CHAPTER 2

LITERATURE REVIEW
PAST STUDIES ON ORAL CONTROLLED RELEASE MATRIX TABLETS

1. Theophylline matrix tablets were prepared by direct compression of drug and different types of methacrylates. The influence of varying the polymer/polymer (w/w) ratio and the drug incorporation method was evaluated. Tablets with a 0.7:0.3 w/w mixture of Eudragit L100-Eudragit RLPO showed highly reproducible drug release profiles and allowed 100% released drug after 360 min.\(^{(111)}\)

2. A mathematical model is developed to describe the transport phenomena of water soluble drug caffeine from poly (ethylene oxide) tablets. \textit{In vitro} studies on swelling, dissolution behavior of PEOs with different molecular weights and drug release were carried out. Drug release profiles using this model are predicted with a very good agreement with experimental data and the overall drug release process is found to be highly dependent on the matrix swelling, drug and water diffusion and polymer dissolution. \(^{(112)}\)

3. A monolithic matrix system for glipizide was developed using hydroxypropyl methylcellulose and poly (ethylene oxide). The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. \(^{(113)}\)

4. Extended-release matrix tablets of zidovudine were formulated using hydrophilic Eudragit RLPO and RSPO alone and in combination with hydrophobic ethyl cellulose. The \textit{in-vitro} drug release studies and \textit{in vivo}
investigations in rabbits were carried out. The results indicated the prepared tablets of zidovudine are effective than conventional systems, with improved efficiency and patient comfort. \(^{114}\)

5. A model for the drug release from matrices was presented and used to study the influence of the drug diffusion coefficient, the drug solubility and the initial drug loading on the drug release profile. The model is verified against drug release data and polymer dissolution data for drug loaded poly (ethylene oxide) tablets, for a drugs metyl paraben and a saligenin. \(^{115}\)

6. The effects of particle size, viscosity and chemical composition of alginates on drug release from alginate matrix tablets were studied using chlorpheniramine maleate as model drug. The results showed that sodium alginate matrices can sustain drug release for at least 8 h, even for a highly water-soluble drug in the presence of a water soluble excipient. \(^{116}\)

7. Sustained release tablets of tramadol hydrochloride were prepared using natural gums like xanthan and guar gum, and with the hydrophilic matrices of hydroxypropyl methylcellulose and carboxymethyl cellulose. The prepared tablets were evaluated drug release patterns and for polymer hydration. The results showed that guar gum only cannot extend the drug release for prolonged period of time, while xanthan gum along various other polymers extended the drug release for an extended period of time. \(^{117}\)
8. Effect of the types of diluent and the diluent to matrix ratio on the drug release behavior from both lipophilic and hydrophilic matrix tablets was studied using ketoprofen, theophylline and sodium sulphadiazine as model drugs. The results obtained with the three examined drugs explained the role of the drug solubility in determining the influence of formulation parameters on drug release rate from the matrix tablets. \(^{(118)}\)

9. Effect of formulation variables on drug release from the prepared three layered matrix tablets was investigated. Chlorpheniramine maleate sustained release tablet were prepared by hot-melt extrusion containing chitosan–xanthan gum as matrix materials. The drug release exhibited pH and buffer species independent attributable to slow media uptake into tablet that resulted from the molten state of preparation process and the inter- and intra-molecular hydrogelation of the matrix materials. \(^{(119)}\)

10. The effect of drug solubility on polymer hydration and drug dissolution from modified release matrix tablets of poly (ethylene oxide) were studied using acetaminophen and ibuprofen as model drugs. Delayed drug release was attributed due to the formation of hydrogel layer on the surface of the tablet and the penetration of water into matrix core through drug dissolution and diffusion. \(^{(120)}\)

11. Matrix tablet formulations of rifampicin and isoniazid combination were prepared using hydrophilic polymers HPMC, HPC and Eudragit L100 55 to study the design parameters and to evaluate in vitro release characteristics.
Formulations containing 80% HPC and 60% Eudragit were found to be of ideal and provided required release profile for both rifampicin and isoniazid.\(^{(121)}\)

12. Influence of interpolyelectrolyte complexes (IPEC) between chitosan and Eudragit L100 or Eudragit L100 55 was investigated using elementary analysis. Diclofenac sodium was used as a model drug. The physicochemical properties of IPECs made up of chitosan and Eudragit L–L100 and L100-55 was investigated. The results indicated that the release of diclofenac sodium was significantly delayed from tablets made up of the IPECs and can be modified by choosing Eudragit L copolymer types.\(^{(122)}\)

13. The effect of variables such as pH and salt concentration on biphasic release characteristics of matrix tablets prepared from the HPMC, pectin and calcium chloride were investigated using indomethacin as model drug. In vivo pharmacokinetic studies were also performed to evaluate the effect of biphasic release. In vivo results indicated that the in situ cross linking HPMC/pectin/calcium matrix tablet could provide sufficient time delay, which may be related with more effective delivery of drugs to the colon.\(^{(123)}\)

14. Poly (ethylene oxide) (PEO) tablets with three layered structure were prepared by direct compression with solid dispersed nifedipine. Carbopol was coated on both sides of the central PEO matrix in PEG4000. The slower swelling and dissolution of the PEO retarded the release of the NP and controlled release was obtained. Various factors such as the molecular weight of PEO, pH of the dissolution medium, ionic strength and buffer
concentration were also investigated for their effect on the dissolution rate. \(^{(124)}\)

15. The influence of polymer level, type and fillers on drug release has been investigated using baclofen as model drug. The matrix tablets were prepared using various grades of Eudragits and hydrogenated castor oil by hot melt granulation process and wet granulation process. The results suggested that higher polymeric content in the matrix decreased the release rate of drug. \(^{(125)}\)

16. Glipizide containing matrices were formulated using ethylcellulose, hydroxylpropyl methylcellulose, xanthan gum and guar gum. The *in vitro in vivo* correlation for matrix tablets and the effect of polymeric blends on *in vitro* release profiles was studied. From the results it was observed that direct compression of drug with gum and other polymers effectively controlled glipizide release. \(^{(126)}\)

17. Metranidazole and theophylline were formulated as matrix tablets using two grades of PEO, and dissolution was performed initially and after storage of tablets at various conditions. Matrix tablets were characterized by molecular modeling. From the results it is found that hydration and molecular weight of polymer has effect on ageing of PEO and on the drug release patterns. \(^{(127)}\)
18. The degree of swelling and the swelling kinetics of poly (ethylene oxide) matrix tablets without any additives for matrices were studied with different molecular weight polydispersities. From the *in vitro* results it was observed that the drug release rate not only depends on the polymer erosion, but also on the swelling kinetics. \(^{(128)}\)

19. Diclofenac sodium was formulated as matrix tablets using poly (ethylene oxide). A mathematical model was used for the characterization of drug diffusion from matrix tablets. The model was developed on the basis of the diffusion theory accounting for the characteristics of the polymer swelling with subsequent dissolution in water. A good agreement of the developed model with experimental results was observed. \(^{(129)}\)

20. Venlafaxine hydrochloride matrix tablets were prepared by using hydrophilic gums and polymers such as xanthan gum and various other polymers. The prepared tablets were studied for excipient compatibility, solution stability of drug, physical parameters of tablets and for *in vitro* patterns. The data showed that guar gum alone or in combination with xanthan gum could not efficiently retard the drug release, while xanthan gum along with HPMC could retard the release of drug for 20 hours. \(^{(130)}\)

21. Diltiazem hydrochloride was formulated as once a day sustained release matrix tablet with a combination of HPMC, different grades of Eudragits and ethyl cellulose. The tablets were evaluated for *in vitro* drug release. The results indicated that the hydrophilic matrix systems containing water
soluble drugs, an initial burst release of the drug is generally observed this can be overcome by using a finely hydrophobic polymer which is to be added to the matrix system.\textsuperscript{(131)}

22. Salbutamol sulfate was formulated as matrix tablet. An artificial neural network was used to optimize the release of the drug from hydrophilic matrix tablets. The formulations were prepared using varying the levels of polymers such as Methocel K100M, xanthan gum, carbopol 974P and surelease. The results revealed that a neural network with nine nodes was optimal for developing and optimizing the formulations for salbutamol. \textsuperscript{(132)}

23. \textit{In vitro} and \textit{In vivo} erosion profiles of two tablet formulations consisting of hydroxypropyl methylcellulose was carried out using gravimetric and scintigraphic methods for tablet. Good correlation was found between \textit{in vitro} gravimetric and scintigraphic erosion profiles for both tablets. The study demonstrated that a matrix formulation with a lower concentration of HPMC and higher lactose concentration is more likely to perform poorly in the \textit{in vivo} environment. \textsuperscript{(133)}

24. Acetaminophen was formulated as extended release tablets with polymer matrices of poly (ethylene oxide) and polyethylene glycol. Polymeric erosion contribution to acetaminophen release from hydrogel matrix tablets was directly quantified using size exclusion chromatography. The matrix erosion profile indicated that the PEG erosion kinetic depends primarily on the composition ratio of PEG to PEO. \textsuperscript{(134)}
PAST STUDIES ON ORAL CONTROLLED RELEASE FORMULATIONS OF VERAPAMIL HYDROCHLORIDE

1. Verapamil hydrochloride sustained release formulations were prepared as ethylcellulose coated pellets in hard gelatin capsules and evaluated for in vivo release studies on healthy human volunteers. The effect of food on the GI transit time and absorption rate of verapamil was studied. From the data obtained it was observed that presence of food the absorption began earlier and more strongly than under fasting conditions due to longer retention of the pellets in the upper gastrointestinal tract, which favors the drug absorption.\(^{(135)}\)

2. Verapamil hydrochloride matrix tablets were prepared using Carbopol 934P and evaluated for the interaction of polymer with drug, effect of the drug to polymer ratio, the pH of the medium, and the ionic strength on the extent of interaction using a \(2^3\) factorial experiment. Results revealed that the drug to polymer ratio had the most influential effect on the rate of water uptake of the polymer matrix for the controlled release of verapamil. \(^{(136)}\)

3. The effect of ionic and non ionic excipients and additives as modulators of swelling and erosion kinetics and verapamil HCl release from guar based matrix tablets was investigated. The results suggested that the physicochemical nature of added excipients significantly influences the release kinetics from guar-based formulations. \(^{(137)}\)
4. Controlled release microparticles of verapamil hydrochloride were prepared with the ultrasonic spray congealing technique using waxes and evaluated for in vitro drug release. The results indicated that by selecting the type and the amount of the carriers, microparticles with a spherical shape and good encapsulation efficiency were prepared. These microparticles showed zero order release for 8 h. \(^{138}\)

5. Verapamil hydrochloride matrix tablets were prepared by using Eudragit RSPO and Eudragit RSPO & RLPO mixture. Succinic acid was added as pH adjuster to the formulations to overcome the pH-dependent solubility of the weakly basic drug Verapamil. Drug release from tablets was studied. From the results it was observed that release of verapamil hydrochloride from Eudragit RLPO and RSPO coated tablets was found to be constant and more pH-independent than matrix tablets containing only Eudragit RSPO. \(^{139}\)

6. The influence of formulation factors on the controlled release of verapamil HCl from matrix tablets was studied by using a \(2^3\) full factorial design using Eudragit RS PO, RL PO, HPMC K4M as polymers and PEG 4000 as channeling agent cum plasticizer. The prepared tablets were evaluated for in vitro dissolution studies. From the results it was observed that the required release pattern was shown by batches containing a low level of Eudragit RS PO/RL PO, low level of HPMC K4M, and high level of PEG 4000. \(^{140}\)
7. Verapamil hydrochloride and papaverine hydrochloride matrix tablets were prepared using a methacrylic polymer Eudragit L100-55 and an acrylic acid polymer Carbopol 71G. The release of basic drugs from the matrix microenvironmental pH was studied using microelectrodes. For verapamil HCl, incorporation of L100-55 resulted in release retardation due to an interaction between the anionic polymer and the cationic drug and the extent of retardation was increased with an increase in the polymer level. (141)

8. A new controlled release chewable tablet formulation of verapamil hydrochloride was prepared by compressing beads coated with multiple layers including drug, HPMC, poly(ethylene oxide), ethyl cellulose and sodium starch glycolate. The tablet formulation was evaluated in three different forms like whole tablet, crushed tablet and tablet chewed in the mouth. Sustained release from the tablets was maintained and was similar to the drug release from commercially available tablet. (142)

9. Matrix tablets of verapamil hydrochloride were prepared by direct compression process using different types of hydroxypropyl methylcellulose polymers and evaluated for in vitro drug release. The drug release profiles of optimized formulations were compared with marketed formulations. The results revealed that increasing amount and viscosity grade of HPMC resulted in a decrease in release of drug from the matrices. (143)
10. Verapamil hydrochloride was formulated as 1 and 3 layer matrix tablets using natural and semi synthetic polymers like HPMC, tragacanth and acacia. The potency of tragacanth and acacia to sustain the release of a verapamil hydrochloride was studied. From the in vitro drug release studies it was observed that tragacanth when used as the carrier produced prolonged release either alone or in combination with the other polymers while acacia did not show enough sustained effect in one and three layer matrix tablets.\textsuperscript{144}

11. The swelling nature and the release of the verapamil from calcium alginate and chitosan treated alginate beads was observed. The morphology of the prepared beads was studied by SEM method. The swelling of beads in various dissolution medium was found to be depended on presence of the polyelectrolytes between alginates and chitosan and the pH of the medium. The chitosan significantly retarded the release of verapamil from alginate beads. \textsuperscript{145}

12. Verapamil hydrochloride matrix tablets were prepared and were compared to a marketed sustained release product of verapamil to investigate the rate of hydration, erosion, and drug release mechanism using different granulating fluids such as Surelease and Eudragit NE 30D. Results revealed that erosion rate of the marketed product was highest than in house prepared formulation. \textsuperscript{146}

13. Controlled release matrix tablets of verapamil hydrochloride were formulated using different grades of poly (ethylene oxides) by direct
compression process. The prepared tablets were evaluated for in vitro drug release studies and compared with marketed tablets. The results indicated that the drug release from the tablets containing high molecular weight poly (ethylene oxides) was extended than the tablets containing low molecular weight poly (ethylene oxides).\(^{147}\)

14. Percolation theory has been applied to multi component hydrophilic matrices to study the existence of critical points governing the water and drug transport inside HPMC matrix systems obtained with different polymer viscosity grades. For this study verapamil hydrochloride was used as model drug. From the point of view of the percolation theory, the optimum concentration for all the studied polymers, to obtain a hydrophilic matrix system for the controlled release of verapamil HCl is higher than 20% of HPMC. \(^{148}\)

15. Verapamil HCl was formulated as sustained release dosage form using glyceryl monostearate and stearic acid as waxy polymers by melt granulation technique. The influence of waxes on the release of drug from matrix tablets and effect of release modifiers was studied. The results indicated that increase in amount of waxes retarded the drug release from matrix. The addition of release modifiers like lactose produces a faster release of drug than MCC. \(^{149}\)

16. Verapamil hydrochloride matrix tablets were prepared by newly synthesized zwitter ionic copolymer and the tablets were evaluated for drug
release profiles. The study results revealed that compared with other investigated matrices like Kollidon SR and HPMC K15 M the verapamil hydrochloride release rate is much higher from zwitter ionic copolymer and these were proved as matrix carriers for basic drugs such as verapamil hydrochloride.\textsuperscript{(150)}

17. Verapamil hydrochloride matrix tablets were prepared using sodium alginate to achieve pH-independent release. pH independent drug release was achieved from matrix tablets consisting of selected alginates. The addition of fumaric acid to drug/alginate based matrix systems increased the solubility of the weakly basic drug at higher pH.\textsuperscript{(151)}

18. Verapamil hydrochloride gastroretentive tablets were developed using different hydrocolloid polymers including carbopol, HPMC and xanthan gum by direct compression process. The tablets were evaluated for the \textit{in vitro} buoyancy studies and \textit{in vitro} dissolution studies. From the results it was observed the tablets exhibited zero order and non fickian release and no significant change in physical appearance, drug content, total buoyancy time or \textit{in vitro} dissolution study after storage for three months.\textsuperscript{(152)}

19. Verapamil hydrochloride sustained release tablets were formulated using glyceryl palmitostearate and evaluated for \textit{in vitro} and \textit{in vivo} drug release studies and compared with marketed formulation. The tablets were prepared by direct compression of the granules which were prepared by melt
granulation technique. The results of in vivo studies showed the sustained action of the formulation with more uniform plasma concentrations. (153)

20. Verapamil hydrochloride was formulated as extended release pellets. The pellets were prepared by extrusion spherization technique and evaluated for in vitro release. The prepared verapamil pellets were evaluated for the influence of organic acids on drug release. The dissolution rate of the drug from pellets containing fumaric acid was high at elevated pH, which may be due to creation of micro environmental pH inside the pellet core. (154)

21. Sustained release microcapsules of verapamil hydrochloride were prepared using various polymers by emulsification method. The prepared microcapsules were evaluated for flow behavior, drug entrapment efficiency, in vitro dissolution studies, in vivo studies and stability studies. The results revealed that the drug release from the microcapsules was found to be following non fickian diffusion. In vivo results for pharmacokinetic parameters revealed that t_{max} of reference and test formulations were almost same. (155)

**PAST STUDIES ON ORAL CONTROLLED RELEASE FORMULATIONS OF LOSARTAN POTASSIUM**

1. Sustained release dosage forms of losartan potassium were developed using response surface methodology (RSM). HPMC K15M, HPMC K100M and sodium carboxymethyl cellulose were used as release retardant polymers. Linearity was observed between the actual and predicted values of
the response variables which suggested the prognostic ability of the RSM design. DSC and FTIR studies and stability study of the optimized formulation proved the integrity of the developed hydrophilic matrix tablets. (156)

2. Losartan potassium was formulated as oral controlled release matrix tablets by using poly (ethylene oxides) .The influence of polymer level and type if fillers on the release rate of losartan potassium from matrix tablets were studied. From the results it was observed that higher polymeric content in the matrix decreased the release rate of drug. Replacement of lactose with anhydrous dibasic calcium phosphate and microcrystalline cellulose had significantly retarded the release rate of losartan potassium. (157)

3. Losartan potassium microspheres were prepared by solvent evaporation method using ethyl cellulose and Acycoat L30D as rate controlling polymers. The prepared microspheres were evaluated for morphology using SEM, particle size distribution, total entrapment of drug into the microparticles and for the release profile. The results revealed that in vitro drug release rate for microspheres was found to be sustained over 8 hours with good entrapment efficiency. (158)

4. Losartan potassium sustained release matrix tablets were prepared using various hydrophilic and hydrophobic polymers. The matrix tablets were prepared according to $2^3$ full factorial designs. The results revealed that hydrophilic matrix of HPMC alone could not control the losartan potassium
release effectively for 24 hours. The matrix tablet prepared with hydrophilic polymer and hydrophobic polymer is a better system for once daily sustained release of losartan potassium.\(^{(159)}\)

5. Losartan potassium controlled release matrix tablets were prepared by direct compression by using Carbopol 934P and HPMC K 100M as release rate retardant polymers. The prepared tablets were evaluated for various parameters. From the results obtained it was observed that irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-fickian release and the polymers HPMC K100M and carbopol 934P were proved as good candidates for preparing controlled release matrix tablets of losartan potassium.\(^{(160)}\)

6. Losartan potassium matrix tablets were prepared by hydrophilic and hydrophobic polymer combinations. Preformulation studies were performed to study the interaction between the drug and polymers. \textit{In vitro} dissolution studies were also carried out. The results of dissolution studies indicated that formulation containing SCMC and ethyl cellulose produced sustained effect over a period of 12hrs. \(^{(161)}\)

7. Losartan potassium controlled release matrix tablets were formulated by simplex lattice design using of HPMC, Eudragit RSPO, Eudragit RLPO and ethylcellulose as polymers. The tablets were evaluated for establishing the relationship and influence of different polymer content levels on the \textit{in vitro} drug release. The results revealed that HPMC caused initial burst release of
drug and hence combining HPMC with Eudragit sustained the drug release for prolonged time. (162)