CHAPTER 2

Literature Survey on Work
Done
# Literature Review

## CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER NO.</th>
<th>TITLE</th>
<th>PAGE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 2</td>
<td>LITERATURE SURVEY ON WORKDONE</td>
<td>36</td>
</tr>
<tr>
<td>2.1</td>
<td>Literature Review on Controlled Porosity Osmotic Pump</td>
<td>36</td>
</tr>
<tr>
<td>2.2</td>
<td>Literature Review on Elementary Porosity Osmotic Pump</td>
<td>43</td>
</tr>
<tr>
<td>2.3</td>
<td>Literature Review on Push-Pull Porosity Osmotic Pump</td>
<td>49</td>
</tr>
<tr>
<td>2.4</td>
<td>Literature Review on Work done on Flurbiprofen</td>
<td>53</td>
</tr>
<tr>
<td>2.5</td>
<td>Literature Review on Work done on Nicardipine Hydrochloride</td>
<td>56</td>
</tr>
<tr>
<td>2.6</td>
<td>References</td>
<td>60</td>
</tr>
</tbody>
</table>
2.1 Literature Review on Controlled Porosity Osmotic Pump

Chauhan CS et al. had formulated Controlled Porosity Osmotic Pump (CPOP) for the Delivery of Flurbiprofen. CPOP contains water-soluble additives in the coating membrane, which in contact with aqueous environment dissolves and results in formation of micro porous membrane. In the present investigation, effort has been made to study release mechanism of drug having low water solubility by means of controlled porosity osmotic pump. The capsule membrane was prepared by phase inversion technique. It was carried by dipping the stainless steel mould in a 15% solution of cellulose acetate containing varying amounts of pore-forming agent, glycerol (50% to 70% w/w), followed by quenching in an aqueous solution (10% w/v glycerol), which resulted in the formation of the asymmetric membrane. The drug selected for this study, Flurbiprofen, has low water solubility and hence is unable to create osmotic pressure to cause drug release. To enhance the solubility and its osmotic pressure, this study was conducted with a solubility enhancer sodium lauryl sulfate (SLS). Release rate studies reveled that less than 10% of drug was released from the system without SLS, while about 75% release was observed from systems containing SLS. The release rate increased as the concentration of pore forming agent increased. (Chauhan and Choudhury 193-98)

Pratim K. et al. had worked on Osmotic Delivery of Flurbiprofen through Controlled Porosity Asymmetric Membrane Capsule. The release of poorly water-soluble drug, flurbiprofen, through asymmetric membrane capsule of cellulose acetate containing different pore forming agents like glycerol, polyethylene glycol 400, and dibutyl phthalate, in presence of sodium lauryl sulfate was investigated. The asymmetric membrane was fabricated in the shape of capsule body and cap by phase inversion technique. The type of pore forming agent incorporated had a marked influence on the porosity of the asymmetric membrane. However flurbiprofen due to its poor solubility was unable to create enough osmotic pressure and hence less than 10% of drug was released from all the systems without SLS. However when the study was conducted with SLS, a maximum release of 72% was observed from the capsule with 70% glycerol. The release rates were found to increase with the increase in the concentration of pore forming agent and the amount of SLS encapsulated. (Choudhury, Chauhan and Ranawat 1135-41)

Ozdemir et al. focused on design of a controlled release osmotic pump system of ibuprofen. The effect of the delivery orifices and the concentration of osmotic agents on the rate of release of the active material was investigated. For this purpose, ibuprofen tablets were prepared and sodium chloride and polyethylene glycol 6000 were used as osmotic agents. The
tablets were coated with a mixture of cellulose acetate and polyethylene glycol 400 by the use of a modified fluidized bed apparatus. Delivery orifices on the coated tablets are produced using a microdrill. Finally, it was observed that the release rate of ibuprofen was influenced by the concentration of osmotic agents sodium chloride and polyethylene glycol 6000. (Özdemir and Sahin 91-97)

Rabiu Yakubu et al. had carried out study to design a 24-hour controlled porosity osmotic pump system that utilizes polyvinyl pyrrolidone (PVP) as an osmotic-suspending/release retarding agent of drugs. Osmotic tablet cores containing various ratios of ketoprofen and PVP were prepared by wet granulation and initially spray coated with similar solution of cellulose acetate. A formulation containing ketoprofen and PVP at a ratio of 1:7 was selected for further studies. The final formulation containing PVP K-30 in the tablet core augmented the release of ketoprofen (poorly water-soluble) up to 90% over 24 hours much higher than either PVP K-25 or PVP K-90 and retarded the release of pseudoephedrine HCl (highly water-soluble) up to 18 hours. This study proposed the dual use of PVP in osmotic pump systems containing solids to modulate the release of either poorly or highly water-soluble drug. (Yakubu, Peh and Tan 1430-38)

Garg et al. developed extended release formulation of glipizide based on osmotic technology. The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane. The manufacturing procedure was found to be reproducible and formulations were stable after 3 months of accelerated stability studies. (Verma and Garg 513-25)

Hui Liu et al. had studied a microbially triggered colon-targeted osmotic pump (MTCT-OP). The gelable property at acid condition and colon-specific biodegradation of chitosan were used to: (1) produce the osmotic pressure, (2) form the drug suspension and (3) form the in situ delivery pores for colon-specific drug release, respectively. The effects of different formulation variables, including the level of pH-regulating excipient (citric acid) and the amount of chitosan in the core, the weight gain of semipermeable membrane and enteric-
coating membrane, and the level of pore former (chitosan) in the semipermeable membrane, have been studied. The amount of budesonide release was directly proportional to the initial level of pore former, but inversely related to the weight of semipermeable membrane. The effects of variations in the level of citric acid and chitosan in the core formulation on drug release were studied. The different levels of enteric-coating membrane could prevent cellulose acetate membrane (containing chitosan as pore former) from forming pore or rupture before contact with simulated colonic fluid, but had no effect on the drug release. Budesonide release from the developed formulation was inversely proportional to the osmotic pressure of the release medium, confirming that osmotic pumping was the major mechanism of drug release. These results showed that MTCT-OP based on osmotic technology and microbially triggered mechanism had a high potential for colon-specific drug delivery. (Liu et al. 115-24)

Garg S. et al. had developed extended release formulations of isosorbide mononitrate (IMN), based on osmotic technology. Formulation variables like type (PVP, PEG-4000, and HPMC) and level of pore former (0–55%, w/w of polymer), percent weight gain were found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. Satisfactory burst strength (more than 320 g) was obtained when PVP was used as pore former (up to 55%, w/w of polymer) at the membrane weight of 7.5% and more. The release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The formulations were found to be stable after 3 months of accelerated stability studies. Prediction of steady-state levels showed the plasma concentrations of IMN to be within the desired range. (Verma, Kaushal and Garg 9-24)

Makhija SN et al. had described a controlled porosity osmotic pump-based drug delivery system in this study. The usual dose of pseudoephedrine is 60 mg to be taken three or four times daily. It has a short plasma half life of 5–8 h. Hence, pseudoephedrine was chosen as a model drug with an aim to develop a controlled release system for a period of 12 h. Sodium bicarbonate was used as the osmogent. The effect of different ratios of drug: osmogent on the in-vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. Different channeling agents tried were diethylphthalate (DEP), dibutylphthalate (DBP), dibutylsebacate (DBS) and polyethyleneglycol 400 (PEG 400). The effect of polymer loading on in-vitro drug release was studied. It was found that drug release rate increased with
the amount of osmogent due to the increased water uptake, and hence increased driving force for drug release. This could be retarded by the proper choice of channeling agent in order to achieve the desired zero order release profile. This system was found to deliver pseudoephedrine at a zero order rate for 12 h. (Makhija and Vavia 5-18)

**Gaylen M. et al.** had manipulated the drug release kinetics from controlled porosity osmotic pumps through application of either solubility- or resin-modulation methods. The solubility of diltiazem hydrochloride was modulated (reduced) for an extended period of 12-14 h through incorporation of controlled release sodium chloride elements into the core tablet formulations. Other diltiazem hydrochloride core tablets were prepared which contained the positively charged anion-exchange resin (poly (4-vinylpyridine). In both instances, *In vitro* diltiazem hydrochloride release profiles that were zero-order and pH-independent were obtained without chemical modification of the drug. Solubility-modulated devices administered to dogs released diltiazem hydrochloride with similar *In vivo*/*In vitro* kinetics. These approaches may be applied in general to extend osmotic pump technology to drugs with intrinsic water solubilities that are too high or low for conventional osmotic pump formulations. (Zentner, McClelland and Sutton 237-43)

**Kazuto Okimotoa et al.** had developed a controlled porosity osmotic pump system for poorly water soluble drugs using sulfobutyl ether-β-cyclodextrin sodium salt, which can act as both a solubilizing and an osmotic agent. The effect of (SBE)$_{7m}$-β-cyclodextrin as the solubilizing and osmotic pump agent was compared with hydroxypropyl-β-cyclodextrin (HP-β-CD), a 7m neutral cyclodextrin, and a sugar mixture (osmotic agent only). Testosterone release from the device was significantly faster with (SBE)$_{7m}$-β-cyclodextrin than with HP-β-CD or the sugar mixture. The solubility of testosterone in the device increased to 76.77mg/ml through complexation with (SBE)$_{7m}$-β-cyclodextrin in the imbibed water. It appears that testosterone release from the device 7m in the presence of (SBE)$_{7m}$-β-cyclodextrin was mainly due to osmotic pumping while for HP-β-CD the major contribution appears to 7m be due to diffusion. In the case of the sugar mixture, testosterone was poorly released, presumably due to the absence of a solubilizer. Therefore, it was concluded that (SBE)$_{7m}$-β-cyclodextrin provides novel properties for the development of controlled- 7m porosity osmotic pump tablets for poor solubility drugs. (Okimoto, Rajewski and Stella 29-38)

**Sutthilug Sotthivirat et al.** had demonstrated the incorporation of sulfobutylether-β-cyclodextrin, (SBE)$_{7M}$-β-CD, results in the complete and sustained release of a sparingly water-soluble drug, prednisolone (PDL) from controlled porosity osmotic pump pellets (CP-
OPP). PDL and CD were prepared in various formulations (physical mixtures and presumed preformed complex). Several factors influencing drug and CD release were explored, and the probable mechanisms of drug release were probed and discussed. A significant improvement in the release of PDL from the CP-OPPs was observed by the incorporation of CD relative to the coated pellet formulation containing lactose in place of the CD. The release profiles of PDL depend on the molar ratio of CD to PDL, thickness of the microporous membrane, and osmotic pressure difference across the membrane. PDL appears to be released as an in situ complex with CD via mainly osmotic pumping during at least the initial portion of the release profiles. (Sotthivirat, Haslam and Stella 2364-74)

Prabakaran D. et al. had developed controlled porosity osmotic pumps of highly aqueous soluble drug containing hydrophilic polymers as release retardants. Diltiazem hydrochloride (DLTZ) is a freely water-soluble drug and the release rates of DLTZ are higher from oral osmotic pumps including CPOPs, in which the drug release is controlled by concentration of pore-forming agents. The effect of appropriate concentration of hydroxypropyl methyl cellulose and sodium carboxy methyl cellulose mixture on the release of DLTZ from CPOPs was studied. In vitro drug release profiles were compared with that of different marketed controlled release formulations and statistically analysed to examine the suitability of CPOP for twice or once daily administration. Drug release from the CPOPs was effectively modified with the concentration of pore-forming agent in membrane and concentration of hydrophilic polymers in the core. CPOPs showed minimum 65% of consistent DLTZ release at 16 h. Statistical analysis confirmed that with an increase in the amount of hydrophilic polymers release rate decreased. Drug release from the systems follows Hixson-Crowell cube root model and mechanism of release follow non-Fickian diffusion. (Prabakaran et al. 435-42)

Lili He et al. had focused on a novel controlled porosity osmotic pump system for sodium ferulate. It was prepared with cellulose acetate (CA) as semipermeable membrane, polyethyleneglycol 400 (PEG 400) as channeling agent and dibutylphthalate (DBP) as plasticizer and release controller. Effects of coating levels, PEG and DBP content and amount of sodium chloride on In vitro release were studied. Coating formulations were optimized by a L9 (34) orthogonal array design (OAD) with three factors at three levels using statistical analysis. Controlled porosity osmotic pump tablets of sodium ferulate made with the optimal formulation were found to have good In vitro and In vivo release characteristics. (He et al. 1022-27)
Kanagale P. et al. had designed a porous osmotic pump–based drug delivery system for controlled release of oxybutynin. The porous osmotic pump contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. Oxybutynin was chosen as a model drug with an aim to develop a controlled release system for a period of 24 hours. Linear and reproducible release similar to that of Ditropan XL was achieved for optimized formulation independent of hydrodynamic conditions. The effect of different formulation variables on the In vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. Oxybutynin release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero-order rate for 20 hours. (Kanagale et al. E13-E19)

Pramod Kumar et al. had prepared and evaluated extended release formulation of tramadol hydrochloride (TRH) based on osmotic technology. Formulation variables such as the level of swellable polymer, plasticizer and the coat thickness of semipermeable membrane (SPM) were found to markedly affect drug release. TRH release was directly proportional to the levels of plasticizer but inversely proportional to the levels of swellable polymer and coat thickness of SPM. Drug release from developed formulations was independent of pH and agitation intensity but dependent on osmotic pressure of the release media. In vivo study was also performed on six healthy human volunteers and various pharmacokinetic parameters (cmax, tmax, AUC0–24, MRT) and relative bioavailability were calculated. The In vitro and In vivo results were compared with the performance of two commercial TRH tablets. The developed formulation provided more prolonged and controlled TRH release compared to the marketed formulation. In vitro-In vivo correlation (IVIVC) was analyzed according to the Wagner-Nelson method. The optimized formulation exhibited good IVIV correlation (R = 0.9750). The manufacturing procedure was found to be reproducible and formulations were stable over 6 months of accelerated stability testing. (Kumar, Singh and Mishra 15-30)

Yueqi BI et al. had developed a controlled porosity osmotic pump system with biphasic release of theophylline for the nocturnal therapy of asthma. The developed system was composed of a tablet-in-tablet (TNT) core and a controlled porosity coating membrane. Release pattern of the developed system was influenced by amount of pore former (18.2—45.5%, w/w of polymer), weight gain (16—26 mg per tablet) of the coating membrane and
osmotic agents used in inner layer of the TNT core. When sodium phosphate and sodium chloride were selected as the osmotic agents in inner and outer layer of the TNT core respectively, target release profile was obtained with coating solution cellulose acetate–polyethylene glycol 400–diethyl phthalate (54.5–36.4–9.1%, w/w) at a weight gain of 16—22 mg per tablet. Theophylline solubility increased as environmental pH exceeded 10.8. At the last stage of the biphasic release, micro-environmental pH in the developed formulation reached 10.9, and theophylline release was promoted by its elevated solubility despite of the decrease of micro-environmental osmotic pressure in the developed formulation.(Bi et al. 1574-80)

Shokri et al. had designed a controlled porosity osmotic pump (CPOP) tablet of diltiazem hydrochloride (DLTZ) to deliver the drug according to the zero order kinetic model over 24 h. CPOPs were prepared by incorporating DLTZ in the tablet core followed by coating with cellulose acetate solution containing various types of pore-formers and plasticizers. In vitro release study was conducted for the prepared formulations and the dissolution profiles were compared throughout four parameters, namely, D24 h (cumulative release in 24 h), tL (lag time), RSQzero (squared correlation coefficient of zero order kinetic) and MPDzero (mean percent deviation from zero order equation). Scanning electron microscopy showed formation of the pores in the semi-permeable membrane after coming in contact with dissolution medium. All formulations released more than 76% of contained drug during 24 h. Drug release rate and lag time were found to be directly proportional to the type and concentration of pore-formers as well as hydrophilicity of plasticizers.(Shokri, Zarrintan et al. 2013)

Adibkia et al. had designed a controlled porosity osmotic pump (CPOP) of diltiazem hydrochloride to deliver the drug in a controlled manner. CPOP tablets were prepared by incorporation of drug in the core and subsequent coating with cellulose acetate as semi-permeable membrane. Non-ionic surfactants were applied as pore-formers as well. The effect of pore-formers concentration on the in vitro release of diltiazem was also studied. The formulations were compared based on four comparative parameters, namely, total drug released after 24 h (D24h), lag-time (tL), squared correlation coefficient of zero order equation (RSQzero) and mean percent deviation from zero order kinetic (MPDzero). It was revealed that drug release rate was directly proportional to the concentration of the pore-formers. The value of D24h in the formulations containing Tween 80 (10%) and Brij 35 (5%) were found to be more than 94.9%, and drug release followed zero order kinetic (RSQzero > 0.99 and MPDzero < 8%) with acceptable tL (lower than 1 h). (Adibkia, Ghanbarzadeh et al. 2013)
2.2 Literature Review on Elementary Porosity Osmotic Pump

**Kanagale P. et al.** focused on pharmaceutical development of solid dispersion based osmotic drug delivery system for nifedipine. Elementary osmotic pumps (EOP) are well known for delivering moderately soluble drugs at a zero order rate. The aim of the present study was to develop a solid dispersion based EOP system for a poorly water-soluble drug, nifedipine and deliver it in a zero order fashion over an extended period of time. Solid dispersions were prepared by hot melt technique using Poloxamer-188 at various ratios of drug and polymer (1:1, 1:5 and 1:10, on weight basis) and investigated for solubility study. Core tablets using solid dispersions were prepared and coated with cellulose acetate and PEG-400. An orifice was drilled manually to create passage for drug release. The system was optimized for amount of osmogeent, membrane weight gain, amount of plasticiser and diameter of the orifice, to achieve desired release profile. The osmotic system was found to deliver nifedipine at a zero order rate for 20 h. The drug release from the developed formulation was independent of pH and agitational intensity. *(Kanagale et al. 306-11)*

**Pramod Kumar et al.** had developed and evaluated elementary osmotic pump (EOP) of highly water soluble drug tramadol hydrochloride (TRH). Formulation variables like levels of swellable polymer (10-21.87 %) and plasticizer (0-20% w/w of polymer), and coat thickness of semipermeable membrane (SPM) were found to affect the drug release from the developed formulations. TRH release was directly proportional to the level of plasticizer and osmotic pressure generated by osmotic agent but inversely proportional to the level of swellable polymer within the core and coat thickness of SPM. Drug release from developed formulations was independent of pH and agitation intensities of release media. The *in-vitro* results of the developed formulations were compared with performance of standard marketed formulation of TRH. The developed formulation provided more prolonged and controlled TRH release as compared to marketed formulation. *(Kumar, Singh and Mishra 130-39)*

**Rani M. et al.** had prepared and evaluated fabricated matrix (FM), osmotic matrix (OM), and osmotic pump (OP) tablets for controlled delivery of diclofenac sodium (DS). All formulations were evaluated for various physical parameters. *In vivo* studies were performed in 6 healthy human volunteers; the drug was assayed in plasma using HPLC, and results were compared with the performance of 2 commercial tablets of DS. Various pharmacokinetic parameters (ie, Cmax, Tmax, area under the curve [AUC0-24], and mean residence time) and relative bioavailability were compared. All fabricated formulations showed more prolonged and controlled DS release compared with commercial tablets studied. The OM and OP tablets,
however, performed better than the matrix tablets. Type of porosigenic agents and osmogens also influenced the drug release. Analysis of In vitro data by regression coefficient analysis revealed zero-order release kinetics for OM and OP tablets, while FM tablets exhibited Higuchi kinetics. In vivo results indicated prolonged blood levels with delayed peak and improved bioavailability for fabricated tablets compared to commercial tablets. It was concluded that the osmotic matrix and osmotic pump tablets could provide more prolonged, controlled, and gastrointestinal environmental independent DS release that may result in an improved therapeutic efficacy and patient compliance. (Rani and Mishra 153-59)

Gan Y. et al. developed cyclodextrin complex osmotic tablet for Glipizide delivery. Poorly soluble glipizide was selected as the model drug to prepare osmotic pump tablets (OPT) with proper accessory material after it was made an inclusion complex by kneading method in order to increase solubility. Polyethylene glycol 4000 (PEG4000) and cellulose acetate (CA) were selected as the coating materials, and acetone–water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push–pull osmotic tablet. The results indicated that glipizide–cyclodextrin inclusion complex OPT had excellent zero-order release characteristics In vitro. (Gan et al. 1015-21)

Mehramizi A. et al. had developed solid carriers for improved solubility of glipizide in osmotically controlled oral drug delivery system using poly vinyl pyrrolidone (PVP). The gli–PVP solid dispersion systems was prepared by physical mixing or spray drying method, and characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transformation- infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM). The elementary osmotic pumps (EOPs) were prepared with gli–PVP complex and the effect of the PVP percentages on the enhancing of gli dissolution rate was studied. The influences of various parameters e.g., drug- PVP ratio, level of solubility modifier, coating weight gain and diameter of drug releasing orifice on drug release profiles were also investigated. The solubility and dissolution rates of gli were significantly increased by solid dispersion using spray dried method as well as their physical mixture. The obtained results indicated that gli–PVP solid dispersion system has suitable solubility behavior in EOP tablets. (Mehramizi et al. 812-23)
Ali Nokhodchi et al. had designed a new type of EOP for the efficient delivery of poorly water-soluble and practically insoluble drugs. In this system, called swellable elementary osmotic pump (SEOP), drug is released from the delivery orifice in the form of a very fine dispersion of drug in gel which is ready for dissolution and absorption. Factors affecting the release of drug from the SEOP containing a poorly water soluble drug, nifedipine, were explored extensively. Interestingly, in the absence or low concentration of a hydrophobic plasticizer (caster oil), the osmotic devices did not retain their integrity in dissolution media. Caster oil in concentration of >1% was necessary for tablets to retain their integrity during dissolution process. A zero-order release kinetics for nifedipine was achieved following the effective optimization of the concentrations of swelling agent, osmotic agent, wetting agent, and also size of orifice and membrane thickness in SEOP. The zero-order release lasted for 10 hr at pH 6.8 dissolution medium. The designed SEOP is suggested as an efficient controlled delivery system for oral delivery of a poorly water soluble drug such as nifedipine.(Nokhodchi et al. 43-48)

Longxiao Liu et al. had developed a method for the preparation of monolithic osmotic pump tablet by coating the indented core tablet compressed by the punch with a needle. Atenolol was used as the model drug, sodium chloride as osmotic agent and polyethylene oxide as suspending agent. Ethyl cellulose was employed as semipermeable membrane containing polyethylene glycol 400 as plasticizer for controlling membrane permeability. The optimal formulation was evaluated in various release media and agitation rates. Indentation size of core tablet hardly affected drug release in the range of (1.00–1.14) mm. The optimal osmotic tablet was found to be able to deliver atenolol at an approximately constant rate up to 24 h, independent of both release media and agitation rate. The method that is simplified by coating the indented core tablet with the elimination of laser drilling may be promising in the field of the preparation of osmotic pump tablet.(Liu and Che 180-84)

Javad Shokri et al. had designed a new type of elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs. Drug release from the system, called swellable elementary osmotic pump (SEOP), is through a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption. SEOP tablets were prepared by compressing the mixture of micronized drug and excipients into convex tablets. The formulations were compared based on four comparative parameters, namely, D24h (total release after 24 h), tL (lag time), RSQzero (R square of zero order equation) and D%zero (percentage deviation from zero order kinetics). The drug release profile from osmotic devices
showed that the type of polymer in the core formulation can markedly affect the drug release. The results showed that increasing the amount of wetting agent to an optimum level (60 mg) significantly increased D24h and improved zero order release pattern of indomethacin. Increasing concentration of caster oil (hydrophobic) in the semipermeable membrane of the device or hydrophilic plasticizer (glycerin) in coating formulation markedly increased tL and decreased D24h. The results also demonstrated that aperture size is a critical parameter and should be optimized for each SEOP system. Optimum aperture diameter for the formulations studied here was determined to be 650 μm for zero order release pattern. tL and D%zero were dramatically decreased whereas D24h and RSQzero increased with increasing the aperture size to optimum level.(Shokri et al. 289-97)

Prabakaran D. et al. had checked the effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps. Diltiazem hydrochloride (DLTZ) is a freely water-soluble drug, because of its higher aqueous solubility, the suitability of the drug with elementary osmotic pumps is restricted. Plain DLTZ elementary osmotic pump had shown higher release rate. Drug entrapment in polymer matrix or addition of release retardant materials (various polymers) can reduce the release rate of drug. In present study, effect of appropriate hydrophilic polymers (HP) on the release pattern was investigated. Ingredients of the system were optimized for parameters like drug:polymer ratio and amount of osmogent, for the desired release pattern. Two optimized formulations were selected for further characterization. Theoretical release rate of the formulations were also determined and compared. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.(Prabakaran et al. 173-79)

Jiang et al. formulated a monolithic osmotic tablet system (MOTS) with two orifices in both side surfaces. Water-insoluble Naproxen was selected as the model drug. Gum arabic was used as an osmotic, suspending and expanding agent, and cellulose acetate (CA) was used as semipermeable membrane. Polyethylene glycol 400 (PEG-400) was employed as plasticizer for controlling membrane porosity. The influences of gum arabic, PEG-400, membrane thickness and orifice size on the naproxen release profiles were investigated, and the optimal MOTS was evaluated in different environment media and stirring rates. The optimal MOTS was found to be able to deliver naproxen at a rate of approximately zero order up to 12 h in pH 6.8, cumulative release at 12 h is 81%, independent on environment media and stirring.
rate. Therefore, MOTS can be used in oral drug controlled delivery field, especially for water-insoluble drug. (Lu et al. 375-82)

**Longxiao Liua et al.** had described monolithic osmotic tablet system, which is composed of a monolithic tablet coated with cellulose acetate (CA) membrane drilled with two orifices on both side surfaces. The influences of tablet formulation variables including molecular weight (MW) and amount of polyethylene oxide (PEO), amount of potassium chloride (KCl), and amount of rice starch as well as Nifedipine loading have been investigated. Orifice size and membrane variables including nature and amount of plasticizers as well as thickness on drug release have also been studied. It was found that PEO with MW of 300 000 g/mol was suitable to be thickening agent, both amount of KCl and amount of PEO had comparable and profoundly positive effects, while nifedipine loading had a strikingly negative influence on drug release. It could be found that the optimal orifice size was in the range of 0.25–1.41 mm. It has also been observed that hydrophilic plasticizer polyethylene glycol (PEG) improved drug release, whereas hydrophobic plasticizer triacetin depressed drug release when they were incorporated in CA membrane. The monolithic osmotic tablet system was found to be able to deliver nifedipine at the rate of approximate zero-order up to 24 h, independent of both environmental media and agitation rate, and substantially comparable with the push–pull osmotic tablet. (Liu et al. 309-22)

**Nuttanan Sinchaipanid et al.** had developed Salbutamol elementary osmotic pump (EOP) tablets and evaluated fundamental variables affecting their release characteristics. The effects of film thickness and compression force on drug release from the tablets containing fixed amount of sodium chloride used as osmogent were evaluated. The core tablets were directly compressed at four compression forces and coated with 3%wt/vol cellulose acetate in acetone to levels of 2%, 3%, and 4%wt/wt. Coated tablets were drilled with CO₂ laser beam to form drug delivery orifice of, 400 mm in diameter. The release rate decreased with the increased film thickness and was not affected by the compression force or porosity. To illustrate the effect of osmogent content, the tablets were prepared at four osmogent levels and compressed at a constant compression force. The release rate was initially increased with osmogent content and then decreased. At higher osmogent contents, the drug fraction in soluble component was decreased and resulted in the reduction of drug release. In conclusion, film thickness and osmogents played important roles in drug release from EOP tablets. (Sinchaipanid et al. 135-42)
Rani M. et al. had designed and evaluated elementary osmotic pump (OP) tablets with the aim to deliver Diclofenac sodium (DS) in a controlled manner. In vitro evaluation was done in various release media and kinetics was evaluated using the regression coefficient analysis. Effects of orifice size, coating membrane type, coating thickness, static and stirred conditions and pH variation were studied. In vivo evaluation was performed on six healthy human volunteers and various pharmacokinetic parameters (Cmax, Tmax, AUC0–24, MRT) and relative bioavailability were calculated. The results were compared with the performance of two commercial tablets of DS. The drug release from OP tablets was dependent on the type and thickness of the coating membrane, but was independent of the orifice size and static and stirred conditions of the release medium. The OP tablets provided a prolonged and controlled DS release compared to commercial sustained-release and conventional tablets of DS.(Rani et al. 263-74)

Lu Xua et al. had evaluated the release In vitro and the absorption In vivo for elementary osmotic pump tablet (EOPT) of Captopril (Cap). In the drug release study In vitro, the influences of the tablet formulation variables, the amount of NaCl, HPMCK15, microcrystalline cellulose (MCC) in the core, the concentration of cellulose acetate (CA), dibutylphthalate (DBP), and polyethylene glycol 400 (PEG-400) in the coating solution have been investigated. The optimal tablet formulation has been proposed. It was found that the drug release was mostly affected by the amount of NaCl, HPMCK15, and MCC in the core, and the amount of PEG-400 in the coating solution. To a certain extent, drug release was less affected by the orifice size, concentration of coating solution, and the coating weight. It was also independent of the pH of the dissolution medium and orifice quantum. The relative bioavailability of EOPT was 119.9%. EOPT showed a good correlation between absorption In vivo and drug release In vitro. Cap EOPT is a safe and effective controlled release preparation.(Xu, Li and Sunada 236-45)

Ouyang et al. prepared a simple elementary osmotic pump (EOP) system that could deliver metformin hydrochloride (MT) and glipizide (GZ) simultaneously for extended periods of time was developed in order to reduce the problems associated with multidrug therapy of type 2 non-insulin-dependent diabetes mellitus. good sustained effect in comparison with the conventional product. The prototype design of the system could be applied to other combinations of drugs used for cardiovascular diseases, diabetes, etc.(Ouyang et al. 817-20)
**Patel G.C. et al.** had developed controlled release osmotic pump tablets (COPT) of glipizide (GZ) solid dispersion (SD). Methods: In elementary osmotic pump (EOP) tablets, an osmotic core with the drug is surrounded by a semi-permeable membrane which is drilled with a delivery orifice. COPT tablets eliminate need of drilling process as controlled release can be achieved by presence of osmogen in the coating. Poorly water soluble drug molecule cannot give satisfactory drug release hence GZ solid dispersion was prepared in the present study. The SDs having different ratio of drug to Poloxamer (PXM) 188 were prepared by hot melt method and optimized by solubility study, drug content estimation and in vitro dissolution study. Effect of two independent variables, amount of osmogen (potassium chloride) and hydrophilic polymer (polyethylene oxide WSR 303), were investigated using 32 factorial design. Core and coated tablets were evaluated for pharmacotechnical parameters. In-vitro drug release profiles of COPT tablets were compared with marketed with push-pull osmotic pump tablet, Glucotrol XL. Results: Prepared core and coated tablets showed acceptable pharmacotechnical parameters. Drug release was directly proportional to initial level of hydrophilic polymer, but inversely related to the osmogen, confirming osmotic mechanism. Zero order drug release pattern was achieved which was comparable to marketed product. Conclusion: Novel oral controlled release of glipizide was successfully achieved by incorporating glipizide solid dispersion into osmotic system. (Gayatri C. Patel 2013)

**Khan et al.** had investigated the feasibility of the design of an enteric coated microporous osmotic pump tablet (ECM OPT) to prolong the drug release of an antipsychotic drug, quetiapine fumarate (QTF). The ECMOPT consisted of an osmotic core coated with a microporous membrane (MPM) made up of cellulose acetate and PEG 4000 as in situ micropore former. The effect of formulation variables such as concentration of sodium chloride, types of pore former (PEG 400, PEG 4000 and PEG 6000), coat thickness (100 and 200 microm) of MPM were evaluated for drug release characteristics. The FTIR, DSC and XRD analyses were carried out to characterize physico-chemical changes of powder blend and final formulation. SEM images have confirmed in situ micropores formation in MPM. A zero order release was obtained for QTF. The formulations were found to be stable up to 3 months when tested for stability at 40 degrees C/75% RH. (Khan, Tripathi et al. 2012)
2.3 Literature Review on Push-Pull Porosity Osmotic Pump

Mishra B. et al. was aimed to formulate and evaluate oral osmotic pumps of Pentazocine HCl that are expected to deliver the drug as solution for prolonged period of time with reduced frequency of drug administration and reduced side effects. Push-Pull osmotic pumps of Pentazocine HCl were prepared using different formulation variables like diameter of pores, presence of surfactant in formulation core, addition of osmopolymer pectin and presence/absence of water-soluble polymer (carboxymethylcellulose sodium). Fabricated osmotic pumps were evaluated for weight variation, coating thickness, pore diameter, drug content and In vitro release studies. Release rates were found to be independent of size of pores, agitation intensity, and pH of the release medium. The presence of surfactant, water-soluble polymer and osmopolymer (pectin) affected the drug release significantly. Almost all the osmotic pumps gave controlled and prolonged drug release profiles beyond 2 h of lag phase. (Mishra, Makesh and Sankar 85)

Patel V. et al. had prepared and evaluated push-pull osmotic pump for zero order delivery of lithium carbonate, a drug with narrow therapeutic index, needs therapeutic drug monitoring and dose adjustment to maintain lithium level within the therapeutic window. Conventional formulations of lithium carbonate exhibit immediate drug release causing swing/fluctuations in the plasma concentration of lithium. The push-pull osmotic pump has been developed for zero order delivery of lithium carbonate for a period of 24h. The effect of various formulation variables on bilayer core tablet and its semi permeable coating along with orifice diameter have been investigated and optimized for desired drug release profile. Drug release was found to be inversely proportional to the membrane thickness but directly related to the amount of pore formers in the semipermeable membrane. Drug release from the developed formulation was found to be independent of pH, agitation intensity and agitation mode but depended on osmotic pressure of dissolution media. (Patel et al. 375-82)

Gondaliya D et al. had focused on the fabrication and evaluation of the formulation variables of a controlled-porosity osmotic drug delivery system with Diltiazem hydrochloride. Diltiazem hydrochloride (HCl) is an ideal candidate for a zero-order drug delivery system because it is water-soluble and has a short half-life. The study used a controlled porosity osmotic pump, which was prepared in the form of a bilayered tablet containing a drug compartment (pull compartment) and an osmogen layer (push compartment), for the delayed release of diltiazem HCl. The effects of various formulation and process variables such as the agitation rate, the pH of the dissolution medium, membrane thickness, surface porosity,
the concentration and nature of plasticizers were analyzed. (Gondaliya and Pundarikakshudu 58-68)

Shu-fang Nie et al. had prepared controlled release bi-layer osmotic pump tablets (BOPT) of water—insoluble allopurinol with large dose (150 mg/BOPT) merely with sodium chloride as osmotic promoting agent and polyethylene oxide (PEO) as suspending agent. Formulations of the two kinds of agents were investigated in order to discuss their effects on the release behavior of BOPT, and then the optimal formulation was evaluated. The pharmacokinetics studies of allopurinol and its active metabolite oxypurinol in two-preparation and two-period crossover design relative to the equivalent dose of commercially common allopurinol tablets were evaluated in six Beagle dogs. And the pharmacokinetics results showed that allopurinol BOPT were able to provide a slow release of allopurinol, and oxypurinol were bioequivalent between allopurinol BOPT and common allopurinol tablets. A good In vitro–In vivo correlation of allopurinol was also proved. In conclusion, water-insoluble drugs with large dose can be designed to BOPT for efficacy and safety use. (Nie et al. 1024-29)

Vincent Malaterre et al. had investigated coating characteristics of push–pull osmotic systems (PPOS) using three-dimensional terahertz pulsed imaging (3D-TPI) and to detect physical alterations potentially impacting the drug release. The terahertz time-domain reflection signal was used to obtain information on both the spatial distribution of the coating thickness and the coating internal physical mapping. The results showed that (i) the thickness distribution of PPOS coating can be non-destructively analyzed using 3D-TPI and (ii) internal physical alterations impacting the drug release kinetics were detectable by using the terahertz time-domain signal. Based on the results, the potential benefits of implementing 3D-TPI as quality control analytical tool were discussed. (Malaterre et al. 21-25)

Wakode R. et al. had developed and characterized an oral push-pull system that can deliver pramipexole for extended period of time. A bilayer osmotic drug delivery system was developed using a basic design consisting of an oral controlled porosity osmotic pump. Unlike other osmotic systems, which require a preformed orifice for drug release, controlled porosity membranes contain water-soluble pore-formers in the coating membrane. In advanced Parkinson's disease the usual dose of pramipexole is 1.5 mg three to four times a day. Hence, an attempt was made to develop a once-a-day controlled release system. This developed push-pull system was compared with other types of osmotic delivery systems, such as an asymmetric membrane coating and a dense coat with mechanical drilling. An optimized system was selected to study the effect of the concentration of a pore-forming agent such as
PEG 400 and dibutyl phthalate, the pH of dissolution media, the effect of agitation and osmotic agents on drug release. The drug release was found to follow zero order kinetics. Drug release increased with an increase in osmotic pressure. The developed push-pull osmotic system showed the desired once-a-day release kinetics. (Wakode, Bhanushali and Bajaj 22-31)

Prabakaran D et al. had formulated and characterized an oral osmotic system which can deliver theophylline and salbutamol sulphate simultaneously for extended period of time to reduce the problems of asthma. A modified two-layered, push–pull osmotic system was developed by using the basic designs of various oral osmotic pumps, such as controlled porosity osmotic pump (CPOP), elementary osmotic pump (EOP) and push–pull osmotic pump (PPOP). Formulations were initially developed for theophylline and the release was optimized by using two different soluble forms of theophylline with varying amount of hydrophilic polymer mixture in upper layer and polyethylene oxide (expandable hydrogel) in lower layer. Further, the release of salbutamol sulphate was optimized by keeping the drug in upper or lower layer or both layers. In vitro release studies showed satisfactory controlled release profiles of both drugs. The release profiles of both drug statistically compared with respective marketed controlled release formulations. An optimized system was selected to study the effect of concentration of pore forming agent and orifice diameter on the release of both drugs. (Prabakaran et al. 95-108)

Malaterrea V. et al. had aimed to understand which factors have an effect on the drug delivery for modelling the drug release and to develop a mathematical model predictive of the drug release kinetics. The influence of the drug property was tested on two model drugs, Isradipine (ISR) and Chlorpheniramine (CPA) which are respectively practically insoluble and freely soluble. Results show that, regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by four factors, (i) the PEG proportion in the membrane, (ii) the tablet surface area, (iii) the osmotic agent proportion and (iv) the drug layer polymer grade. The influence of each key formulation factors on the release mechanism was investigated defining their applicability range. A mathematical approach was developed to predict the drug delivery kinetics varying the PPOP controlling factors and helps to more efficiently design PPOP. (Malaterre et al. 56-62)

Zhi-hong Zhang et al. had aimed to build an expert system for the development and formulation of push–pull osmotic pump tablets (PPOP). Hundreds of PPOP formulations were studied according to different poorly water-soluble drugs and pharmaceutical acceptable excipients. The knowledge base including database and rule base was built based on the
reported results of hundreds of PPOP formulations containing different poorly water-soluble drugs and pharmaceutical excipients and the experiences available from other researchers. The prediction model of release behavior was built using back propagation (BP) neural network, which is good at nonlinear mapping and learning function. Formulation design model was established based on the prediction model of release behavior, which was the nucleus of the inference engine. Finally, the expert system program was constructed by VB.NET associating with SQL Server. Expert system is one of the most popular aspects in artificial intelligence. To date there is no expert system available for the formulation of controlled release dosage forms yet. Moreover, osmotic pump technology (OPT) is gradually getting consummate all over the world. It is meaningful to apply expert system on OPT. Famotidine, a water insoluble drug was chosen as the model drug to validate the applicability of the developed expert system.(Zhang et al. 41-47)

Malaterre V. et al. had developed a push–pull osmotic system to deliver poorly soluble drugs in a modified-release fashion. The aim of this study was to investigate the influence of the tablet core factors on the drug release kinetics and loadability. The release kinetics was efficiently modulated by varying either the proportion of osmotic agent or the drug layer polymer grade as an alternative to change the membrane characteristics. High osmotic agent proportions and viscous-grade polymers were recommended to formulate high drug loads up to 20% without losing both the release completeness and the zero-order drug release kinetics.(Malaterre et al. 433-39)

Wei Li et al. had developed a novel push–pull osmotic pump (PPOP) for delivery of water-insoluble drug gliclazide. The In vitro drug-release behavior of both novel PPOP and conventional PPOP were studied and compared; it was found that the drug-release rate of both kinds of PPOP could be influenced by coating level and core hardness whereas orifice size did not have much influence on it, and the study also showed that none of the former factors could influence the similarity of the drug-release profiles of the two kinds of PPOP. Mechanism of drug release from novel PPOP was illustrated using Poiseuille’s law of lamina flow, and it was found that under regular formulation, the dissolution profiles of the two kinds of PPOP were similar. In vivo study also showed that the concentration–time profiles of gliclazide in plasma of the two PPOP were comparable and both of them had good In vitro–In vivo correlation. By simply drilled on both side surfaces, the novel PPOP did not need side identification when drilled, so it was more suitable for industrial manufacture than the conventional ones.(Li et al. 1350-55)
Gong et al. had developed osmotic pump with subcutaneous infusion, which was composed of three primary components: water chamber, osmotic pump chamber and support base. Ceftriaxone sodium (CRO) was selected as the model drug and osmotic pump tablets were prepared. The influence of osmotic agents on drug release profiles was evaluated. The in vitro release profiles of the optimum formulation achieved to the predetermined value. The pharmacokinetic profiles of this drug delivery system were evaluated in Beagle dogs. In vivo results demonstrated that the osmotic pump subcutaneous infusion administration was equivalent to intravenous injection administration in terms of bioavailability. Moreover, constant drug plasma levels with minimized fluctuations could be achieved with this osmotic pump subcutaneous infusion system, compared with intravenous injection. (Gong, Ma et al. 2013)

Shahrzad et al. had developed and evaluated Push-pull osmotic pump (PPOP) tablets of a practically insoluble model. The formulation factors such as the viscosity grade of polyethylene oxide as the primary polymer as well as the level and location of osmogen within the bilayer tablets led to a difference in performance of osmotic tablets and hence should be critically evaluated in the design of such dosage forms. The influence of varying dose and aqueous solubility of other model drugs (i.e., theophylline, acetaminophen, and verapamil HCl) on the developed PPOP template was also investigated. Results showed that irrespective of the perceived complexity of development and manufacturing of osmotic pumps, the osmotictablets in this study demonstrated a robust and yet flexible platform in accommodating different types of drug candidates, regardless of solubility, for the dose levels below 25% w/w of the pull layer formulation. (Shahrzad Missaghi 2013)

Zhang et al. had developed glipizide push-pull osmotic pump (PPOP) tablets by using an artificial neural network (ANN). Firstly, the expert system for the formulation design of osmotic pump of poor water-soluble drug was employed to design the formulation of glipizide PPOP, taking the dissolution test results of Glucotrol XL as the goal. Then glipizide PPOP was prepared according to the designed formulations and the in vitro dissolution was carried out. The range of the factors of formulation and procedure, which could influence the drug release, was optimized using artificial neural network. It was found that the target formulation which was similar to Glucotrol XL in dissolution test could be obtained in a short period by using the expert system. The samples which were similar to Glucotrol XL were bio-equivalent to the Glucotrol XL in Beagle dogs. It could be concluded that a well-controlled product of glipizide PPOP was developed since the dissolution test standard of our product was more strict than that of Glucotrol XL. (Zhang, Wang et al. 2012)
2.4 Literature Review on Work Done on Flurbiprofen

Orlu et al. had design novel colon specific drug delivery system containing flurbiprofen (FLB) microsponges. Microsponges containing FLB and Eudragit RS 100 were prepared by quasi-emulsion solvent diffusion method. Additionally, FLB was entrapped into a commercial Microsponge 5640 system using entrapment method. Afterwards, the effects of drug:polymer ratio, inner phase solvent amount, stirring time and speed and stirrer type on the physical characteristics of microsponges were investigated. The colon specific formulations were prepared by compression coating and also pore plugging of microsponges with pectin:hydroxypropylmethyl cellulose (HPMC) mixture followed by tabletting. The microsponges were spherical in shape, between 30.7 and 94.5microm in diameter and showed high porosity values (61-72%). Mechanically strong tablets prepared for colon specific drug delivery were obtained owing to the plastic deformation of sponge-like structure of microsponges. In vitro studies exhibited that compression coated colon specific tablet formulations started to release the drug at the 8th hour due to the addition of enzyme, following a modified release pattern while the drug release from the colon specific formulations prepared by pore plugging the microsponges showed an increase at the 8th hour which was the time point that the enzyme addition made. This study presents a new approach based on microsponges for colon specific drug delivery.(Orlu, Cevher and Araman 103-17)

Shah et al. has worked on design oral sustained release matrix tablets of water-insoluble drug, flurbiprofen, using natural gums as the matrix polymers and to evaluate the drug release characteristics using response surface methodology. The central composite design for two factors at five levels each was employed to systematically optimize drug release profile. Matrix tablets were prepared by direct compression technique. Xanthan and acacia gums were taken as the independent variables. Percent drug release in 2 hours and percent drug release in 8 hours were taken as response variables (Y₁ and Y₂, respectively). Both the polymers were found to have significant effect on the drug release. Polynomial mathematical models, generated for the response variables using multiple linear regression analysis, were found to be statisitically significant (P < 0.05). Contour plots were drawn to depict the relationship between response variables and independent variables. The formulated matrix tablets followed zero-order kinetics with negligible drug release in 0.1 N HCl at pH 1.2, which was the objective of this study to produce a formulation avoiding the gastric effects of flurbiprofen.(Shah et al. 1470-78)
Govindarajan and Nagarsenker has aimed to investigate *In vivo* advantages of a flurbiprofen (FPN)-hydroxypropyl β-cyclodextrin (HP-β-CD) solid dispersion (SD) in rats, to study factors affecting the drug release from SD formulations, and to evaluate the pharmacokinetic profile of the drug when administered as SD, in humans. The SD was prepared by coevaporation from dilute aqueous NH$_3$ and evaluated in rats. The release of the drug from tablet formulations and capsules of SD was studied in simulated gastric fluid and phosphate buffer, pH 7.2. The bioavailability of drug when administered as SD was evaluated in humans. HP-β-CD enhanced the solubility of the drug, and SD improved bioavailability and reduced ulcerogenicity of the drug in rats. Presence of microcrystalline cellulose, a hydrophilic polymeric excipient, resulted in uptake of water and stabilization of the resulting gels-like structure of HP-β-CD-containing tablets. This adversely affected drug release. The release from capsules filled with SD was comparable to that obtained from plain SD powder. The bioavailability (which could suffer in case of higher association constant) was enhanced on administration of SD-filled capsules to humans. (Govindarajan and Nagarsenker 105-14)

Veerareddy and Vemula et al. had investigated colon targeted compression coated flurbiprofen pulsatile release tablets that retard the drug release in the upper gastro intestinal system but progressively release in the colon. Flurbiprofen core tablets were prepared by direct compression method and were compression coated with hydroxypropyl methylcellulose and Eudragit S100. The formulation is optimized based on the *In vitro* drug release study and further evaluated by X-ray imaging and pharmacokinetic studies in healthy humans for colonic delivery. The optimized formulation showed negligible drug release (7.26 ± 0.05%) in the initial lag period followed by progressive release (99.27 ± 0.46%) for 24 h. The X-ray imaging study in human volunteers showed that the tablets reached the colon without disintegrating in the upper gastrointestinal tract. Development of pulsatile release compression coated tablets using combination of time dependent and pH sensitive approaches was suitable to target the flurbiprofen to colon. (Veerareddy and Vemula 703-14)

Oh et al. had developed a novel flurbiprofen-loaded solid dispersion without crystalline change, various flurbiprofen-loaded solid dispersions were prepared with water, sodium carboxymethyl cellulose (Na-CMC), and Tween 80. The physicochemical properties of solid dispersions were investigated using SEM, DSC, and X-ray diffraction. The dissolution and bioavailability in rats were evaluated compared to commercial product. Flurbiprofen-loaded solid dispersion gave a relatively rough surface and changed no crystalline form of drug. These solid dispersions were formed by attaching hydrophilic carriers to the surface of drug
without crystal change, resulting in changing the hydrophobic drug to hydrophilic form. Furthermore, the flurbiprofen-loaded solid dispersion at the weight ratio of flurbiprofen/Na-CMC/Tween 80 of 6/2.5/0.5 improved ~60-fold drug solubility. The solid dispersion improved almost 1.5-fold bioavailability of drug compared to commercial product in rats. Thus, the flurbiprofen-loaded solid dispersion would be useful to deliver poorly water-soluble flurbiprofen with enhanced bioavailability without crystalline change.(Oh et al. 46-53)

Idrees et al. was aimed to develop flurbiprofen microemulsion for enhanced transdermal delivery and investigate the effects of different surfactants and cosurfactants on its delivery and phase behavior. Various surfactant-cosurfactant mixtures in ratio of 2:1 (Smix) along with oleic acid (oil) were selected and phase diagrams were constructed. Six microemulsions each containing 5% drug, 5% oil, 56% Smix and 34% water, were prepared and compared for their permeation and phase behaviors to determine the effects of the type of Smix. In vitro transdermal permeation through rabbit skin of all microemulsions was high than saturated aqueous drug solution. Tween 20 and ethanol as Smix produced the highest flux amongst all the Smix, and were used to prepare formulations with different values of oil and Smix. Decrease in oil or Smix concentration resulted in decrease of the droplet size and increase in permeation flux while decrease in viscosity also increased the permeation flux of microemulsions. Finally the selected microemulsion formulation comprising 5% flurbiprofen, 5% oleic acid, 46% Tween 20:ethanol (2:1) and 44% water, showed the highest transdermal flux and caused no skin irritation. Type of surfactant and cosurfactant affect both the phase behavior and transdermal drug delivery of microemulsion; and results of this study showed that they are promising vehicles for improved transdermal delivery and sustained action of flurbiprofen.(Idrees et al.)

Akhlaq et al. had designed once-daily controlled release hydrophilic hydrophobic matrix tablets of flurbiprofen with cellulose derivative polymers using direct compression technique. Tablets were compressed using a single punch machine and various physical parameters were tested including hardness, friability, weight variation, content uniformity, thickness and diameter. In vitro release study was conducted in phosphate buffer solution, pH 7.4 and different kinetics parameters were applied on dissolution data. Dissolution study showed a controlled release profile for formulations containing ethylcellulose and hydroxypropylmethylcellulose and released 98.29 and 97.49% drug after 12 and 18 hrs, respectively. The release exponent, “n” indicated an anomalous release behavior with the values 0.599 and 0.776 and the linearity of 0.986 and 0.971, respectively.(Akhlaq et al. 20-23)
2.5 Literature Review on Work Done on Nicardipine Hydrochloride

Pavan K Rawat et al. has focused on development and characterization of an oral sustained release matrix tablet of Nicardipine Hydrochloride (NH) by employing hydrophilic and hydrophilic polymers. Due to poor water solubility of the drug its bioavailability is dissolution rate limited. So, the purpose of the study was to increase the solubility of NH by solvent evaporation technique. Complexes of different molar ratio were prepared and matrix tablets were prepared by direct compression technique using different concentration of polymers and selected complex. The *In vitro* dissolution study was carried out in acidic medium (pH 1.2) for 2 hr, followed by phosphate buffer dissolution medium (pH 6.8) for next 10 hr. The blended powders showed satisfactory flow properties and compressibility. The *In vitro* release pattern indicated that optimized formulation releases the drug for period of 12 hr and was best fitted to Higuchi release profile. The present study has demonstrated that combination of hydrophobic and hydrophilic polymers effectively sustained the drug release for prolonged period of time 12 hr. (Rawat Article ID- "Inventi:pndds/605/13", 2013)

Nakamichi et al. has developed a floating dosage form composed of Nicardipine Hydrochloride (NH) and hydroxypropylmethylcellulose acetate succinate (enteric polymer) using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of die outlet, and by controlling the barrel temperature, it was possible to prepare a puffed dosage form with very small and uniform pores. It was found that the porosity and pore diameter could be controlled by the varying amount of calcium phosphate dihydrate. In the shaking test, the puffed dosage form was found to have excellent floating ability and mechanical strength in acid solution (JP First Fluid, pH 1.2). The dissolution profile of NH was controlled by the amount of wheat starch. In the dissolution test using JP Second Fluid (pH 6.8), rapid dissolution of NH and loss of buoyancy were observed. It was shown that the puffed dosage form, consisting of enteric polymer prepared using the twin-screw extruder, was very useful as a floating dosage form that was retained for a long period in the stomach. (Nakamichi et al. 103-12)

Mrhar et al. has prepared microspheres which would release nicardipine at a decreased rate in gastric and increased rate in intestinal juice during a 12 hr interval. Pharmacokinetic modeling based on compartment analysis and supported by analog computer and digital simulation technique showed that the target steady state peak plasma concentrations of 32
µg/l and trough plasma concentration of 7 µg/l would be maintained if nicardipine were incorporated in a formulation releasing the drug as follows: 25% after 1 hr, 40% after 2 hr, 65% after 4 hr, 80% after 6 hr, 90% after 8 hr and 100% by 12 hr. Microspheres have been prepared from hydroxypropylmethylcellulose phthalate polymer using the solvent evaporation method. Drug content, scanning electron micrographs, particle size distribution and dissolution profile were determined. *In vitro* nicardipine release was described by a biphasic square root of time kinetics and was in accordance with the above values relating to the dissolution. Furthermore, a composed first-pass pharmacokinetic model with derived release function as an input was developed to predict nicardipine plasma concentrations after single- and 12 hr multiple-dosage-regimen scheme administration of controlled release microspheres. (Mrhar et al. 55-61)

**Moursy et al.** has was formulated sustained release floating capsules of Nicardipine Hydrochloride. The inclusion of sodium bicarbonate to allow evolution of CO2 to aid buoyancy was studied. Polymers that retard drug release were included as coprecipitates with the drug and/or as additives in the formulated capsules. Both simple powder mixing of the ingredients and granule preparation via wet granulation were used. Seven capsule formulae were prepared and evaluated *In vitro* by testing drug dissolution, floating time and the kinetics of drug release. *In vitro* evaluation of a commercially available conventional 20 mg capsule of nicardipine hydrochloride, "Micard", was carried out for comparison. The hydrocolloid used succeeded in effecting capsule buoyancy. Floating time increased with increasing the proportion of the hydrocolloid. Inclusion of sodium bicarbonate increased buoyancy. All of the seven floating capsule formulae prepared proved efficient in controlling drug release. The sustained release floating capsule formulation of choice was evaluated *In vivo* in comparison to "Micard" capsules using rabbits. Plasma concentration time curves revealed a longer drug duration for administration in the sustained release formula than the conventional "Micard" capsule being 16 hr in the former versus 8 hr for the latter.(Moursy et al. 38-43)

**Fernandes et al.** has examined the feasibility of using complexes with cyclodextrins (CDs) in nicardipine (NC) controlled delivery, with a view to extending the pharmaceutical applications spectrum of these carriers. For a fast release fraction, a hydroxypropyl-beta-cyclodextrin was employed to form a water-soluble complex. For the sustained-releasing portion, triacetyl-beta-cyclodextrin (TAbetaCD) was used to provide complexes with appropriate hydrophobicity. An optimal formulation was designed by the combination of each fraction in different mixing ratios. The formulations released the drug
rapidly at the initial stage, followed by a slow release. The drug release rate was markedly retarded in the increasing order of the amount of NC/TAbetaCD complex. When NC was administered to rabbits, its absorption was very rapid with a short elimination half-life, while a prolonged maintenance of the plasma levels was obtained for the two selected formulations. The drug bioavailability was considerably improved especially after the administration of the mixture of hydrophilic and hydrophobic complexes. The results suggested that the critical combination of hydrophilic and hydrophobic CDs complexes, in appropriate ratios, could be a promising drug delivery system with a prolonged therapeutic effect coupled with a more balanced bioavailability. (Fernandes et al. 127-34)

Maurin et al. has indicated nicardpine hydrochloride (NH), a calcium channel blocker, used in the treatment of chronic stable angina and mild essential hypertension was investigated. Two techniques that are known to improve solubility, complexation and salt formation, were examined. The solubility of NH was enhanced exponentially via complexation with aliphatic carboxylic acid buffer systems in a pH dependent fashion. The solubility increased from 5 to 68.6 and 270 mg/ml as the acetate or propionate buffer concentrations, respectively, increased from 0.001 to 5 M, showing a positive deviation from linearity. The conversion of NH to the phosphate salt resulted in an approximately 10-fold solubility improvement. The surface tension of the nicardipine phosphate in water as a function of concentration indicated a critical micelle concentration of 5-6 mg/ml. The critical micelle concentration was greater than the equilibrium solubility of the hydrochloride salt in water, suggesting that a self-association phenomena is responsible for the enhanced solubility of the phosphate salt. Both routes provided potential alternatives for the solubilization of nicardipine. (Maurin et al. 1418-20)

Roy et al. had developed and characterized an oral sustained release matrix tablet of complexed Nicardipine Hydrochloride (NH) by employing hydrophilic and hydrophilic polymers. The purpose of the study was to increase the solubility of NH by cyclodextrin inclusion complex technique. Complexes of different molar ratio were prepared by kneading method. Among different complexes, a complex with 1:1 molar ratio of drug and β-CD showed the highest dissolution rate. Matrix tablets were prepared by direct compression technique using different concentration of polymers and selected complex. The In vitro dissolution study was carried out in acidic medium (pH 1.2) for 2 hrs, followed by phosphate buffer dissolution medium (pH 6.8) for next 12 hrs. The In vitro release pattern indicated that optimized formulation was good releasing the drug for period of 12 hrs and was best fitted to Higuchi release profile. The present study has demonstrated that combination of hydrophobic
and hydrophilic polymers effectively sustained the drug release for prolonged period of time and a minimum of 28 % sodium alginate is required to retard the release of NH from matrix tablet for the period of 12 hrs.(ROY et al. 128-32)

Al-Zein, Sakeer and Alanazi et al. has aimed to prepare a sustained release tablet for a nicardipine hydrochloride (NC) which has poor solubility in alkaline medium using complexation with cyclodextrin. Firstly the most suitable binary system NC-HPβCD was selected in order to improve drug solubility in the intestinal media and then embedding the complexed drug into a plastic matrix, by fusion method, consists of glycerol monostearate (GMS) as an inert waxy substance and polyethylene glycol 4000 (PEG4000) as a channeling agent, after that the final solid dispersion [(NC:HPβCD):GMS:PEG4000] which was prepared at different ratios was mixed with other excipients, avicel PH101, lactose, and talc, to get a tablet owning dissolution profile complying with the FDA and USP requirements for the extended release solid dosage forms. Dissolution profile of NC enhanced significantly in pH 6.8 from NC:HPβCD inclusion complex prepared by the rotavapor (t-test Student p < 0.05). The release of NC from tablet containing [(NC:HPβCD):GMS:PEG4000] [(1):0.75:0.5] (w/w/w) solid dispersion was complying with the FDA dissolution requirements for extended release dosage forms. The prepared waxy matrix tablet containing NC complexes with CD shows promising results as extended release tablets.(Al-Zein, Sakeer and Alanazi 245-53)
2.6 Literature Review on Work Done on OCDDS in Patents

The present invention is for an oral osmotic controlled drug delivery system for a sparingly soluble drug comprising:

a. A core comprising (i) finely particulate anhydrous carbamazepine (ii) a polymeric swelling agent consisting of one or more swellable hydrophilic polymers selected such that the polymeric swelling agent exhibits controlled swelling and the wall does not rupture or burst, (iii) a crystal habit modifier in whose presence, upon contact with an aqueous medium, the anhydrous carbamazepine being transformed into cuboidal or rod-shaped crystals of the dehydrate of carbamazepine, or mixtures thereof, and (iv) water-soluble compounds for inducing osmosis,

b. A wall made of acylated cellulose which is impermeable to the components of the core, but permeable to water, and

c. A passageway through the wall for releasing the components present in the core to the surrounding environment. (Puthli, Menon et al. 2003)

A sustained release dosage form is provided comprising a pharmaceutically active agent and pharmaceutically acceptable salts thereof and adapted to release as an erodible solid over a prolonged period of time, wherein the dosage form provides burst release of the pharmaceutically active agent without the use of an immediate release drug coating. The dosage form is able to deliver high doses of poorly soluble or slowly dissolving active agents at a controlled rate. Methods of using the dosage forms to treat disease or conditions in human patients are also disclosed. (Cruz, Li et al. 2005)

A system and method for manufacturing oral osmotic drug delivery devices including the use of a mathematical model in deriving relationships between parameters used in manufacturing the devices for a desired release rate of the active drug substance contained therein. The derived relationship is then used to control the parameters so that the active substance within the device is delivered at a desired rate. Methods of administering the oral osmotic drug delivery devices are also provided. Use of mathematical model in deriving relationships between parameters used in the drug granulation process for a desired range of percentage fines of the drug granulation substance. The derived relationship is then used to control the parameters in the drug granulation process so that the desired percentage fines are obtained in the drug granulation substance. (Patel 2008)

The present invention relates, generally, to oral osmotic drug delivery systems, methods of preparing same, and methods of using oral osmotic drug delivery systems to provide
controlled delivery of a drug. The oral osmotic drug delivery systems include a drug layer, an osmotic layer, and an outer coating surrounding the drug layer and osmotic layer, where the outer coating includes at least one opening therein that is provided adjacent the drug layer. The composition (% fines), shape and weight gain of the oral osmotic delivery systems may be modified in order to provide for optimized release of the drug contained therein. (Patel 2008)

The present invention is directed to the oral osmotic delivery of therapeutic compounds that have limited solubility in an aqueous environment due to inherent hydrophobicity or to saturation limitations in the core of the osmotic system. The present invention is suitable for the osmotic delivery of glipizide and other hydrophobic drugs, but runs the spectrum to other therapeutic agents with higher aqueous solubilities, yet having a solubility limitation in an osmotic dosage unit due to high drug load. (Kidane, Ray et al. 2005)

Disclosed is an osmotic pharmaceutical delivery system comprising (a) a semi-permeable wall that maintains its integrity during pharmaceutical delivery and which has at least one passage therethrough; (b) a single, homogenous composition within said wall, which composition consists essentially of (i) a pharmaceutically active agent, (ii) at least one non-swelling solubilizing agent which enhances the solubility of the pharmaceutically active agent, (iii) at least one non-swelling osmotic agent and (iv) a non-swelling wicking agent dispersed throughout the composition which enhances the surface area contact of the pharmaceutical agent with the incoming aqueous fluid. (Rudnic, Burnside et al. 2004)
2.7 References


