CHAPTER 6

SUMMARY AND CONCLUSION

SUMMARY

The aim of present research was to design and optimize the following three novel osmotic drug delivery systems for water-soluble and low water-soluble drugs and compare.

1. Swellable Porous Osmotic System (SPOP)
2. Monolithic Osmotic Tablet System (MOTS)
3. Controlled Porosity Osmotic System (CPOP)

– **SPOP**

The aim of the current study was to design a novel swellable porous osmotic pump (SPOP) based drug delivery system using various viscosity grade polymers of hydrophilic polymers, hydroxypropyl methylcellulose (HPMC) as swellable pore formers, for controlled release of highly water soluble drug, venlafaxine HCl (VH) and water insoluble drug glipizide (GZ). The current study was also focussed on the effect of various viscosity grade pore formers, HPMC K100LV, HPMC K4M and HPMC K15M. In case of VH, effects of various ratios of drug to osmogent on the drug release were studied. In order to enhance the solubility of GZ, meglumine was used as solubilizing agent in the core formulation and the quantity was optimised.

The SPOP controlled-release system is based on hydrophilic polymer coating. When the formulation is administered orally and reaches the stomach, gastric fluid enters inside the core through semipermeable membrane and dissolves the water-soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. Meanwhile, high viscosity grade swellable agent (s) present in the coating film swells and creates sponge like appearance in the membrane. The drug release occurs through the sponge like structure by osmotic mechanism. As formulation moves through the gastrointestinal tract, high viscosity grade swellable agent (s) present in the coating film swell and create more sponge like structure in the membrane and the drug release occurs through theses sponge like structure by osmotic mechanism. The formation of number of sponge like structure is irrespective of pH and time, and drug release occurs continuously by osmotic mechanism.

The mechanisms by which drug release is controlled in SPOP system are dependent on many variables. One of the principles of drug release would be osmotic pressure.

However, it is obvious that the water-soluble polymer, coated throughout the tablet, hydrates on the tablet surface to form a gel layer and the drug molecules are diffused out and hence the diffusion mechanism cannot be ruled out for the present study. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents by changing the proportion of the semipermeable polymer, pH insensitive high viscosity grade swellable agent (s).

- **MOTS**

The aim of the current study was to design a novel monolithic osmotic tablet system (MOTS) based drug delivery system for controlled release of highly water soluble drug, metoprolol tartrate (MT) and water insoluble drug nifedipine (NP). In case of metoprolol, various molecular weight polymers of polyethylene oxide (PEO) were used as a swelling agent and to retard the drug release. In order to enhance the solubility of nifedipine, PEG 6000, Mannitol and Poloxamer-188 were explored as solid dispersant. The current study was also focussed on the effect of various molecular weight polymers of PEO 1, 3 and 6 Lac g/mol and the effect of amount of solid dispersing agent for metoprolol and nifedipine respectively.

Monolithic osmotic tablet systems are reported in the patent literature [10,11]. The information regarding the effect of tablet formulation variables, orifice size and membrane variables on drug release of this system are less well known. The MOTS controlled-release system, which is composed of a monolithic tablet coated with cellulose acetate membrane with an orifice drilled mechanically, has been described.

When the formulation is administered orally and reaches the stomach, gastric fluid enters inside the core through semipermeable membrane and dissolves the water soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. The drug release occurs through the orifice by osmotic mechanism. The drug release is irrespective of pH and time, and occurs continuously by osmotic mechanism.

The mechanisms by which drug release is controlled in MOTS are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and

poorly soluble active agents by changing the proportion of the hydrophilic polymer (s) in the core and semipermeable polymer in the coating.

- **CPOP**

The aim of the current study was to design a controlled porosity osmotic system (CPOP) based drug delivery system for controlled release of highly water soluble drug, oxybutynin chloride (OC) and sparingly water soluble drug, atenolol (AT).

The current study was also focussed on the effect of concentration of pore formers, Sorbitol, HPMC and PEG-6000.

In case of OC, effects of various ratios of drug to osmogent on the drug release were studied. In order to enhance the solubility of AT, tartaric acid was used as acidifying agent in the core formulation and optimized the quantity.

Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role. The mechanisms by which drug release is controlled in CPOP are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents.

PART I : SWELLABLE POROUS OSMOTIC PUMP (SPOP)

The dosage form developed was designed as a tablet core coated with a rate controlling membrane. Tablet core consists of drug along with solubility modifier (meglumine, in case of Glipizide), osmogent, and other conventional excipients to form the core compartment. Solubility modifiers used in the core are formulated in a controlled release fashion so that the alkalinizing agents are available for longer duration with the drug and capable of modifying the microenvironmental pH of the core above the pKa of drug. The core compartment is surrounded by a membrane consisting of a semipermeable

membrane-forming polymer, high viscosity grade pore forming polymers and at least one plasticizer capable of improving film-forming properties of the polymers.

The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug (In case of Glipizide, the solubility modifier dissolves and elevates the microenvironmental pH of the tablet core above the pKa of the drug, thus increasing its solubility). The dissolved drug is released through the pores created after swelling of water-soluble polymer (s) in the membrane.

Cellulose acetate and HPMC (HPMC K100LV, HPMC K4M and HPMC K15M) were used as water-insoluble polymer and waters-soluble polymers, respectively. PEG-400 was used as a plasticizer.

To optimize the amount of osmogent to be used in the venlafaxine formulations and to study the effect of drug to osmogent ratio, core formulations were prepared were prepared using sodium chloride with 0, 20, 40, 60 and 80 mg per tablet. All the core formulations were coated with coating composition having 6 % w/w (of total solids) of HPMC K100LV. The osmogent enhanced the release of drug and had a direct effect on drug release. This is evidenced from a formulation that was devoid of any osmogent in the core, showed 48.28 % drug release even after 12 h. The use of osmogent enhanced the release beyond 50 % drug release after 12 h depending on the amount of osmogent present in the core formulation which might be due to the increased water uptake and hence increased driving force for drug release.

Glipizide is a weakly acidic drug that is practically insoluble in water and buffer media of acidic pH. Meglumine was added as a solubility modifier to increase the microenvironmental pH of the core above the pKa of glipizide. The effect of level of solubility modifier was studied and optimized. In the initial trial, core tablets of glipizide without osmogent and solubility modifier were coated, however no drug was released till 14 h. This phenomenon could be expected either because of low osmotic pressure of the core formulation or due to poor water solubility of glipizide. To increase the osmotic pressure of core compartment, sodium chloride (osmotically active agent) was added. But this approach failed since negligible amount of drug was released even after 14 h. The amount of solubility modifier, meglumine studied were 0, 50, 100, 150 and 200 mg per

tablet. All the core formulations were coated with coating composition containing 6 % w/w (of total solids) of HPMC K100LV. The use of solubility modifier enhanced the release depending on the amount of solubility modifier present in the core formulation. The drug release after 14 h for 0, 50, 100, 150 and 200 mg meglumine per tablet formulations was 10.18, 51.58, 59.47, 89.52 and 101.14 % respectively. However, the drug was completely released from formulation containing 200 mg meglumine with 95.85 % after 8 h. Hence core formulation with 150 mg meglumine was chosen for further development.

In the present study, effect of viscosity grade of HPMC as pore former on drug release from VH and GZ tablets was also studied. HPMC K100LV, HPMC K4M and HPMC K15M were used as pore forming agent because they form a strong viscous gel on contact with aqueous media, which might help in controlling the delivery of highly water-soluble drugs.

It was evident from release profile from the formulation of venlafaxine and glipizide containing without HPMC coating, with HPMC K100LV, with HPMC K4M and HPMC K15M that the viscosity grade of HPMC had a direct effect on drug release and it is possible to achieve the desired release by using different types and/or combination of pore former. In case of venlafaxine, $MDT_{50\%}$ was found to be 7.12, 9.25 and 12.47 h for formulations containing HPMC K100LV, HPMC K4M and HPMC K15M respectively and in case of glipizide, $MDT_{50\%}$ was found to be 6.82, 10.01 and 13.14 h for formulations containing HPMC K100LV, HPMC K4M and HPMC K15M respectively. There was statistically significant difference ($P \leq 0.05$) between the different formulations. This might be attributed to the high viscosity nature of HPMC K15M and K4M when compared to HPMC K100LV. HPMC K15M and K4M form a stronger viscous gel on contact with aqueous media and restrict the delivery of drug. Comparative faster release of the drug from the and HPMC K100LV coating was probably due to faster dissolution of the highly water-soluble drug in the core and its diffusion out from the low viscous porous structure. In case of formulation containing without HPMC coating, only 2.65 ± 1.65 % and 10.25 ± 2.58 % drug released from venlafaxine and glipizide formulation respectively. No swellable porous structures were formed which was confirmed from the SEM studies.

To study the effect of level of pore forming agent and to optimize the release profile, core formulations of VH and GZ were coated with higher level of HPMC K100LV and HPMC K4M containing 12 % w/w of cellulose acetate. HPMC K15M was not studied as it was observed that the drug release was highly restricted even with lower polymer concentration level and difficulty in performing the coating experiment due to the high viscosity of the coating solution.

In case of HPMC K100LV coating, $MDT_{50\%}$ was found to be 7.12 and 3.68 h for formulations containing 6% and 12% HPMC K100LV respectively for venlafaxine. And for glipizide, $MDT_{50\%}$ was found to be 6.82 and 5.12 h for formulations containing 6 % and 12 % HPMC K100LV respectively. In case of HPMC K4M coating, $MDT_{50\%}$ was found to be 9.25 and 7.22 h for formulations containing 6% and 12% HPMC K4M respectively for venlafaxine. And for glipizide, $MDT_{50\%}$ was found to be 10.01 and 9.12 h for formulations containing 6% and 12% HPMC K4M respectively. These values confirmed the effect of level of hydrophilic polymers on the release from osmotic system. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. This observation was less prominent in the case of HPMC K4M coating which could be due to more viscous pores. Increasing the level from 6% to 12% increases the number of swellable pores however these pores are of very high viscosity and hence the passage for the drug gets saturated. On the other hand HPMC K100LV coating proved that the effect of level of polymer was directly proportional to the drug release. This phenomenon was observed in both the drugs. Other workers have also obtained similar results (Zentner et al., 1985a, Okimoto et al., 1999c). The level of pore former also affects the burst strength of exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of HPMC, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports (Zentner et al., 1985a, Verma et al., 2003).

From earlier experiments, it was observed that the level of pore former also affected the extent of drug release. More than 95 % VH and GZ was released after 8 h and 10 h respectively, with 12 % HPMC K100LV coating where as there was no complete release (>95%) with 6 % HPMC K100LV coating in case of both the drugs. Hence in order to release the drug completely, get optimum drug release and decrease the level of pore

forming polymers, a combination of coating solution with 7 % HPMC K100LV and K4M (3.5 % each of total solids) was prepared and coated with similar process as mentioned earlier. The drug release and the burst strength were satisfactory with the formulations containing a combination of HPMC K100LV and K4M as the pore former.

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products. Effexor XR marketed by Wyeth Inc., USA is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids where as Glucotrol XL marketed by Pfizer Inc., USA is based upon push–pull osmotic pump technology. It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming into contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice.
The advantages of the in house developed system the are that it is simpler in design (single layer vs. bilayer), requires less number of manufacturing steps (no need for laser drilling), economical, and easily amenable to mass production.

The f_1 *and* f_2 values were 11.12 and 68.51 for venlafaxine and 12.22 and 71.47 for glipizide.

Drug release from in house optimized formulation fitted well into zero-order kinetics, which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior. The second best model describing the release was Higuchi's followed by first-order and Hixson-Crowell. The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the n value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The n value obtained for the optimized formulation was more than 0.5 (n =

0.5894, r = 0.9864 and k = 2.157) suggesting the release from this formulation follows non-Fickian diffusion.

It was expected that varying the viscosity grade and the level of swellable pore former, porosity of the membrane would vary because of swelling of pore former from the membrane. This was reflected in the release studies, wherein the release varied with varying the viscosity grade and level of swellable pore former. To further confirm this, the membrane structure of formulations of SPOP containing swellable polymers were observed after dissolution studies.

In case of membrane containing 0 % level of swellable pore former, there were no pores or sponge like appearance in the membrane. With 6% (w/w of CA) HPMC K100LV, SEM micrograph showed formation of sponge like structure in the membrane. With 6% (w/w of CA) HPMC K4M, SEM micrograph showed formation of significantly enhanced spongy structure as compared to C-II membrane. This could be due to the high viscosity nature of HPMC K4M. In case of 6% (w/w of CA) HPMC K15M, SEM micrograph showed formation of denser sponge like appearance than former the membranes. This could be due to higher viscosity nature of HPMC K15M than HPMC K100LV and K4M. The results were consistent with the drug release studies.

In case of 12% (w/w of CA) HPMC K100LV, SEM micrograph showed formation of thick dense skin having spongy appearance than 6% (w/w of CA) HPMC K100LV. This could be due to higher viscosity resulting from 12% coating compared to 6%. In case of 12% (w/w of CA) HPMC K4M, SEM micrograph showed formation of significantly thick spongy appearance than 6% (w/w of CA) HPMC K4M in the membrane. This could be due to higher viscosity resulting from 12% coating. The results were consistent with the drug release studies. In case 3.5% (w/w of CA) each of HPMC K100LV and HPMC K4M, SEM micrograph showed formation of uniform spongy like appearance than all other coating membranes. This could be due to combined effect of higher and lower viscosity grade HPMC polymer. The results were consistent with the drug release studies.

PART II : MONOLITHIC OSMOTIC TABLET SYSTEM (MOTS)

The dosage form was designed as a tablet core, coated with a rate controlling membrane. Tablet core consists of drug along with solid dispersing carrier (Poloxamer 188, in case of Nifedipine), osmogent, and other conventional excipients. Solid dispersing carrier used in the core was formulated to enhance the solubility and drug release. The core compartment was surrounded by a membrane consisting of cellulose acetate (CA), a semipermeable membrane-forming polymer and PEG-400 as plasticizer capable of improving film-forming properties of the polymers.

CA is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug (In case of nifedipine, the solid dispersing carrier first gets dissolved and then increases the solubility of nifedipine). The dissolved drug is released through orifice.

The intrinsic solubility of nifedipine, a poorly water-soluble drug, is ~ 5 μg/ml at 37°C in water.

The solubility of nifedipine solid dispersions having maximum carrier (1:10) with PEG-6000, Poloxamer-188 and Mannitol as a carrier was 23.51 ± 0.17, 47.71 ± 0.52 and 7.37 ± 0.07 μg/ml respectively. There was a ~9 fold increase in the solubility of nifedipine from Nifedipine Poloxamer-188 Solid Dispersion (NPSD) from 1:10 ratio as against pure nifedipine at 37°C. This might be attributed to the surface active property of Poloxamer-188 as it is a polyoxyethylelne-polypropylene block copolymer nonionic surfactant with an HLB value of 18-23. Poloxamer-188 reduces the activity coefficient of the drug by reducing the hydrophobic interaction. The solubility of nifedipine increased linearly with increasing concentration of Poloxamer-188 and maximum solubility obtained was with NPSD 1:10. Hence a 1:10 (drug:polymer) ratio was used for further development

When subjected for DSC study, pure nifedipine crystals gave a sharp melting endotherm at 173.89 °C, Poloxamer-188 exhibited a single sharp melting endotherm at 51.29 °C and NPSD exhibited a melting endotherm at 51.16°C and the absence of nifedipine melting peak was observed in the thermogram. These results suggest that on heating in DSC, nifedipine progressively dissolve in Poloxomer-188 and dissolves completely below the

melting temperature of crystalline nifedipine. The relationship was found to be consistent with the results obtained by previous works (Vippagunta et al. 2002). The powder X-ray diffractogram of pure nifedipine from 5 to 20° 2θ showed numerous distinctive peaks that indicated a high crystallinity. Poloxamer-188 also exhibited some crystallinity, as indicated by the two peaks of high intensity at 19.25° and 23.45° 2θ. The XRD patterns of NPSD exhibited the absence of characteristic diffraction peaks of nifedipine, indicating that the crystalline characteristics of nifedipine had disappeared in these solid dispersions. Nifedipine at low concentrations may have either converted to a metastable amorphous form or may have dissolved in the matrix system to form a solid solution, or may exist in a microcrystalline form in the matrix.

The influence of tablet formulation variables mainly amounts and ratio of PEO on metoprolol release was studied and optimized. All the core formulations were coated with a uniform coating composition containing 20 % w/w (of CA) PEG-400 and an orifice was drilled with 0.7 mm diameter. Initially a batch was prepared without PEO and the drug release was very quick with more than 85% released after 8h. For a batch with total PEO of 50 mg per tablet with higher ratio of drug (2:1, Drug:PEO) and higher ratio of low mol. wt. polymer (4:1, PEO 1: PEO 3 Lac g/mol), the drug release in initial hours was controlled however around 80% drug got released after 8h. For a batch with the PEO 1: PEO 3 ratio of 1:1, the drug release was controlled by ~ 8% with ~72% drug release after 8h compared to the earlier batch. One more batch was prepared with same composition as that of later except that the total amount of PEO was doubled to 100 mg per tablet with drug: total PEO of 1:1. The drug release was further controlled to 69.47 ± 2.33 % after 8h. In order to further control the drug release, another batch was prepared same as that of later except that the PEO:PEO ratio was changed to 1:1. The initial burst release as well as the whole release profile was controlled with 11.25 ± 1.58, 62.46 ± 2.18 and 85.35 ± 2.11 % released after 1, 8 and 12 h respectively.

It is well known that, for a water-soluble polymer, higher the amount, higher is the viscosity of the polymer solution and slower dissolution rate. In the case of higher ratio of drug to total PEO (2:1, Drug:PEO), PEO swelled and dissolved quickly, but gave a solution with low viscosity, which could not hold MT suitably. As a result, the release

rate was fast in formulation with higher amount of 1 Lac g/mol. On the other hand, in the case of equal ratio of drug to total PEO (1:1, Drug:PEO), PEO gave a solution with high viscosity, which could hold MT; however, PEO swelled and dissolved slowly. Therefore, the liquefaction of the tablet core and the release of MT were depressed and the release rate was slow. Higher ratio of low mol. wt. polymer (4:1, PEO 1: PEO 3 Lac g/mol) was studied and found that PEO swelled and dissolved quickly, but gave a solution with low viscosity, which could not hold MT suitably. As a result, the release rate was fast in formulation with higher amount of 1 Lac g/mol (MB and MD). On the other hand, in the case of equal ratio of both PEO polymer (1:1) PEO gave solution with high viscosity, which could hold MT; however, PEO swelled and dissolved slowly (MC and ME). Therefore, the liquefaction of the tablet core and the release of MT were depressed and the release rate was slow.

To study the effect of osmogent in the core formulation, core tablets with 1:10 (Drug : Poloxamer-188) ratio based formulations with varying amounts of potassium chloride were prepared and coated with same coating formulation and a uniform orifice was drilled with 0.7 mm diameter. The coated formulations were studied for in-vitro dissolution studies. The amount of potassium chloride had a marked influence on the nifedipine release. The release rate increased as the amount of potassium chloride increased. This could be due to the following hypothesis.

The more potassium chloride was incorporated into tablet, amount of water imbibed was much higher and the more core formulation could be dissolved. As a consequence, more nifedipine was released. The percent release after 20 h with 0, 50, 100 and 200 mg potassium chloride per tablet was 42.57 ± 2.75, 66.26 ± 2.84, 86.98 ± 3.11 and 91.74 ± 4.95 respectively, suggesting that an optimum amount of osmogent is required in an osmotic system to completely release the drug.

To study the influence of membrane thickness of the coating on drug release, core tablets were coated so as to get tablets with different weight gains (~ 6, 9 and 12 % w/w). An orifice was drilled with 0.7 mm diameter. Release profile figures shows that release rate decreased as the membrane thickness increased. This could be due to the following hypothesis.

As the thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased and, in turn, the liquification rate of the tablet core decreased, resulting in the drug release rate decreasing. The relationship was found to be consistent with the results obtained by previous works (Verma et al. 2004). No burst effects were observed in any of the empty shells.

To study the effect of plasticiser, the core tablets were coated by cellulose acetate containing PEG-400 of 10, 25 and 40 % w/w of cellulose acetate with a weight gain of around 6 % and orifice of 0.7 mm diameter. Increasing the amount of PEG in the semipermeable membrane increases void space after leaching and results in higher permeability of the membrane followed by higher drug release rate. As PEG is a hydrophilic plasticizer, it could be leached easily leaving behind the wholly porous structure, which increases membrane permeability and drug release rate.

To study the effect of orifice diameter on developed formulations, core tablets were coated and subsequently a circular orifice diameter was drilled on the surface coated tablets to achieve 0.41 ± 0.01 mm, 0.76 ± 0.01 mm and 1.24 ± 0.02 mm diameter. No significant difference existed in the release profiles for orifice diameters of 0.41 to 0.76 mm. However, the release was somewhat rapid with an orifice diameter of 1.24 mm. This may be due to the influence of diffusion from the bigger orifice. On the other hand, a longer lag time and a lower release rate were exhibited at an orifice diameter of 0 mm (i.e., without an orifice). The continuous water influx into the system without an orifice produced an increase in the volume of drug solution inside the system, therefore leading to an increase in the hydrostatic pressure inside the system. The pressure formed would cause membrane disruption and crack formation on the membrane. Subsequently, drug release was initiated via the crack. As the time of formation and the size of the crack could not be controlled or predicted, the system without an orifice was uncontrollable.

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products. Toprol XL marketed by AstraZeneca Inc., USA is formulated as an extended-release tablet for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids where as Procardia XL marketed by Pfizer Inc., USA is based upon push–pull osmotic pump technology. It is a bilayer tablet coated with a semipermeable membrane. Drug along

with osmogents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming into contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice.

The advantages of the in house developed system the are that it is simpler in design and requires less number of manufacturing steps (single layer vs. bilayer) economical, and easily amenable to mass production.

The f_1 *and* f_2 values were 10.55 and 81.54 for metoprolol and 12.54 and 69.29 for nifedipine.

Drug release from *in house* optimised formulation fitted well into zero-order kinetics for both the formulations (Metoprolol and Nifedipine), which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior.

For metoprolol, the next best model describing the release was Hixson-Crowell, first-order and Higuchi's and for nifedipine, the next best model describing the release was first-order, Hixson-Crowell, and Higuchi's.

The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the *n* value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The *n* value obtained for the optimized formulation was more than 0.5 suggesting the release from this formulation follows non-Fickian diffusion.

To confirm the influence of amount of PEG on membrane, CA membranes plasticised with 10, 25 and 40 % (% w/w of CA) were studied by SEM. SEM micrographs shows that the increase of PEG level led to increase in formation of void space after leaching and in turn higher permeabiity of the membrane. The results were consistent with the drug release studies.

PART III CONTROLLED POROSITY OSMOTIC SYSTEM (CPOP)

The dosage form developed was designed as a tablet core coated with a rate controlling membrane. Tablet core consists of drug along with osmogent, and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble pore forming additives, and at least one plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. Cellulose acetate was used as water-insoluble polymer and sorbitol, HPMC and PEG-6000 were used as waters-soluble additive. PEG-400 was used as plasticizers.

The solubility of atenolol (37 °C) in deionized water was 27 mg/ml hence concentration of atenolol in various concentrations of tartaric acid aqueous solution was studied. It was clear that the concentration of atenolol in tartaric acid aqueous solution increased with the increase of original tartaric acid concentration. A more than 20-fold increase in atenolol concentration was achieved at original tartaric acid concentration of 200 mg/ml. It could be explained by its molecular structure. Atenolol had an imide group exhibiting alkalinity. When atenolol contacted with tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased markedly. It could be concluded that this method should be much more suited for the solubilization of atenolol and the preparation of monolithic osmotic pump tablet compared with technologies of solid dispersion and cyclodextrin inclusion

To optimize the amount of osmogent to be used in the formulation and to study the effect of drug to osmogent ratio, core formulations were prepared with drug to osmogent ratio of 1:0, 1:5, 1:10 and 1:20. All the core formulations were coated with similar coating composition containing 15 % w/w (of CA) of sorbitol. Osmogent enhances the release of drug and had a direct effect on drug release. This is evidenced from a formulation, which

was devoid of any osmogent in the core, showed 61% drug release at 24h. However, the use of osmogent enhanced the release beyond 80% drug release at 24h depending on the amount of osmogent present in the core formulation which might be due to the increased water uptake and hence increased driving force for drug release.

To optimize the amount of solubility modifier, tartaric acid to be used in the atenolol formulation, core tablets were prepared with 2.5, 5 and 7.5 mg per tablet. All the core formulations were coated with coating composition containing 15 % w/w sorbitol (of total solids). The solubility modifier enhanced the release of drug and had a direct effect on drug release. Core tablets of AT without solubility modifier showed around 20 % drug release even after 20 h. This phenomenon could be expected due to poor water solubility of atenolol. As reported earlier, when atenolol contacted with tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased markedly. Hence, the use of solubility modifier enhanced the release depending on the amount of solubility modifier present in the core formulation. The drug release after 20 h for formulations with 2.5, 5 and 7.5 mg tartaric acid per tablet was 40.18 ± 1.88, 59.52 ± 2.81 and 81.02 ± 3.35 respectively. Hence core formulation with 7.5 mg tartaric acid was chosen for further development.
To study the effect of osmogent in the core formulation, core tablets were prepared with varying amounts of potassium chloride and coated with similar coating formulation. The coated formulations were studied for in-vitro dissolution studies. The release rate increased as the amount of potassium chloride increased. The more potassium chloride incorporated into tablet, the more water was imbibed and the more core formulation could be dissolved and, as a consequence, more atenolol was released. The percent release after 20 h with 25, 50 and 75 mg potassium chloride per tablet was 81.02 ± 1.75, 89.84 ± 3.47 and 101.28 ± 5.02 respectively, suggesting that an optimum amount of osmogent is required in an osmotic system to completely release the drug.

To study the effect of level of pore former (sorbitol), core tablets were coated with coating composition containing 0, 7.5, 15 and 20 % (w/w of total solid) of sorbitol. It was found that the drug release increases with the level of sorbitol. As the level of pore former increases, the membrane becomes more porous after coming in contact with the

aqueous environment, resulting in faster drug release. Other workers have also obtained similar results (Zentner et al., 1985a; Okimoto et al., 1999a). The level of pore former also affected the extent of drug release with maximum drug release after 24 h was 28.25, 61.58 and 91.34 % in formulations containing 0, 7.5 and 15 % (w/w of total solid) of sorbitol for OC. However with 20% of sorbitol, 101.29 % of the drug release took place in 20 h itself.

Similar observation were seen with AT where maximum drug release after 20 h was 41.26, 59.96 and 89.37 % in formulations containing 0, 7.5 and 15 % (w/w of total solid) of sorbitol and with 20% of sorbitol, more than 99.16 % of the drug release took place in 16 h itself.

As the pore former level increases, the membrane becomes porous after coming in contact with the water (when the pore former leaches out of the membrane). At levels up to 10% (w/w) of pore former, numbers of pores are not sufficient to contribute to significant drug release. On the other hand, membranes that initially contained 15% (w/w) of pore former; the membrane becomes more porous after coming in contact with water. The explainable reason for the sudden change in the release profile may be that the threshold might not have reached in formulations containing 15% and less of pore former. Therefore, it can be concluded that drug release is directly proportional to the level of pore former in the membrane and this parameter can be varied to control the drug release. Another parameter affected by the level of pore former was burst strength of the exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of sorbitol, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports (Appel and Zentner, 1991; Jensen et al., 1995). Since, satisfactory drug release and adequate burst strength were obtained in case of formulations with 15% pore former level , this concentration was selected for further studies.

To study the effect of type of pore former, formulations were prepared by coating core tablets of OC and AT with coating compositions containing different pore formers (Sorbitol, HPMC and PEG-6000). The type of pore former affected drug release and it is possible to achieve the desired release by using different types and/or combination of

pore formers. $MDT_{50\%}$ in case of OC was found to be 12.25, 10.24 and 7.46 h for formulations containing HPMC, Sorbitol and PEG-6000 respectively. Similar observation were obtained with AT and found to be 12.01, 10.12 and 7.59 for formulations containing HPMC, Sorbitol and PEG-6000 respectively

There was statistically significant difference ($P \leq 0.05$) between the different formulations.

In addition to release, type of pore former also affected the burst strength of the exhausted shells and this parameter should also be taken into consideration while selecting the pore former. The drug release and the burst strength were satisfactory with the formulations containing sorbitol as the pore former. This formulation was selected as the "optimized" formulation and used for further evaluation

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products. Ditropan XL marketed by Alza Inc., USA is formulated as an extended-release tablet for once-a-day oral administration. Drug release is controlled by osmotic pump technology. The drug compartment is connected to the outside environment via a delivery orifice. The advantages of the in house developed system is that it is simpler in design and requires less number of manufacturing steps, economical, and easily amenable to mass production. The f_1 *and* f_2 values were 13.59 and 62.51.

Drug release from *in house* optimised formulation fitted well into zero-order kinetics for both the formulations (OC and AT), which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior.

For OC, the next best model describing the release was first-order, Higuchi's and Hixson-Crowell, and for AT, the next best model describing the release was first-order, Hixson-Crowell, and Higuchi's.

The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the *n* value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The *n* value

obtained for the optimized formulation was more than 0.5 suggesting the release from this formulation follows non-Fickian diffusion.

It was expected that with an increase in the level of pore former, porosity of the membrane would increase because of leaching of pore former from the membrane. This was reflected in the release studies, wherein the release increased with the increase in level of pore former. To further confirm this, the membrane structure was observed after dissolution studies.

In case of membrane containing 0 % level of sorbitol as pore former, there were no pores in the membrane. It was concluded that the membrane did not develop significant porosity after coming in contact with the aqueous environment. In case of 7.5% (w/w of CA) of sorbitol, SEM micrograph showed formation of significantly fewer pores in the membrane and 15% (w/w of CA) of sorbitol micrograph showed formation of thin denser pores in the membrane than later. In case of 20% (w/w of CA) of sorbitol, SEM micrograph showed considerable uniform porosity after dissolution studies. The results were consistent with the drug release studies.

In case of membrane containing sorbitol, formation of uniform pores was observed. For membrane containing HPMC, formation of dense pores than sorbitol was observed which could be due the gelling and swelling property of HPMC. For membrane containing PEG-6000 formation of non-uniform pores were observed. From these observations it can be concluded the type of pore former affects the drug release and the same has to be optimized. The results were consistent with the drug release studies.

PART IV PERFORMANCE EVALUATION OF OPTIMIZED FORMULATIONS

Effect of pH

In order to study the effect of pH on drug release from water-soluble drugs (VH, MT and OC), release studies were conducted in media of different pH (SGF, pH 1.2; acetate buffer, pH 4.5; and SIF, pH 6.8). Release profile was similar ($P>0.05$) in all the media demonstrating that the developed formulations show pH-independent release.

In order to study the effect of pH on drug release from low water soluble drugs (GZ, NP and AT), release studies of optimized formulation were conducted according to pH

change method to assure a reliable in vivo performance and also to study the effect of pH on drug release. It was clearly evident that the release profiles were similar in both the media (P>0.05).

Effect of agitational intensity

To study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in USP dissolution apparatus type I at varying rotational speed (50, 100, and 150 rpm). It was clearly evident that the release was independent of the agitational intensity (P>0.05).

Based on the above results of pH and agitational intensity, it can be concluded that drug releases from optimized formulations are independent of the agitational intensity of the release media. Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body (Verma and Garg, 2004).

Effect of osmotic pressure

To study the effect of osmotic pressure, release studies of the optimized formulation were conducted in media of different osmotic pressure. Drug release was found to be highly dependent on the external osmotic pressure and drug release from the formulations decreased with an increase in the osmotic pressure of the release media (P<0.05). From these figures it was confirmed that osmotic pumping is the major mechanism of drug release from the developed formulations (Appel and Zentner, 1991; Jensen et al., 1995).

IN-VIVO PHARMACOKINETIC STUDY

In -vivo evaluation of glipizide SPOP tablets Vs Glucotrol XL tablets and nifedipine MOTS tablets Vs Procardia XL tablets were performed in six beagle dogs using a two-way comparative cross-over design in accordance with GLP compliance for conducting pharmacokinetics studies.

The mean T_{max} for glipizide SPOP tablets was 6.11 hours compared to 8.95 hours for the Glucotrol XL tablets. This indicated that the time taken to reach maximum plasma glipizide concentrations were comparable in both the formulations, thus providing controlled release of the drug. The mean $AUC_{0\text{-}24\ h}$ of the glipizide SPOP was 3648.49 ng.h/ml as compared to 4155.76 ng.h/ml that of Glucotrol XL. Also the C_{max} of the

glipizide SPOP was 411.97 ng/ml as compared to 425.27 ng/ml that of Glucotrol XL. However the T/R ratio was within the limit of 80-125%, taking the values of glipizide SPOP as T and the value of Glucotrol XL as R, suggesting that the developed glipizide SPOP tablets were bioequivalent with Glucotrol XL.

The mean T_{max} for nifedipine MOTS tablets was 11.68 hours compared to 12.05 hours for the Procardia XL tablets. This indicated that the time taken to reach maximum plasma nifedipine concentrations were comparable in both the formulations, thus providing controlled release of the drug. The mean $AUC_{0\text{-}24\ h}$ of the nifedipine MOTS was 5439.24 ng.h/ml as compared to 6084.45 ng.h/ml that of Procardia XL. Also the C_{max} of the nifedipine MOTS was 325.47 ng/ml as compared to 361.76 ng/ml that of Procardia XL. However the T/R ratio was within the limit of 80-125%, taking the values of nifedipine MOTS as T and the value of Procardia XL as R, suggesting that the developed nifedipine MOTS tablets were bioequivalent with Procardia XL.

STABILITY STUDIES

Based on the results of in vitro drug release studies, optimized formulations were found to provide the required oral controlled drug delivery and hence stability studies were carried out by storing the formulations at 40 °C / 75 % RH for 3 months (Climate zone IV conditions for accelerated conditions-ICH guidelines) to assess the long term stability. During and at the end of the storage period, studies were conducted on different optimized formulations to assess their stability with respect to their physical appearance, hardness of core tablets, burst strength, drug content and drug release characteristics.

Physical Stability and Drug Content

All the formulations during and after storing at 40 °C / 75 % RH for 3 months showed no change in physical appearance. Slight variation in the hardness was observed with all the core tablet formulations however the difference was statistically insignificant ($P>0.05$). The burst strength values during and after storage were higher than the reported values of mechanical destructive forces in the GIT (Kamba et al., 2000) ensuring the formulations to be intact in the GIT without any incidence of dose dumping. The drug content was also found to be within the pharmacopoeial limits during and after the storage period. Any

variations observed were within the limits hence the formulations were found to be stable in terms of drug content and physical appearance.

Drug Release Characteristics

Drug release properties of various optimized formulations were determined during and after complete storage period for three months. The *f1* and *f2* value were calculated with initial analysis was taken as a reference and the 1M, 2M and 3M data was taken as test. It was observed that the *f1* value increased and *f2* value decreased for all formulations. However the values were within the limit of < 15 and > 50 for *f1* and *f2*, respectively.

CONCLUSIONS

Based on the present work it is clear that extended release formulations of varying solubility profile drugs can be developed using swellable porous osmotic system (SPOP), monolithic osmotic tablet system (MOTS) and controlled porosity osmotic system (CPOP). While developing formulations using these technologies, following considerations / conclusion may be kept in mind.

✍ **SPOP**

Extended release formulations of Venlafaxine HCl and Glipizide were developed based on swellable porous osmotic pump (SPOP) technology. Meglumine was added as a solubility modifier to increase the microenvironmental pH of the core above the pKa of glipizide and optimised the quantity. The effect of different formulation variables was studied to optimize release profile. SEM studies confirmed the formation of pores in the membranes after coming in contact with the aqueous environment. The driving force involved in the drug release was osmotic pumping as well as swelling layer, which results in a gel formation and diffusion of drug molecules. Drug release was directly proportional to the type and level of pore former, but inversely related to the membrane weight.

✍ **MOTS**

Extended release formulations of Metoprolol Tartrate and Nifedipine were developed based on monolithic osmotic tablet system (MOTS) technology. Poloxamer-188 was

effective in increasing the solubility of nifedipine. Formation of complex and decrease in crystallinity of nifedipine was confirmed from DSC and XRD study. The effect of different formulation variables was studied to optimize release profile. The system was optimized for amount of osmogent, membrane weight gain, amount of plasticiser and diameter of the orifice, to achieve desired release profile. The osmotic system was found to deliver at a zero order rate for 20 h. Drug release was inversely related to the membrane weight. SEM micrographs shows that the increase of PEG level led to increase in formation of void space after leaching and in turn higher permeability of the membrane. The in-vivo pharmacokinetic study in beagle dog confirmed that the developed nifedipine MOTS tablets were bioequeivalent with Procardia XL tablets.

✍ **CPOP**

Extended release formulations of Oxybutynin chloride and Atenolol were developed based on controlled porous osmotic pump (CPOP) technology. Tartaric acid was added as a solubility modifier to decrease the microenvironmental pH of the core atenolol and optimised the quantity. The effect of different formulation variables was studied to optimize release profile. Drug release was directly proportional to the level of pore former, but inversely related to the membrane weight. SEM studies confirmed the formation of pores in the membranes after coming in contact with the aqueous environment. Drug release was directly proportional to the type and level of pore former, but inversely related to the membrane weight.

✍ **Performance evaluation of optimized formulations**

The drug release from the all the developed formulations was independent of pH and agitational intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Drug release was found to be highly dependent on the external osmotic pressure confirming osmotic pumping is the major mechanism of drug release from the developed formulations.

✍ **In-vivo studies**

The in-vivo pharmacokinetic study in beagle dog confirmed that the developed glipizide SPOP tablets were bioequivalent with Glucotrol XL tablets and nifedipine MOTS tablets were bioequeivalent with Procardia XL tablets.

✍ **Stability Studies**

Developed formulations were found to be stable for 3 months when stored at accelerated stability conditions.