SUMMARY
AND
CONCLUSIONS
Summary

Last century has witnessed spectacular developments in the field of pharmaceutical sciences especially novel drug delivery systems. The goal of such systems has been to provide a therapeutic amount of drug to a proper site in the body to achieve promptly and then maintain the desired drug concentration. This well defined objective incorporates two aspects which are most important for the clinical use of such systems. They are spatial placement and temporal delivery of a drug. Spatial placement is concerned with the targeting of a drug to a specific organ or tissue, whereas temporal delivery is responsible for controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug delivery systems can be very effective in solving these problems. It is for this reason that the science and technology of dosage form design for the development of controlled release formulations are the focus of great deal of attention in both industrial and academic laboratories. Currently, there exist numerous controlled release dosage forms which cover a wide range of prolonged action formulations providing continuous release of their active ingredients at a predetermined rate and for a predetermined time. The majority of these formulations are designed for oral administration that satisfy the temporal aspect of drug delivery; however, recently such devices have also been introduced for parenteral administration, ocular insertion and for transdermal application. The most important objective for development of these systems is to furnish an extended duration of action and thus assure greater patient compliance. Such formulations may also exhibit decreased incidence and intensity of adverse effects, more uniform blood concentrations and produce more
consistent and prolonged therapeutic effect. Ideally the optimization of therapeutic
efficacy and safety may be attained as a result of providing a nearly constant
pharmacological response, thereby avoiding the normal peak and valley pattern
associated with multiple dosing of conventional drugs.

This study is confined to the development of a controlled release dosage form
of one of the most extensively used calcium channel blocking agent, diltiazem based
on the principle of osmosis. It is a unique phenomenon which seizes the attention for
its exploitation in zero order drug delivery systems.

Diltiazem hydrochloride (DL) is a calcium channel-blocking agent of the
benzothiazepine class. The drug preparation available clinically contains the di-cis
isomer. It is an effective and well-tolerated drug for the treatment of angina pectoris
due to coronary arterial spasm and chronic stable angina pectoris. It is beneficial in
these conditions probably due to its coronary vasodilating properties and its
hemodynamic effects. DL has also shown efficacy in the treatment of hypertension
and cardiac arrythmias. Although approximately 90% of an orally administered dose
of DL is absorbed, only 40% of an oral dose reaches systemic circulation as an
unchanged drug, since it undergoes extensive first pass metabolism in the liver.

Compatibility of various excipients used to formulate osmotically controlled
system of DL was studied. Physical observations of blends of DL and exipients were
taken initially and then at 1 month and 3 months intervals. After three months, these
samples were analysed for drug content. Initially these blends were also tested for
compatibility by Differential Thermal Calorimeter (DSC).
Various trials were taken for the selection and/or optimization of osmotic agent, polymer for semipermeable membrane, osmotic polymer, binder and lubricant. Process parameters for compression of bilayered osmotic tablets, coating of semipermeable membrane, drug coating and coloured film coat were also optimized. The $\lambda$-max of DL was scanned through spectrophotometer and found to be 237nm. The standard curves of DL were prepared in distilled water, 0.1N HCl, mixed phosphate buffer pH 6.8 (USP) and mixed phosphate buffer pH 7-4 (USP) and the absorbance data obtained were subjected to linear regression. This analysis indicated significant (P<0.05) correlation (2-50µg/ml) and absorbance, and reproductivity of method.

*In vitro* characterization of the polymeric membrane is essential for optimization of the membrane formulation. Polymer (CA) dispersions containing different plasticizers (DEP, PG, PEG) were cast into membranes on a glass plate mould. The films were evaluated for film thickness, membrane permeability, glass transition temperature and mechanical properties.

The prepared films were found to be of uniform thickness. The glass transition temperatures of films were seen to decrease with increasing plasticizer concentration. The water permeability of films in case of PEG and PG was found to increase with increased plasticizer levels but in case of DEP water permeability was found to decrease with increased plasticizer concentration. Modulus of elasticity and tensile strength were seen to decrease with increasing plasticizer concentration with all the plasticizers. The work done, extension at break and strain at maximum load values were seen to increase with increasing plasticizer at the lower plasticizer level and then
to decrease with higher plasticizer concentration for the films plasticized with DEP and PEG. However, reverse trend was seen in the case of films plasticized with PG.

DEP was found to be the most efficient plasticizer for CA among the three plasticizers tested. PEG was found to be as effective as DEP. The permeability studies showed that DEP reduces the rate of water permeability from the films and PEG and PG increases it.

Push pull osmotic pump (PPOP) of DL containing osmotic agents, osmotic polymers and other tablet excipients was developed. Granules for both the layers were prepared by wet granulation method. These granules were then compressed on bilayered tablet compression machine to form a bilayered tablet core. The tablet core was then coated in a coating machine having perforated coating pan with a semipermeable and/or microporous semipermeable membrane. A small hole was drilled on drug layer of the coated tablet with the help of a mechanical drilling machine and laser beam. Coating of drug layer on the osmotic pump for immediate release of drug was also done using the perforated pan coating machine.

Response surface methodology (Box-Behnken design) was applied for the optimization of osmotically controlled drug delivery system of DL and the effect of various factors and their interactions on dissolution of DL from osmotic pump was studied. This work was done in two parts: in part I, levels of excipients used in the drug-compartment (and coating thickness) were changed and in part II, levels of excipients used in push compartment were changed to study their effect on dissolution of DL from osmotic pump.
Mathematical relationships in the form of polynomial equations were generated and contour graphs were plotted to study the interaction of various of various factors. The theoretical (predicted) values and observed values were in close agreement. The significance of ratio of mean square variation due to regression and residual was tested using ANOVA. The ANOVA indicated a significant (P< 0.050) effect of factors on response. The factors coating levels (F1) and amount of NaCMC in drug compartment (F3) and push compartment (E2) showed significant effect on the release of DL from the osmotically controlled tablet formulation. Optimization was performed using Box-Behnhen design to yield tablets that released a >90% drug in 24 hours. Theoretical (predicted) values and observed values were in close agreement. Interaction of various factors on dissolution of DL at Y5 was also studied. The optimization model predicted a 98.97 % of DL dissolved in 24 hours when the coating thickness, amounts of NaCMC and NaCl in drug compartment were 0.10 mm, 125 mg and 75 mg respectively. A new batch of tablets prepared according to these levels yielded a response of 95.12 %. Therefore, it was possible to fabricate an optimized formulation of DL osmotic pumps by using the response surface methodology.

All the batches of osmotic pump of DL were evaluated for the parameters like hardness, friability, sieve analysis, angle of repose, bulk density, adhesion of layers, thickness of coating membrane and uniformity of weight, diameter of the hole, assay and water content. All the values were found within the limits/satisfactory. Dissolution study of osmotic pump was done in USP dissolution apparatus II (paddle) at 37°C and 100 rpm.
To determine effect of dissolution media, stirring conditions and pore diameter, dissolution was performed in different media (purified water, 0.1N HCl, pH 6.8 buffer, pH 7.4 buffer), at different stirring speeds and with different pore diameter. The results of these studies exhibited a constant release rate at different stirring speeds. Also the release rate was independent of the pH of the environment. Within a range the diameter of the hole did not affect release rate.

Effect of coating thickness and microporous semipermeable membrane was also studied. Dissolution was found dependent on thickness of the coating and rate of release increased with decrease in coating thickness. Combination of microporous and semipermeable membrane increased dissolution rate as compared to only semipermeable membrane of the same thickness. Effect of number of pores on rate of release of drug was also studied and results showed that rate of release did not change when number of pores were increased to three from one. Effect of mechanical drilling and laser drilling was also studied. Dissolution of DL from osmotic pump was found to be independent of mechanism or method of drilling an orifice in semipermeable membrane. Effect of presence of push compartment on rate and extent of release of drug was also studied, which showed that osmotic pump without the push compartment released less drug and at lesser rate as compared to osmotic pump having push compartment. To study the reproducibility and effect of batch size and equipment batches with different batch size and instruments were made. Results indicated the reproducibility of the dissolution profile. Incorporation of immediate release dose of DL helped in removing lag period.
Stability study was undertaken on three batches of DL osmotic pumps. The tablets were packed in blister pack with a forming laminate of PVC (250-micron thickness) and Aluminium lidding foil (20-micron thickness). All batches were stored at 2-8°C, 25°C with relative humidity 60%, 40°C with relative humidity 75% and 60°C with normal humidity. Either no or very minor changes, were seen in description, average tablet weight, thickness, crushing strengths and pack weights. The lack of change in average tablet weight and pack weights indicated lack of moisture ingress into the pack, or insignificant loss from the pack. The dissolution and assay of all batches at all conditions remained within specifications.

Bioavailability study of DL osmotic pump was conducted and compared with a formulation containing controlled release pellets namely Cardizem CD manufactured by Hoechst Marion Roussel.

*Study I-* The study on the osmotically controlled preparation was carried out in 3 healthy subjects in a single dose.

*Study II -* A two way cross-over study in 8 healthy subjects, in which the pharmacokinetic performance of osmotic pump of DL (240 mg) was compared with Cardizem CD (DL 240 mg) (pellets based formulation not an osmotic pump).

Results of study I showed that the value of plasma drug concentration was below the therapeutic concentration. With this release profile it might not have been possible to achieve therapeutic plasma concentration even at steady state. Based on these findings a new osmotic pump of DL was developed which released 40 mg of DL within one hour (loading dose) which helped in achieving higher plasma
concentration initially. The subsequent zero order release of drug from osmotic pump helped in maintaining the drug plasma concentration within the therapeutic range.

Results of the study II confirm the effectiveness of the new developed osmotic pump of DL. Mean Cmax value increased to 124.36 ng/ml (study II) from 50.95 ng/ml (study I) and tmax also decreased to 2.0 hour from 10.0 hour. At the same time AUC increased by almost 100% and half life of drug increased to 11.952 hour from 6.986 hour.

No significant difference was observed between various pharmacokinetic parameters (AUC, Cmax, MRT, Koc) of DL obtained after administration of Osmotic pump of DL and Cardizem CD. Differences between tmax was high and which may be attributed to difference in the in vitro release profiles of both the formulations. Low Tmax (2.0 hr) obtained in the case of osmotic pump of DL helped in achieving fast minimum effective concentration of the drug whereas in case of Cardizem CD high Tmax (10.6 hr) it was much delayed (Fig. 20).

Conclusions

- It is clearly evident from above experiments that the methods used to characterize semipermeable film are capable of evaluating the performance of films of CA with different compositions. Results of this study provided valuable information for optimization of the membrane formulation like osmotically driven controlled release devices of DL.
 Quadratic equations to optimize composition of osmotic pump of DL were generated. Coefficients obtained through these equations helped in understanding the effect of levels of various variables and to study interactions among the variables. Difference between observed and predicted value (residual) was insignificant. Hence equations generated through Box Behnken design are capable to predict response and optimize composition of osmotic pump of DL.

The release rates for DL osmotic pumps are controlled by membrane composition and weight, and independent of batch size and scale of the equipment. Hence, osmotic pump of DL can be made with reproducible results and it can be mass-produced for commercial purpose. Dissolution of DL from osmotic pump is independent of the orifice diameter within a size range of factor of three and number of pores. Dissolution of DL from osmotic pump is also independent of type of orifice drilling device used. This indicates that a drilling machine with very high precision is not required and small variation in diameter of the orifice will not change the rate of dissolution from osmotic pump significantly. Low cost mechanical drilling device can be used in place of high cost laser drilling device.

Rate of drug release is also independent of pH with in the physiologic range of 1.2 to 7.4. The release rates of DL from osmotic pump are also independent of stirring rate between 50 to 150 revolutions/minute, in the physiologic analogous range. Therefore, it is very easy to predict in vivo of release profile (plasma concentration) of drug when administered orally in the form of osmotic pump. Pharmacokinetic parameter like half-life, volume of distribution, bioavailability and hepatic first pass effect should be considered while prediction.
The results obtained from *in vitro* dissolution study of osmotic pump of DL showed that drug is released at zero order from the osmotic pump and duration of the drug release is up to 24 hours. Rate of dissolution of drug from osmotic pump of DL is not affected by pore size, number of pores, pH of dissolution media, stirring conditions and batch size. Hence an osmotic pump of DL is developed which is suitable for once-daily administration.

Scale up batches of osmotic pump of DL were made and it was observed that release profile remained unchanged. Thus it is possible to manufacture osmotic pump of DL at commercial level with reproducible results.

The physical, chemical and dissolution stability of the product has been demonstrated, and the suitability of the pack confirmed.

In-vivo study showed that osmotic pump of DL provided effective plasma concentration up to 24 hour and minimum effective concentration of the drug was achieved much faster than that of from an international formulation Cardizem CD.