In the present investigation pan coating and fluid bed coating techniques were employed for the preparation of diltiazem HCl and verapamil HCl pellets. In both the methods, a core material is coated with the drug substance following a secondary coating process in which the release controlling polymer material is introduced.

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.

Verapamil hydrochloride is a calcium channel blocker and a class IV antiarrythmic 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.
The present investigation was mainly focused on the development of controlled release pellets of diltiazem HCl and verapamil HCl with ethyl cellulose and hydroxylpropyl methyl cellulose phthalate by employing pan coating and fluid bed coating techniques. 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 regulate the drug release at varied G.I pH conditions. 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. Croscaremellose 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.

Pelletization was one of the popular methods employed to formulate controlled release dosage forms. Several methods of pelletization were discussed in the introduction part. The present study was mainly focused on the comparative evaluation of processing variabilities in the formulation of controlled release pellets by pan coating technique with that of fluid bed coating technique based on in vitro dissolution studies and by characterization of prepared pellets by SEM, IR and DSC studies.

The selected pellet formulations of diltiazem HCl and verapamil HCl were subjected to in vivo studies. These studies were carried out in male New Zealand rabbits. The pharmacokinetic parameters such as $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{(0 \text{ to } t)}$, $AUMC_{(0 \text{ to } t)}$, ...
K_{el} and MRT were calculated using software by PK summit solutions. The plasma concentrations of diltiazem HCl and verapamil HCl were determined by HPLC methods.

Selected pellet formulations of diltiazem HCl and verapamil HCl were subjected to accelerated stability studies. These formulations were stored at temperature and relative humidity of 25 ± 2^{\circ}C, 60 ± 5\% RH for 12 months and 40 ± 2^{\circ}C, 75 ± 5\% RH for 6 months. Then after storage, these formulations were evaluated for their physical parameters such as weight uniformity, hardness, friability and drug content and finally drug release studies were carried out.

**The following conclusions were drawn from the results**

1. Based on the physicochemical and biopharmaceutical properties and clinical relevance, diltiazem HCl and verapamil HCl were found to be suitable drug candidates for developing controlled release pellet formulations.

2. Diltiazem HCl and verapamil HCl controlled release pellets were prepared by pan coating process. All the batches of pellet formulations were manufactured under identical conditions by maintaining specific process parameters.

3. Diltiazem HCl and verapamil HCl pellets were also prepared by fluid bed coating process. All the batches of pellet formulations were manufactured under identical conditions by maintaining specific process parameters.

4. All the batches of pellet formulations were evaluated for the physical parameters such as particle size, % yield, friability and drug content.
5. The average particles size obtained for all the batches of pellet formulations of diltiazem HCl and verapamil HCl were in the range of 720 to 760 μm.

6. The percentage yield of all the prepared pellet formulations were in the range of 90 – 96%.

7. The drug content estimated in all the batches of pellet formulations were in the range of 95-105%.

8. The friability loss for all the pellets formulations were negligible and less than 0.2% which is within the limits.

9. The drug release from the pellets prepared by pan coating were found to release at a faster rate than compared to the pellets prepared by fluid bed coating method.

10. The release of drugs from pan coated and fluid bed coated pellets were extended up to 10 to 16 hrs (FVL 1 – FVL 12 & FDL1 – FDL 12)

11. 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 is extended for a prolonged period of time.

12. 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.
13. Log percentage drug undissolved versus time plots for first order release rate constant of all the prepared pellet formulations were found to be linear with $R^2$ values of 0.959-0.999.

14. Amount of drug release versus square root of time plots for all the pellet formulations of verapamil HCl and diltiazem HCl were linear with $R^2$ values in the range of 0.969 to 0.998 which indicated that the drug release from the pellet formulations is by diffusion process.

15. The release exponent (n values) for all the pellet formulations of verapamil HCl and diltiazem HCl were in the range of 0.62 to 0.89, 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.

16. The difference factor $f_1$ values obtained were in the range of 7 – 58 and similarity factor $f_2$ values were in the range of 19 – 82 for all the pellet formulations. The formulations FDL6/FVL6 and FDL12/FVL12 showed the similarity factor values above 50, indicated that the release profiles for these formulations were similar to that of marketed formulation.

17. SEM analysis was performed for the pellets indicated that the pellets prepared by pan coating (FDL6 and FVL6) were having rough surface with wide pores on its surface but were coated uniformly, while the pellets prepared by FBC (FDL12 and FVL12) were having smooth surface with minimal pores with uniform coating of the pellets.
18. DSC analysis 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) revealed that there were no major interactions between the pure drugs and the polymers used for coating process.

19. 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 and thus these studies indicated that there were no major interactions between the drug, polymers and diluents incorporated in the pellet formulations.

20. The in vivo pharmacokinetic parameters performed for the optimized pellet formulations containing diltiazem showed that diltiazem HCl administered as plain drug alone reached peak plasma concentration of 350 ng/ml after 1 hr of administration and 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 t\(_{1/2}\) values obtained were 3.04 hrs, 5.22 hrs and 6.15 hrs. The AUC\(_{(0-t)}\) values obtained were 1242, 2871 and 3143ng-hr/ml, MRT values obtained were at 4.3 hr, 11.6 hr and 13.9 hr and the elimination rate constant (k\(_{el}\)) obtained were at 0.228/hr, 0.132/hr and 0.095/hr for oral solution, FDL6 and FDL12 respectively.
21. The *in vivo* pharmacokinetic parameters performed for the optimized pellet containing verapamil 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 with the maximum concentration reached is 220 ng/ml and 213 ng/ml for FVL6 and FVL12 respectively. The $t_{1/2}$ values obtained were 3.22 hrs, 4.80 hrs and 5.22 hrs, the AUC$_{(0-t)}$ values obtained were 1031, 2489 and 2744 ng-hr/ml, MRT values obtained were at 3.5 hr, 11.0 hr and 13.5 hr and the elimination rate constant ($k_{el}$) obtained were at 0.086/hr, 0.142/hr and 0.140/hr for oral solution, FVL6 and FVL 12 respectively.

22. No significant changes were observed in the physical characteristics and in the drug release profiles of selected pellet formulations of diltiazem hydrochloride and verapamil hydrochloride after storing them at accelerated storage conditions.

23. Thus results of *in vitro* and *in vivo* pharmacokinetic studies on diltiazem hydrochloride and verapamil hydrochloride pellets indicated that these formulations were capable of prolonging the drug release to sustain the therapeutic effect could be possible. Hence these formulations may be considered as suitable candidates for once a day administration.
RECOMMENDATIONS

The results of the present investigation clearly indicated that the diltiazem HCl and verapamil HCl are suitable as controlled release pellet formulations prepared by pan coating and fluid bed coating process. 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 is extended for a prolonged period of time. 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. From the comparative in vitro studies it was observed that the pellets prepared by FBC are more uniform in shape with glossy finish, which lead to better control on uniform drug release. The advantage of FBC coating over pan coating was that it can be set up on commercial scale, no manual intervention, can reduce processing time, easy reproducibility and can comply the regulatory aspects. The results of in vitro and in vivo pharmacokinetic studies on diltiazem hydrochloride and verapamil hydrochloride pellets indicated that these formulations were capable of prolonging the drug release to sustain the therapeutic effect could be possible. Hence these formulations may be considered as suitable candidates for once a day administration. Thus the main aim and objective of the present investigation was fulfilled and achieved.