Multiparticulate dosage forms (MPDF) are receiving an immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical preparations produced. The most increasingly interesting area in the development of MPDF’S is incorporation into tablets instead of hard gelatin capsules in order to make it more economical to the consumers and gaining more attention currently. The present research work focuses on the pelletized form of multiple units, they are prepared by process called Pelletization which is referred to as a size enlargement process and the final product obtained is called pellets. Pellets provide a reduction in the dosage regimen and gastrointestinal irritation moreover controlling the drug release and increasing the absorption of the active ingredient. Also one of the advantageous properties of the pellet formulations is being good candidates for the delivery of the drug substances due to minimizing the dose dumping effect. The reproducibility of the release characteristics from pellet formulations is also much better with respect to the single-unit dosage forms. They are suitable systems for film coating with respect to the low surface area-volume ratios. Also, resistance to external factors such as moisture, air and light are the most advantageous properties of these dosage forms (Celine et al, 2007; Ghebre 1989).

In the present investigation pan coating and fluid bed coating process were employed for the preparation of diltiazem HCl and verapamil HCl pellets.
Fluidized bed processor is equipment that can perform multiple functions like coating, drying, granulation and pelletizing. FBC has high efficient drying system and also uniform, continuous pellet coating can be achieved. It is ideal for a wide range of process applications includes coating, heating, drying, agglomeration and granulation. This process protects the product against moisture, light and air. It is ideal for control release film coating, pellet granulation and hot melt coating. It is applied to specific manipulation of the particle surface characteristics. With fluid bed coating, particles are fluidized and the coating fluid sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating. In the pan coating method, a core material is coated with the drug substance following a secondary coating process in which the release controlling polymer material is introduced. The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. The some of the Coating equipments used for the pan coating processes are standard coating pan and the perforated coating pan.

Diltiazem HCl is a calcium channel blocker which is widely used in the treatment of variant angina, hypertension and supraventricular tachyarrhythmias. It is freely soluble in distilled water, chloroform and methanol. Diltiazem HCl is rapidly absorbed (90%) after oral administration but availability in only 30-40% in systemic circulation and bioavailability varies between individual. The low bioavailability after oral administration is due to its high first pass hepatic metabolism. It has elimination half-life of 3 – 5 hrs and slightly prolonged after multiple dosing (Class et al, 2005; Connor et al,1999).
Verapamil hydrochloride is a calcium channel blocker and a class IV antiarrhythmic drug. It is a white crystalline powder, soluble in water; sparingly soluble in alcohol, freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.5. verapamil is approximately 90% absorbed from the GI tract but the bioavailability is only about 20% due to first-pass metabolism in the liver. It has terminal elimination half-life of 2 to 8 hours and prolonged after repeated oral doses. Its plasma protein binding is up to 90%. Based on the above physical, chemical, biopharmaceutical, properties and clinical relevance, diltiazem HCl and verapamil HCl were selected as drug candidates for developing controlled release pellet formulations (Anavekar et al, 1981; Bauer et al, 1992).

Analytical methods used for the estimation of diltiazem hydrochloride and verapamil hydrochloride were simple sensitive UV spectrophotometric methods. These spectrophotometric methods were adopted for the estimation of diltiazem hydrochloride and verapamil hydrochloride in the pellets and in the in vitro dissolution studies. Diltiazem hydrochloride in distilled water was estimated by spectrophotometric method at a wavelength of 238 nm. The method used for estimation of diltiazem HCl was found to be liner with the Beers law in the concentration range of 0-10 μg/ml (Lakshmana et al., 2009). The calibration curve values were given in the table 5.

Verapamil hydrochloride in buffer solutions was estimated by spectrophotometric method based on the measurement of absorbance at 278 nm. The method used for estimation of verapamil HCl was found to be liner with the
Beers law in the concentration range of 0-50 μg/ml (Bistra et al., 2007). The calibration curve values were given in the table 6.

*In vivo* pharmacokinetic studies of diltiazem hydrochloride and verapamil hydrochloride were carried in rabbits. The diltiazem hydrochloride and verapamil hydrochloride concentrations in the rabbit plasma were estimated by RP HPLC methods. These methods were found to be suitable for determining the plasma concentrations of the drugs. The calibration curve for the diltiazem HCl and verapamil HCl in rabbit plasma samples were given in the tables 7 and 8.

Diltiazem hydrochloride and verapamil hydrochloride pellets were prepared by pan coating process. Non pariel sugar spheres were used to coat the verapamil HCl. The drug layer was further coated with HPMC sub coating and further coated with HPMCP as release modifier and finally the spheres were coated with ethyl cellulose. Ethyl cellulose 7cps a high viscosity grade controlled release polymer was mainly used as coating agent for regulating the drug release from pellets. HPMCP, an enteric coating polymer was used in the present study to prevent burst effect of the drug from pellets during the first two hours of the dissolution. An attempt was made to optimize the composition of these two polymers to achieve the controlled release of drugs from the pellets. HPMC E5 was used a film former in the present investigation. Croscaremelloose sodium was used as disintegrant to create channels in the coating for drug release. Povidone was used as binder to achieve uniform drug layering in the present investigation. All batches of pellet formulations were manufactured under identical conditions by maintaining specific process parameters. The composition
of various diltiazem hydrochloride and verapamil hydrochloride controlled release pellets were given in tables 9-16.

Diltiazem hydrochloride and verapamil hydrochloride pellets were prepared by fluid bed coating process. Non pariel sugar spheres were used to coat the verapamil HCl. The drug layer was further coated with HPMC sub coating and further coated with HPMCP as release modifier and finally the spheres were coated with ethyl cellulose. Ethyl cellulose 7cps a high viscosity grade controlled release polymer was mainly used as coating agent for regulating the drug release from pellets. HPMCP, an enteric coating polymer was used in the present study to prevent burst effect of the drug from pellets during the first two hours of the dissolution. An attempt was made to optimize the composition of these two polymers to achieve the controlled release of drugs from the pellets. HPMC E5 was used a film former in the present investigation. Croscarmellose sodium was used as disintegrant to create channels in the coating for drug release. Povidone was used as binder to achieve uniform drug layering in the present investigation. All batches of pellet formulations were manufactured under identical conditions by maintaining specific process parameters. All the batches of pellet formulations were evaluated for the physical parameters such as particle size, % yield, friability and drug content. The composition of various diltiazem hydrochloride and verapamil hydrochloride controlled release pellets were given in tables 9-16.

All the batches of controlled release diltiazem hydrochloride and verapamil hydrochloride pellets prepared by both pan coating and fluid bed coating were
evaluated for percentage yield of the pellets. The percentage yield of all the prepared pellet formulations were in the range of 90 to 96%. Thus the methods adopted for the preparation of pellet formulation were found to be suitable and recovery is very high than compared to other microencapsulation process. The percentage yield values were given in the tables 17 to 18.

The average particle sizes of all the pellet formulations were analyzed by simple sieve analysis method. The average particles size obtained for all the batches of pellet formulations of diltiazem hydrochloride and verapamil hydrochloride were in the range of 720 to 760 \( \mu \text{m} \). The average particle size of various pellet formulations obtained by both pan coating and fluid bed coating process were highly uniform and found to be spherical with uniform coating. The surface characteristics of the pellets were further evaluated by SEM analysis. The average particle size range of various pellet formulations were given in the tables 17 to 18.

The diltiazem hydrochloride and verapamil hydrochloride content in the pellet formulations prepared by both pan coating and fluid bed coating were evaluated by UV spectrophotometric method. The known quantities of the pellets were taken at random and were crushed to a fine powder. The powdered material was transferred into a 100ml volumetric flask and distilled water was added to it. It was shaken for 30 minutes and the volume was made up to 100ml by adding distilled water. About 10ml of the solution from the volumetric flask was filtered by using millipore filter. Then the filtrate was subsequently diluted and the absorbance was measured at 238 nm for diltiazem HCl; for verapamil HCl
instead of distilled water take pH 7.5 buffer and measure the absorbance at 278 nm. The drug content in all the pellet formulations were in the range of 98 to 101%. The percentage drug loading in the pellets thus indicated that all the batches of diltiazem hydrochloride and verapamil hydrochloride pellet formulations were in the acceptable range as specified in IP. The drug content for all the pellet formulations were given in the tables 17 to 18.

The friability of the core pellets of diltiazem hydrochloride and verapamil hydrochloride were determined as % weight loss after 100 revolutions of 10 g of pellets in a friabilator. Friability test for all the pellet formulations were performed to determine the ability of pellets to withstand abrasion during packing and transportation. The test was carried out in roche friabilator. Surface damages to the pellet formulations were found to be negligible. The friability loss values for all the pellet formulations were given in the tables 17 to 18.

*In vitro* dissolution studies

Dissolution studies were performed on all the diltiazem HCl controlled release pellets prepared by both pan coating and fluid bed coating methods. The studies were performed by using USP paddle method with 900 ml of distilled water as a medium. The drug release from the pellets prepared by pan coating were found to release diltiazem HCl at a faster rate than compared to the pellets prepared by fluid bed coating method. The faster release rate of the drug from pan coated pellets was mainly due to irregular coating application. The surface characteristics were further investigated by SEM analysis, the release of
diltiazem HCl from pan / FBC coated pellets were extended up to 10 to 16 hrs (FDL 1-12). The drug release from all the pellet formulations was dependent on proportion of ethyl cellulose. As the proportion of ethyl cellulose is increased the drug release from the pellets (FDL 1-12) is extended for a prolonged period of time. The proportion of HPMCP was varied in some of the formulations (FDL13-22) by keeping ethyl cellulose at a constant proportion to check its influence on the drug release from the pellets. As the concentration of HPMCP varied in the formulations the drug release during the first two hours was slow and after two hours there was no influence of HPMCP on the release patterns of drugs from pellet formulations. This delayed drug release at the initial time period was due to swelling of HPMCP upon prolonged exposure to huge volume of dissolution fluids. The dissolution profiles were depicted in tables 19 to 22 and shown in graphs 6 to 9.

The dissolution profiles of diltiazem hydrochloride pellet formulations were compared with marketed pellet formulation of diltiazem hydrochloride (diltiazem HCl SR Pellets by Meenakxi Pharma, Hyderabad). The difference factor and similarity factor were calculated for these pellet formulations. The difference factor $f_1$ values were in the range of $7 – 58$ and similarity factor $f_2$ values were in the range of $19 – 79$. The formulations FDL6 and FDL12 showed the similarity factor values above 50 indicated that the release profiles for these formulations were similar to that of marketed formulation. The similarity factor values were given in the table 31. It was also observed that among the formulations prepared formulations FDL 6 & FDL 12 showed the drug release up to 80 % at the end of
16hrs matching with USP dissolution test 6 (USP., 2004) for diltiazem HCl extended release capsules.

Dissolution studies were performed on all the verapamil HCl controlled release pellets prepared by both pan coating and fluid bed coating methods. The studies were performed by using USP paddle method with 900ml of 0.1 N HCl for first 2 hrs and pH 7.5 phosphate buffer for remaining period of time as dissolution medium. The drug release from the pellets prepared by pan coating were found to release verapamil HCl at a faster rate than compared to the pellets prepared by fluid bed coating method. The faster release rate of the drug from pan coated pellets was mainly due to irregular coating application. The surface characteristics were further investigated by SEM analysis. The release of verapamil HCl from pan/FBC coated pellets were extended up to 10 to 16 hrs (FVL 1-12). The drug release from all the pellet formulations was dependent on proportion of ethyl cellulose. As the proportion of ethyl cellulose is increased the drug release from the pellets (FVL 1-12) is extended for a prolonged period of time. The proportion of HPMCP was varied in some of the formulations (FVL13-22) by keeping ethyl cellulose at a constant proportion to check its influence on the drug release from the pellets. As the concentration of HPMCP varied in the formulations the drug release during the first two hours was slow and after two hours there was no influence of HPMCP on the release patterns of drugs from pellet formulations. This delayed drug release at the initial time period was due to swelling of HPMCP upon prolonged exposure to huge volume of dissolution
fluids. The dissolution profiles were depicted in tables 23 to 26 and shown in graphs 10 to 13.

The dissolution profiles of verapamil hydrochloride pellet formulations were compared with marketed verapamil hydrochloride extended release pellet formulations (Verlan Capsules, Mumbai). The difference factor and similarity factor were calculated for these pellet formulations. The difference factor $f_1$ values were in the range of 9 – 64 and similarity factor $f_2$ values were in the range of 6 – 82. The formulations FVL6 and FVL12 showed the similarity factor values above 50, indicated that the release profiles for these formulations were similar to that of marketed formulation. The similarity factor values were given in the table 32.

**Comparative evaluation of pellets prepared by pan coating and fluid bed coating methods**

The releases of drug from the pellets prepared by both methods along with marketed pellets were given in graphs 38 to 39. The results indicated that pellets prepared by fluid bed coating process (FDL12 & FVL12) extended the drug release over a prolonged period than that of the pellets prepared by pan coating process (FDL6 and FVL6). The variation in the release patterns from the pellets prepared by these methods may be due to alterations in the film formation. The surface characteristics of pellets prepared by these two methods were further characterized by SEM analysis, DSC studies and FTIR spectral analysis.

All the pellet formulations were found to be linear with first order release rate with $R^2$ values in the range of 0.985 to 0.999 (Table 27 - 30), thus the rate of
drug release from all the pellet formulations were concentration dependent and were linear with first order release rate constant \( (K_1) \). The higuchi’s plots for the all the pellet formulations were found to be linear with \( R^2 \) values in the range of 0.969 to 0.998 (Table 27 - 30) and the drug release from the pellet formulations was found to be by diffusion process. The release exponent (n values) for all the pellet formulations were in the range of 0.62 to 0.89 (Table 27 - 30), indicated that the drug release was by non-Fickian diffusion. Thus the drug release from the pellet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. Thus mechanism of drug release from all the pellet formulations was by both polymer erosion and diffusion of the drug from the pellet systems. The first order plots, higuchi plots and peppas plots for the diltiazem HCl and verapamil HCl pellet formulations were given in the graphs 14-37.

**Characterization of Diltiazem HCl and Verapamil HCl Pellets**

The optimized diltiazem HCl and verapamil HCl pellets were further characterized by SEM analysis, DSC studies and FTIR spectral analysis.

SEM analysis was performed for the pellets prepared by pan coating and fluid bed coating. The pellets prepared by pan coating (FDL6 and FVL6) were having rough surface with wide pores on its surface but were coated uniformly. The pellets prepared by FBC (FDL12 and FVL12) were having smooth surface with minimal pores indicated the uniform coating of the pellets. The SEM images of diltiazem hydrochloride and verapamil hydrochloride pure drugs and selected pellet formulations were shown in figure 17 to 19 and 29 to 31 respectively.
DSC analysis was performed for the pure drugs diltiazem HCl and verapamil HCl, and their pellets prepared by pan coating and fluid bed coating techniques (FDL6, FDL12, FVL6 and FVL12). The diltiazem HCl pure drug exhibited a sharp endothermic peak at 214.8 °C where as the pellets prepared by pan coating exhibited a broad endothermic peak at 213.8 °C and the pellets prepared by fluid bed coating exhibited a broad endothermic peak at 215.7 °C. Thus the DSC thermograms revealed that there were no major interactions between the pure drug diltiazem HCl and the polymers used for coating process.

The verapamil HCl pure drug exhibited a sharp endothermic peak at 146.62 °C where as the pellets prepared by pan coating exhibited a broad endothermic peak at 146.22 °C and the pellets prepared by fluid bed coating exhibited a broad endothermic peak at 148.66 °C. Thus the DSC thermograms revealed that there were no major interactions between the pure drug verapamil HCl and the polymers used for coating process. The thermograms of diltiazem hydrochloride and verapamil hydrochloride pure drugs and selected pellet formulations were shown in figure 14 to 16 and 23 to 25 respectively.

FTIR spectral studies were performed on some selected pellet formulations of diltiazem hydrochloride and verapamil hydrochloride to study any drug excipients interactions. FTIR spectral studies were performed on BRUKER FTIR spectrophotometer using potassium bromide pellets. FTIR spectra of pure drugs of diltiazem hydrochloride and verapamil hydrochloride were taken initially to check the basic functional groups present in them. The spectra of diltiazem
hydrochloride and verapamil hydrochloride pure drugs and selected pellet formulations were shown in figure 20 to 22 and 26 to 28 respectively.

The FTIR spectra of diltiazem HCl showed characteristic peaks at 3457 cm\(^{-1}\) (aliphatic C-H stretching), 2966 cm\(^{-1}\) (O-CH\(_3\), C-H stretching), 2389 cm\(^{-1}\) (amine HCl, N-H stretching), 1743 cm\(^{-1}\) (acetate C=O stretch), 1680 cm\(^{-1}\) (lactam C=O stretch), 839 cm\(^{-1}\) (O-substituted aromatic C-H out of plane-deformation), 781 cm\(^{-1}\) (p-substituted aromatic C-H out of plane-deformation). The spectra of pellet formulations exhibited all the principle peaks present in the diltiazem hydrochloride pure drug.

The spectra of Verapamil hydrochloride exhibited principle peaks at wave numbers of 2961 cm\(^{-1}\) (C-H Stretching), 2236 cm\(^{-1}\) (C≡N Stretching), 1593 cm\(^{-1}\) (C≡N Stretching), 1518 cm\(^{-1}\) (C=C Aromatic Stretching) and 1260 cm\(^{-1}\) (C-O Stretching). The spectra of pellet formulations exhibited all the principle peaks present in the verapamil hydrochloride pure drug.

The spectral studies of both verapamil hydrochloride and verapamil hydrochloride pellet formulations exhibited no more changes in the principle peaks and all the peaks were observed at specific wave numbers as that of their respective pure drugs. Thus these studies indicated that there were no major interactions between the drug, polymers and diluents incorporated in the pellet formulations.

The \textit{in vivo} pharmacokinetic parameters for the optimized pellet formulations containing diltiazem were performed in white rabbits. The serum concentrations of diltiazem hydrochloride were estimated by HPLC method
The formulations FDL6 and FDL12 containing DTZ were selected for in vivo studies. The results showed that diltiazem HCl administered as plain drug alone reached peak plasma concentration of 350 ng/ml after 1 hr of administration. The pellet formulations prepared by pan coating and fluid bed coating reached after 4 hrs of administration and also the maximum concentration reached is 215 ng/ml and 218 ng/ml for FDL6 and FDL12 respectively. The t1/2 values obtained were 3.04 hrs, 5.22 hrs and 6.15 hrs for oral solution, FDL6 and FDL 12 respectively. The AUC (0-t) values obtained were 1242, 2871 and 3143ng-hr/ml for oral solution, FDL6 and FDL 12 respectively. MRT values obtained were at 4.3 hr, 11.6 hr and 13.9 hr for oral solution, FDL6 and FDL 12 respectively. The elimination rate constant (k_e) obtained were at 0.228/hr, 0.132/hr and 0.095/hr for oral solution, FDL6 and FDL 12 respectively. Thus the in vivo pharmacokinetic studies on diltiazem HCl pellets showed prolonged release and were able to sustain the therapeutic effect over a prolonged period of time up to 24 hrs. The plasma concentrations vs time profile curve for diltiazem HCl oral solution and pellets was shown in the graph 40. The in vivo pharmacokinetic parameters obtained were given in table 34.

The in vivo pharmacokinetic parameters for the optimized pellet containing verapamil were performed in white rabbits. The serum concentrations of verapamil hydrochloride were estimated by HPLC method (Yalcin et al., 2000). The formulations FVL6 and FVL12 containing verapamil were selected for in vivo studies. The results showed that verapamil HCl administered as plain drug alone reached peak plasma concentration of 390 ng/ml after 1 hr of administration. The
pellet formulations prepared by pan coating and fluid bed coating reached after 4 hrs of administration and also the maximum concentration reached is 220 ng/ml and 213 ng/ml for FVL6 and FVL12 respectively. The t₁/₂ values obtained were 3.22 hrs, 4.80 hrs and 5.22 hrs for oral solution, FVL6 and FVL 12 respectively. The AUC(0-t) values obtained were 1031, 2489 and 2744 ng-hr/ml for oral solution, FVL6 and FVL 12 respectively. MRT values obtained were at 3.5 hr, 11.0 hr and 13.5 hr for oral solution, FVL6 and FVL 12 respectively. The elimination rate constant (kₑ) obtained were at 0.086/hr, 0.142/hr and 0.140/hr for oral solution, FVL6 and FVL 12 respectively. Thus the in vivo pharmacokinetic studies on verapamil HCl pellets showed prolonged release and were able to sustain the therapeutic effect over a prolonged period of time up to 24 hrs. The plasma concentrations vs time profile curve for verapamil HCl oral solution and pellets was shown in the graph 41. The in vivo pharmacokinetic parameters obtained were given in table 36.

**Stability Studies**

The formulations which showed good in vitro performance were subjected to stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of the pellets and on drug release from the pellets as per ICH guidelines. Formulations FDL6, FDL12, FVL6 and FVL12 were subjected to stability studies. The results of these studies were given in tables 37 - 42. The results indicated that there was no visible and physical changes observed in the pellet formulations after storage. It was also observed that there was no significant change in drug release from the pellet formulations.
The slow and controlled drug release characteristics of the pellets remained unaltered. Thus the drug release characteristics of controlled release pellet formulations designed were found to be quite stable.