogel through disulfide crosslinking of polyethylene oxide (PEO) was developed for controlled release. The crosslinking rate was highly dependent on temperature, and incubation at about 40-50°C, was required for efficient crosslinking. The crosslinked PEOS hydrogel showed controlled release of a model drug-Fluorescein isothiocyanate (FITC)-labelled dextran-because the disulfide bond. The temperature sensitive crosslinking and the hydrogel formation have the potential for use as an injectable biogel precursor (Heebeom Koo, 2009).

The *in-vitro* and *in-vivo* evaluation were done in the mini matrices by hot-melt extrusion method with the change of PEO or PEG ratio for 30% w/w drug and E.C as sustaining action. The polymer used was helped to increase drug release. An increase in concentration yields faster drug release (irrespective of M.W). Smooth extrudates were obtained when it was processed at 40°C & 70°C. Raman spectra showed the drug distribution was homogeneous in mini matrices which was independent of hydrophilic polymer concentration & M.W. with a oral dose of 200mg of drug was administered to dogs for immediate release as a sustained-release or as experimental mini matrices. The S.R effect was limited and the relative Bio-availabilities of 66.2% & 148.2% were obtained for 5% & 20% PEO 1,000,000 mini matrices (Verhoeven E., 2009).
This study was to demonstrate the possible use of dynamic neural networks to the drug release from PEO hydrophilic matrices for various formulations by direct compression. Fractions of polymers & compression force were used on most influential factors on drug release profiles. In vitro release profile were used as dynamic neural networks, because it has an advantage in drug release. The assessment was done to determine the correlations between predicted and experimentally obtained data. For accurate prediction calculated difference ($f_1$) & similarity ($f_2$) factors are indicate the dynamic neural work. Then it was compared with static network & multi-layered per captions. This study also demonstrated differences between the used polyox in respect to drug release and suggests explanations for the results obtained (Jelena Petrovic, 2009).

The matrix erosion profile shows the PEG erosion kinetic depends on the ratio of PEG to PEO. The release mechanism of Acetaminophen along with PEO & PEG at different ratios from the extended-release matrix tablets were observed through magnetic resonance imaging (MRI), and the polymeric erosion of the drug from the matrix tablets was quantified using size – exclusion chromatography (SEC). The ability of hydrogel forming were observed and the layer thickness is corresponding to the diffusion length of the drug has got a good correlations with drug release profile (Tomokazu Tajiri, 2010).

**Past studies on Verapamil Hydrochloride:**

A rapid, simple and sensitive validated visible spectrophotometric method has been described for the assay of verapamil hydrochloride either in pure form or in pharmaceutical formulations. The method involves the oxidation of the verapamil hydrochloride with N-bromosuccinimide in perchloric acid medium at room temperature, leading to the formation of a yellow colored product, which absorbs maximally at 415 nm. Under the optimized experimental conditions. Results of analyses were optimized and validated statistically and through recovery studies (Nafisur Rahman; 2005).

Two spectrophotometric methods have been described for the assay of verapamil hydrochloride in drug formulations. Method A is based on the oxidation of the drug with potassium metaperiodate in sulfuric acid medium to give colored product, which absorbs maximally at 425 nm. Method B involves the formation of colored chloroform extractable...
ion-pair complex of the drug with tropaeolin 000 No.1 at pH 4.0 showing absorption peak at 400 nm. Results of analyses were validated statistically and through recovery studies. Both methods have been successfully applied to the determination of verapamil hydrochloride in drug formulations (Nafisur Rahman 2004).

The purpose of the research work was development and evaluation bi-layer floating tablets for verapamil hydrochloride. Verapamil hydrochloride has pH dependent solubility. Verapamil hydrochloride bi-layer floating tablets have two layers one immediate release layer and second floating sustained release layer. Verapamil hydrochloride bi-layer floating tablet releases drug in two phases i.e. immediate and sustained drug release. Direct compression method was used to formulate bi-layer floating tablets. All bi-layer formulation float more than 12 h and sustained drug release above 12 h. Kinetic release study suggests that release mechanism is quasi Fickian. This showed that, tablet significantly float in rabbit stomach for more than 7 h (Londhe S, 2010).

The C.R. matrix tablets were prepared by direct compression and evaluated for hardness, friability, thickness, drug content and its dissolution parameters. Tablets were prepared by using calpal 934P & MPMC k-100 M as polymer, pH 6.8 phosphate buffer as medium for 24 hrs a medium to its dissolution profile determined. Losortan potassium release shown close to zero order and follow diffusion dependent release. Drug release follows non-fickian release with an irrespective of polymer & its concentration. And found finally the polymer were used have a good candidates for preparing C.R. matrix tablets of Losortan potassium (Vidyadhara S, 2010).

A sensitive high-performance liquid chromatographic assay suitable for the simultaneous detection of Verapamil Hydrochloride and its major active metabolite non Verapamil Hydrochloride in human plasma is described. Plasma samples were extracted using a mix of n-hexane and n-butyl alcohol (12:1) to given mean recovers of >92% in both. Extracts were chromatographed on a C18 RP column a mobile phase composed of methanol, water and Triethanolamine (67:33:0.4, Ph 6.7) UV (max 279nm) detection. The curves were linear over a wide range of conc(25-1000 ng/ml). By this assay plasma cone of both were detected in six volunteers after a single oral dose of 120mg of Verapamil Hydrochloride (Kalta R.R, 2008).
A bioanalytical HPLC procedure for the detection of Verapamil Hydrochloride in plasma was validated. The plasma samples after extraction were analysed HPLC RP-18 column. The method sensitivity, specificity, linearity, accuracy, precision and sample stability were reported. The method was suitable for ph.co.kin studies of Verapamil Hydrochloride (Srinivasa Rao K, 2010).

Formation of complex by the interacts between Verapamil Hydrochloride and Human Serum Albumin in water at 25°C was investigated using a range of physicochemical techniques. Measurement of the solution conductivity and the electrophoretic mobility of the complexes showed an ionic adsorption of the drug on the protein surface leading to surface saturation at a Vpm core between 10 & 15 m mol/Kg. The results indicate decreasing stability of the colloidal dispersion of the drug-protein complex be in the core of added drug (Mariadel Rosario Brunetlo, 2009).

A highly sensitive spectrofluorometric method was developed for the detection of Verapamil Hydrochloride in formulations & Biological fluids. It is based on the investigates of the fluorescence. Spectral behavior of Verapamil Hydrochloride in micellar system. Fluorescence was measured at 310nm after excitant at 231nm. The Fluorescence cone plots were rectilinear other the range of 0.02-0.2 and 0.02-0.025μg/ml 2n Sodium dodecyl/sulphate (SDS) and beta cyclodextrin (beta-CD), respectively. This method was applied to the detection of Verapamil Hydrochloride in real and spiked human plasma. There was also extended to the stability studies of Verapamil Hydrochloride after exposure to UV radiation and upon oxidation H₂O₂ (Kathnesan K, 2008).

The work was done base on to release immediately and later shows a sustained release. Tablets were prepared by Direct Compression. The kinetic study suggests that release mechanism is quasi fickian. The optimized formation was selected based on in vitro characteristics and used in In-vivo radiographic studies in rabbits (Vanessa Mariados passos MAID, 2005).
Past Studies on Losartan Potassium:

The Angiotensin II antagonists block the blood pressure response to exogenous angiotensin II in healthy volunteers, decrease baseline blood pressure in both normal & hypertensive Patients, Produce a marked rise in plasma renin activity and endogenous angiotensin II and rise renal blood flow out altering glomerular filtration rate. The extent of blood pressure reduction in dependent on physiological factors such as sodium and water balance. This also tells further refinement for designing optimal therapeutic regimens and proposing dosage adaptations in specific condition (Sivakumar T, 2007).

A multicentre randomized, double-blind, comparative study of antihypertensive efficiency and safety of Losartan Potassium and Metoprolol was carried out in 77 patients mild to moderate essential hypertension. There was no significant difference between the treatment regimen found during the study in regard to Si SBP and Si DBP decrease. No significant difference between treatment regimen were observed in regard to complete normalization of blood pressure and overall blood pressure response. In both groups heart rate decreased significantly & similarly. Both treatments were well tolerated and there were no serious adverse events (Kavitha J, 2010).

This study was conducted in an open, randomised, 2-period cross over design and a 1-week washout period. The plasma samples after 24 hr’s were analyzed by combined RP HPLC & LC-MS. Various pharmacokinetics parameters were obtained and it was concluded that the Losartan Potassium immediate release 50mg tablets was bioequivalent to the cozaar immediate release 50mg tablets according to both the rate and extent of absorption (Thomas A.B, 2010).

The bioavailability of new Losartan Potassium preparation was compared the reference preparation of the drug in 24 healthy male volunteers, aged between 19 and 32. The open, randomised cross over study design was performed. The plasma cover of Losartan Potassium & its metabolites were analyzed by a rapid & sensitive HPLC method UV detection. The pharmacokinetic parameter included $AUC_{0-36L_v}$, $C_{max}$, $t_{1/2}$ and $K_e$ values of $AUC_{0-\infty}$ demonstrate nearly identical bio availability of Losartan Potassium from
the examined formulation. No statistical difference were observed for $C_{\text{max}}$ and the area under the plasma concentration time curve for both Losartan Potassium and its metabolites. This study shows that the test formulation is bioequivalent to the reference formulations for L.P and its main active metabolite (Gan-Linchen 1996).