Chapter 6

DISCUSSION OF RESULTS

During the recent years timed-release preparations has received increasing attention, which release the drug rapidly and completely after a lag time following oral drug administration. This type of delivery system is not only rate controlled but also time and/or site controlled to deliver the drug when it is required. Such time and/or site controlled formulations have been widely investigated for a number of diseases and therapies.

In the past, many different approaches have been used for delivering the drugs as time and/or site specific includes, Timeclock® system, Chronotropic® system, Pulsincap® system, Port® system, TimeRx® system, Cotin® technology, Ceform® technology, OROS® system, CODAS® system, Egalet® technology and Geomatrix® system. These systems are developed with the intention to meet the needs of chronopathologies with symptoms mostly recurring at night time or early morning hours. The principle advantage of Chronotherapeutic drug delivery system includes consideration of a person’s biological rhythm in determining the timing and the amount of medication to optimize a drug’s desired effects and minimize the undesired effects. As a consequence there is reduction of dose requirement and this is likely to improve the patient compliance.

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed in relation to our body’s natural rhythm (circadian rhythm) to produce maximum health benefits. It is becoming
increasingly evident that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. For example, researchers have reported that nocturnal asthma is an asthma phenotype in which airway inflammation is increased during the hours of sleep. The airway inflammation is associated with increased airway hyper-responsiveness and worsened expiratory airflow limitation, which combine to cause physiologic worsening at night and disruptive nocturnal symptoms such as cough and dyspnea. Especially these symptoms are worst in the early morning hours between 4 am to 6 am, when cortisol levels in the body are low and histamine concentrations are at their highest level.

In such circumstances chronotherapeutics plays a prominent role. Here the formulation is administered in the evening, which provides treatment for disease in which symptoms are experienced in the early morning hours. A site controlled/time-delayed release preparation is the cornerstone of the new drug delivery technology that addresses emerging chronotherapeutic requirements.

In spite of the difficulties faced by releasing actives due to the variable gastrointestinal environment, orally administered timed-release delivery systems are most preferred because they offer flexibility in dosage-form design and are relatively safe. Compression coating is one of the novel drug delivery system to target the active pharmaceutical ingredient to the different sites of GIT and is composed of an inner core that contains an active pharmaceutical ingredient and inert excipients surrounded by an outer coating layer. The outer coating material may be compressed onto
the inner core as compression coat which dissolves or erodes or
disintegrates slowly to produce a lag time before the release of active
ingredient. Such a type of drug delivery system is not only rate controlled
but also time and or/site controlled to deliver the drug when it is
required. The compression coated (press-coated) tablets were prepared by
direct compression method and it may be used to replace the complicated
coating process and also protects the drug from possible degradation due
to moisture.

In this research work an attempt was made for the development of
press-coated tablets containing theophylline anhydrous as a model drug
by utilizing different types of cellulose derivative polymers, pH dependent
and enzyme dependent polymers.

In the first phase, effect of various types of cellulose derivative polymers
in presence of Mg stearate as a coating material was studied by using
Taguchi design of experiment. This design was adapted as a screening
design to identify the potential contribution of hydrophilic polymers with
hydrophobic polymer of cellulose derivative in presence or absence of Mg
stearate.

In the second phase, the screened polymers from Taguchi design were
further evaluated for formula composition by using D-optimal design of
experiment.

In the third phase, the effect of pH, time and enzyme depended polymers
as a coating material were evaluated for formula composition by using D-
optimal design of experiment.
In the fourth phase, an attempt was made for the development of controlled release tablets containing Terbutaline sulphate as a model drug. In this study, a central composite design was implanted to study the effect of amount of HPC and GG on the release properties.

For the generation of optimal formulation, a numerical optimization technique by desirability function was used as an optimization tool. The developed optimal formulations were validated to check the reproducibility and practicability. Further these optimal dosage forms were subjected to stability studies as per ICH guidelines for 6 months. Finally, the in vivo behavior of these optimal dosage forms was evaluated by using rabbit as an animal model.

6.1. PREFORMULATION STUDIES

6.1.1. Drug excipients compatibility studies

The FT-IR spectra of theophylline and its physical mixture are presented in Figures 5.2 & 5.3. The characteristic absorption peak of theophylline was found to be 1716cm⁻¹ (C=O stretching), 1666cm⁻¹ (C=C stretching), 2987cm⁻¹ (C-H stretching), 1438cm⁻¹ (C-H bending), 3119cm⁻¹ (N-H stretching), 1562cm⁻¹ (N-H bending) and 1236cm⁻¹ (C-N stretching). These characteristic peaks were also present in the FT-IR spectra of physical mixtures but with reduced intensity which may be due to the presence of other excipients.

Similarly, the FTIR- spectra of terbutaline and its physical mixture are presented in Figure 5.4. The characteristic absorption peak of terbutaline was found to be 3330cm⁻¹ (OH stretch), 3050cm⁻¹ [aromatic CH stretch], 2720-2900cm⁻¹ [secondary amine salt stretch], 1600cm⁻¹,
1485cm\(^{-1}\) [aromatic ring stretch], 1400-1380cm\(^{-1}\) [t-butyl symmetric bent] 1200cm\(^{-1}\) [phenolic C-O stretch], 1065cm\(^{-1}\) [secondary alcohol C-O stretch]. These characteristic peaks were also present in the FT-IR spectra of physical mixtures but with reduced intensity which may be due to the presence of other excipients.

The DSC thermogram of theophylline shows a sharp endothermic peak at 272.76\(^\circ\)C. Whereas in case of physical mixtures of drug with excipients and polymers exhibited endothermic peaks ranging from 268.73 to 273.21\(^\circ\)C (Figures 5.5 & 5.6) corresponding to the melting point of the drug. Based on the results of FT-IR and DSC studies, it may be concluded that there was no interaction between the drug-excipients and drug-polymers used in this study.

The DSC thermogram of terbutaline shows a sharp endothermic peak at 268.48\(^\circ\)C. Whereas in case of physical mixtures of drug and polymers exhibited endothermic peaks ranging from 255.24 to 267.70\(^\circ\)C (Figure 5.7) corresponding to the melting point of the drug. Based on the results of FT-IR and DSC studies, it may be concluded that there was no interaction between the drugs-polymers used in this study.

6.1.2. Standard calibration curve

The standard calibration curve of theophylline anhydrous was developed by using 0.1N HCl as solvent. The beer’s law range of 2 to 16mcg/ml (Table 5.9) showed a correlation coefficient of 0.9983. Straight line equation (Figure 5.8) obtained was used to calculate the drug content.

Similarly, the standard calibration curve of terbutaline sulphate was developed by using 0.1N HCl as solvent. The beer’s law range of 2 to
100mcg/ml (Table 5.10) showed a correlation coefficient of 0.9992. Straight line equation (Figure 5.9) obtained was used to calculate the drug content.

6.2. DEVELOPMENT OF CORE TABLET

A core tablet in the press-coated tablet should disintegrate rapidly and release the medicament within a short period of time. In order to achieve this, SSG was included as a superdisintegrant along with PVPk30 as binding agent and finally diluted with directly compressible lactose (Table 4.1). A method of direct compression was adopted for the preparation of core tablet.

6.2.1. Pre-compression parameters

The results of pre-compression parameters are presented in Table 5.11. The bulk density values are between 0.63 ± 0.03 to 0.67 ± 0.03 g/cm³ and the tapped density values are between 0.72 ± 0.03 and 0.76 ± 0.03 g/cm³. The flow property of the powder blend was evaluated by fixed funnel method and was found to be less than 25⁰ indicating an excellent flow property. The propensity of a powder blend to consolidate was calculated by using compressibility index and the values were found to be below 15% which indicated excellent flow properties.

6.2.2. Post-compression parameters

The average drug content in the core tablets was between 96.19 ± 2.21 to 97.72 ± 2.81% of the theoretical value. The average percentage weight deviations for 20 core tablets of all the formulations were found to be less than ± 5%. The hardness was found to be with in the fixed limit of 4 ± 0.5 Kg/cm² for all the tablets and the thickness of the tablets ranged from
2.68 ± 0.02 to 2.74 ± 0.03mm. The friability was found to be less than 1% for all the three formulations indicating a good mechanical resistance of the tablets. Based on the results of post-compression parameters it may be concluded that all the physical parameters (Table 5.12) were found to be within the permissible limits.

As the amount of SSG was increased (C1 to C3), the DT of the tablets decreased from 5.03 ± 0.14 to 1.23 ± 0.27 min respectively (Table 5.12). Similar but opposite effect was observed in case of cumulative percent drug release i.e. as the amount of SSG increases, the drug release from the core tablets also increases from 63.41 ± 2.17 to 102.11 ± 2.12% at the end of 30min of dissolution studies (Table 5.13 & Figure 5.10).

Based on the results of DT and dissolution studies, formulation C3 was identified as the best formulation which exhibited least disintegration time with complete drug release at the end of dissolution studies. Thus formulation C3 was used for the preparation of press-coated tablets.

6.3. DEVELOPMENT OF ORAL PRESS-COATED TABLETS

At the outset the main aim of this thesis work was to develop a dosage form to meet the requirements of chronotherapy i.e. a dosage form which releases the drug after a specified lag time to prevent the symptoms of nocturnal asthma. Hence, cellulose derivative polymers like HPMCk100, HPC, HEC and NaCMC were selected as hydrophilic polymers. EC was included as a hydrophobic polymer which is also a pH dependent erodable polymer. Commonly Mg stearate is used as hydrophobic lubricant in the preparation of tablets but in this work it was included with the intention to increase the lag time of the dosage form. Though
various technologies are available for the development of chronotherapeutic drug delivery systems we have identified compression coated (press-coated) tablets as the novel dosage form. A press-coated tablet is composed of an inner core which contains theophylline anhydrous as a drug and polymers with or without excipients as an outer coating material. Design of experiment has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on dependent (response) variables. Hence computer optimization technique was adapted in the whole thesis work utilizing commercially available Design Expert® software, version 6.0.5.

6.3.1. Development of Timed-Release Press-Coated Tablets

6.3.1.1. Experimental Design

Taguchi method as design of experiment was chosen for the organization of the experiments and analysis of the results. Normally a full factorial design for such experiment would yield $4 \times 4 \times 2 = 32$ experiments. In the present case, $L_{16}$ orthogonal array, a mixed-level design (2 factors at 4 levels and one factor at 2 levels) was considered and the size of experimentation was represented by symbolic arrays i.e. 16 experiments (Table 4.2). The use of more than two factors makes it possible to study some of the eventual non-linear effects with interactions between the factors.

Formulations of timed-release press-coated tablets were prepared following direct compression method. The compositions of outer coating layer following Taguchi design are presented in the Table 4.2.
6.3.1.2. Physical evaluation

The average percentage weight variation for all the 16 formulations were found to be less than ± 5% and the thickness of the tablets ranged from 4.84 ± 0.02 to 5.38 ± 0.05mm (Table 5.14). Such variation in thickness is due to variation in the amount and physical properties of the polymers used.

6.3.1.3. Selection of best model fit

The statistical analysis to select the model that best fits the data was obtained by analyzing the results of sequential model given in the Table 5.16. As seen from the table, though the linear model was found to be significant but the PRESS value for a two factor interaction model (2FI) was found to be least. Hence, 2FI model was considered to analyze the response lag time. For the response percent drug release at 8hr, linear model was found to be significant with low PRESS value and the same model was further used for ANOVA studies.

Effect of type of hydrophilic polymers

Figures 5.11-5.14 shows the release profile of press-coated tablets in accordance to type of hydrophilic polymer. HPMC is a hydrophilic polymer, increasing the amount of HPMC in the coating layer, formulations T1, T2 and T3 exhibited a minimal drug release at the end of dissolution studies. Such a type of decrease in drug release may be due to increased amount of EC in the coating layer which retarded the rate of hydration of HPMC which in turn hindered the drug release. In case of formulation T4, the release from the tablet was more in a sustained manner than a burst release which may be due to slower
hydration of HPMC and also this formulation contains least amount of EC than the other formulations of HPMC.

Similar but opposite result was observed in case of NaCMC, that all the formulations show a relative, slow initial drug release for first 2hrs followed by increased release to 100% with in 8hrs of dissolution studies. This behavior of increase in drug release may be due to high solubility of NaCMC at pH 6.8 and this polymer also undergoes a quick gel erosion rate and complete disintegration of polymer matrix. In case of HPC a hydrophilic polymer, the dissolution behavior was characterized by sigmoid, S-shaped curve release profile with a prolonged lag time and a complete drug release from the core tablet was observed at the end of dissolution studies due to separation of coating layer into two halves allowing the core tablet to be exposed to dissolution medium. This observation was made during the dissolution studies. In case of HEC as hydrophilic polymer, the release at the end of dissolution studies were found to be less than 18% which may be due to high viscosity of the polymer, decreased water uptake to form a gel matrix and presence of hydrophobic components such as EC and Mg stearate which further prevented the hydration rate.

Effect of hydrophilic/EC ratio

EC, a cellulose ether derivative most widely used as water insoluble polymer for coating of solid dosage forms. Besides as controlled release barrier, they have also been used as moisture barrier to improve stability of hydrolytically affected drugs. The effect of hydrophilic/EC ratio in presence and absence of Mg stearate on the release properties are
summarized in Table 5.15. On comparison of the values, increasing the hydrophilic/EC ratio, HPMC containing formulations exhibited a negative effect on lag time where as a positive effect was observed in case of other hydrophilic polymers. HPMC and HEC containing formulations showed no complete drug release from the tablet even at the end of dissolution studies which is probably due to slow hydration rate (because of hydrophobic components) and also the hydrogel layer formed was strong enough and could inhibit further water penetration into the inside of core tablet.

In case of NaCMC and HPC, they did not show any significant difference in their release profile at the end of dissolution studies except that NaCMC containing formulations exhibited shorter lag time with complete drug release within 8hrs of dissolution studies where as in case formulations containing HPC exhibited longer lag time with complete drug release at the end of dissolution studies. Such a type of release behavior may be due to faster hydration followed by a combination of disintegration and high erosion rate for the former where as moderate swelling with low erosion rate for the latter.

Effect of Mg stearate

The effect of Mg stearate on the lag time and percent drug release at 8hr can be visualized from the Table 5.17. The formulations containing Mg stearate exhibited an improved lag time but no improvement was observed in case of percent drug release at 8hr. The beneficial effect of Mg stearate on the lag time is probably due to its hydrophobic nature
which prolongs the lag time by significantly decreasing the water uptake and penetration through the coating layer.

6.3.1.4. Statistical Analysis

The model terms for $Y_1$ (lag time) were found to be significant with an $F$ value of 42.10 (0.0052), high $R^2$ value of 0.9940 indicate the adequate fitting of two factor interaction model. As shown in Table 5.18 factors $X_1$, $X_3$ and interaction factors $X_1X_2$ and $X_1X_3$ were found to be significant. At lower level of factors $X_2$ and $X_3$, changing the type of hydrophilic polymer from HPMC to HEC the lag time decreases but at higher level of factors $X_2$ and $X_3$, the lag time increases to a greater value if HPMC and HPC were used as the type of hydrophilic polymer, whereas in case of NaCMC and HEC the effect was found to be negative. (Figures 5.15 & 5.16)

Changing the factor $X_3$ from lower to higher level, a significant positive effect on the lag time was observed irrespective of type of hydrophilic polymer and hydrophilic /EC ratio.

The interaction effect between the factors $X_1X_2$ can be studied with the help of Figures 5.17 & 5.18.

In presence or absence of Mg stearate, if $X_2$ was increased from lower to higher level and by changing the type of hydrophilic polymer, only HPMC containing formulations showed negative effect whereas other hydrophilic polymers showed positive effect on the lag time.

The interaction effect between the factors $X_1X_3$ can be studied with the help of Figures 5.19 & 5.20.
From these plots it may be concluded that presence of Mg stearate in the coating layer exhibited a positive effect on the lag time irrespective of levels of factors $X_1$ and $X_2$.

A linear model for $Y_2$ (percentage drug release at 8hr) was found to be significant. In this case, only factor $X_1$ was found to be significant (Table 5.18). As the factor $X_1$ was increased from lower to higher level, formulations containing NaCMC and HPC exhibited an increased amount drug release whereas incase of formulations containing HPMC and HEC exhibited very less amount of drug release (Figures 5.21 & 5.22). This type of behavior may be attributed due to low hydration rate of these polymers in presence of EC and Mg stearate. Also these polymers hydrate slowly to form a dense layer which further decreases the water diffusion into the core layer of press-coated tablets leading to decrease in drug release.

6.3.1.5. Optimization

To optimize the studied responses with different targets, a multi-criteria decision approach, like numerical optimization technique by the desirability function was used to generate the optimum settings for the formulation. The variables were optimized for the response $Y_1$ and $Y_2$ and the optimized formulation settings were arrived by maximizing the percent drug release at 8hr and lag time was kept at a range between 6 to 7hrs (Table 5.20). According to the statistical prediction (Table 5.21), the optimal values obtained were: HPC for type of hydrophilic polymer, 2.5:1 to 4:1 for hydrophilic polymer/EC ratio and 26-30mg for Mg stearate. Since, the Taguchi design is used to screen the formulation
variables and to study their significant effect, the results from optimization studies were found to be in wider range and suggested further studies to arrive at the optimal settings.

6.3.2. Development of Oral Timed-Release Press-Coated Tablets by D-optimal Design

6.3.2.1. Experimental design

In this part of research work an attempt was made to identify the optimal composition of ternary blend of HPC, EC and Mg stearate by D-optimal design of experiment. As per the design, 6 runs were chosen to establish the model, 2 runs for measuring the lack-of-fit, and 2 runs were replicated for the experimental error, making it to a total of 10 experimental runs (Table 4.4).

6.3.2.2. Physical evaluation

The average percentage deviation for 20 core tablets and press/coated tablets were found to be less than ± 5%, thickness was between 5.27 ± 0.03 to 5.45 ± 0.05mm for all the formulations. The friability was found to be less than 1% indicating good mechanical resistance for tablets and the hardness was found to be within the fixed limit of 14 ± 0.5 kg/cm². Thus, all the physical parameters presented in Table 5.22 were found to be within in the permissible limits.

6.3.2.3. Selection of best model fit

The first step of statistical analysis is to select the model that best fits the data obtained by analyzing the results of sequential model. As seen from the Table 5.24, the quadratic model was found to be statistically significant (p<0.0001, 0.0009) with small standard deviation, high R²
value and low PRESS value with non-significance of lack-of-fit ($p>0.05$) which adequately describe their suitability to fit in the data. Thus the quadratic model was deemed suitable for describing all the studied variables and it was subjected to ANOVA studies.

### 6.3.2.4. Statistical analysis

The model term for $Y_1$ (% drug release at 8hr), $Y_2$ (% drug release at 10hr) and $Y_3$ (lag time) were found to be significant with an F value of 21478.32 ($< 0.0001$), 1845.29 ($< 0.0001$) and 230.54 ($< 0.0001$) respectively. Since the $R^2$ value for the studied variables were found to be nearing to 1 indicating the adequate fitting of quadratic model. As shown in Table 5.25, factors $X_1$, $X_2$, $X_3$ (linear mixture) and interaction factors $X_1X_2$, $X_1X_3$ and $X_2X_3$ were found to be significant for all the studied responses.

A positive sign of coefficient indicates a synergistic effect while a negative sign indicates antagonistic effect of the responses. As depicted in Table 5.27, factor $X_1$, interaction factors $X_1X_3$ and $X_2X_3$ exhibited a negative effect on the responses $Y_1$ and $Y_2$, where as positive effect on response $Y_3$. Similar but opposite effect was observed in case of factor $X_2$, $X_3$ and interaction factor $X_1X_2$. Among all, coefficient $X_1X_3$ and $X_2X_3$ was largest, which showed the effect of combination of EC with Mg stearate and HPC with Mg stearate. These coefficients were found to be the main influence factor on the studied responses. The probable reason for such behavior can be studied with the help of data presented in Table 5.23.

As seen in case of formulations H1, H5 and H10, the amount of Mg stearate was increased from lower level to higher level by keeping factor $X_1$ at lower level and factor $X_2$ at higher level, the drug release from these
dosage forms were found to be high with shorter lag time (Figures 5.23 & 5.24). Such behavior may be due to well dispersion of Mg stearate over the entire surface of the tablet, the wettability of Mg stearate could be improved by the gel layer of HPC. Thus at higher amount of HPC, the intended hydrophobic property of Mg stearate was decreased. But incase of formulations H2, H6 and H8 they exhibited a prolonged lag time with minimal drug release even at the end of dissolution studies (Figures 5.23 & 5.24). This behavior may be attributed due to hydrophobic nature of EC, further at high amount it prevented the water uptake of HPC leading to slow hydration rate. Also presence of Mg stearate enhances the hydrrphobicity of tablet leading to poor penetration of dissolution medium through the coating layer. 

The data of pure error and lack of fit are summarized in Table 5.26, which can provide a mean response and an estimate of pure experimental uncertainty; the residuals are the differences in the observed and predicted values. Since, the computed F values were respectively less than the critical F value, which denotes non-significance of lack of fit.

6.3.2.5. Optimization

An optimal timed-release press-coated tablet must have an appropriate lag time with complete drug release in a specified time period. Therefore optimization of ternary mixture is required in developing such dosage forms. A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent variables (Table 5.28) Y₁ – Y₃
and the optimal formula was arrived at by restricting to $60\% \leq Y_1 \leq 80\%$; $90\% \leq Y_2 \leq 100\%$; $6hr \leq Y_3 \leq 8hr$. The optimal levels of factor $X_1$, $X_2$ and $X_3$ were 169.43, 140.52 and 20mg respectively with a maximum desirability value of 1 (Table 5.29). To gain the reliability of the mixture design model, new optimal formulation was prepared according to the predicted model and evaluated for the responses. The results in Table 5.30 showed a good relationship between the experimental and predicted values, which confirms the practicability and validity of the model.

6.3.2.6. Stability studies

Stability studies were performed for optimal press/coated tablets as per ICH guidelines. The drug content and hardness was evaluated before and after 6 months of stability studies and was found to be $102.49 \pm 1.37\%$ and $99.86 \pm 1.02\%$; $14.65 \pm 0.23\text{kg/cm}^2$ and $13.75 \pm 0.38\text{kg/cm}^2$ respectively (Table 5.31). The results thus obtained were subjected to statistical analysis by using t-test and based on the p value (drug content- 0.1978 and hardness- 0.2747). It was concluded that no significant differences were observed before and after stability studies. The in vitro drug release profiles of the optimal press/coated tablets before and after stability studies were presented in Figure 5.25. The release profiles appear to be almost super imposeable and the calculated $f_2$ value is 72.06. These findings suggest that the developed timed-release press-coated tablets were found to be stable with similarity in release profile.
6.3.2.7. In vivo studies

For *in vivo* pharmacokinetic studies in rabbit, the optimal formula obtained from D-optimal design was reduced to half the quantity and compressed by using 7 and 9mm for core and press-coated tablets respectively. The mean concentration versus time profile curve for core tablet and press-coated tablets are shown in Figure 5.27 and the pharmacokinetic parameters are presented in Table 5.35. The core tablet showed a slightly high $C_{\text{max}}$ and half-life values than the press-coated tablets and were found to be statistically significant ($p<0.01$). The mean $T_{\text{max}}$ values for press-coated tablets ($7.33 \pm 0.29\text{hr}$) was markedly delayed and exhibited a high statistically significant difference ($p<0.001$) as compared to that of core tablet ($2.67 \pm 0.29\text{hr}$). The $\text{AUC}_{\text{total}}$ was $129.21 \pm 17.23\mu\text{h/ml}$ in case of core tablet and $139.06 \pm 32.17\mu\text{h/ml}$ for the press-coated tablet and they were found to be statistically non significant ($p>0.05$). The mean residence time for press-coated tablet was almost double the core tablet with high statistically significant difference ($p<0.001$) and the time point at which the theophylline first appeared in the plasma for core and press-coated tablets were $0.5\text{hr}$ and $5.16 \pm 0.29\text{hr}$ respectively. Level A *in vitro- in vivo* correlation was performed by using the percent theophylline dissolved versus the percent theophylline absorbed data of press-coated tablet at the same point (Figure 5.28). A high $R^2$ value of 0.9628 indicated a good linear regression relationship between the fraction dissolved and fraction absorbed. The results of *in vivo* studies depicted that the formula generated by using D-optimal design of experiment is reliable and it may also be concluded that the
developed optimal press-coated tablet exhibited a time controlled release profile of theophylline.

6.3.3. Development of Oral Time, Enzyme and pH Dependent Release of Press-Coated Tablets

6.3.3.1. Experimental design

In this part of the research work an attempt was made for the development of oral press-coated tablets utilizing time, enzyme and pH dependent polymers such as HPC, guar gum and Eudragit S-100 respectively utilizing D-optimal design of experiments. As per the design, 6 runs were chosen to establish the model, 4 runs for measuring the lack-of-fit, and 4 runs were replicated for the experimental error, making it to a total of 14 experimental runs (Table 4.6). From the previous part of the research work it has been identified that HPC is an ideal polymer (time dependent) and it is included in this part of work. Eudragit S-100 which exhibits a pH dependent solubility above pH 7 and guar gum a highly swellable polymer widely used as tablet binder, viscosity builder and also exhibit gelling and enzyme dependent decomposition properties were also included as outer coating material.

6.3.3.2. Physical evaluation

The average percentage deviation for 20 core tablets and press-coated tablets were found to be less than ± 5%, thickness was in the range of 4.75 ± 0.01 to 4.82 ± 0.02mm for all the formulations. The friability was found to be less than 1% indicating good mechanical resistance for tablets and the hardness was found to be within the fixed limit of 14 ±
0.5 kg/cm² for all the formulations (Table 5.36). Thus, all the physical parameters were found to be within the permissible limits.

6.3.3.3. Selection of best model fit

The first step of statistical analysis is to select the model that best fits the data was obtained by analyzing the results of sequential model. As seen from the Table 5.38, the quadratic model was found to be statistically significant (p=0.0001, 0.0026, 0.0007) with small standard deviation, high R² value and low PRESS value with non-significance of lack-of-fit (p>0.05) which adequately describe their suitability to fit the data. Thus the quadratic model was deemed suitable for describing all the studied variables and it was further subjected for ANOVA studies.

6.3.3.4. Statistical analysis

The model term for Y₁ (% drug release at 8hr), Y₂ (% drug release at 10hr) and Y₃ (lag time) were found to be significant with an F value of 488.27 (< 0.0001), 42.24 (< 0.0001) and 112.71 (< 0.0001) respectively. The R² value for the studied variables was found to be high which indicated the adequate fitting of quadratic model. As shown in Table 5.39, factor X₁, X₂, X₃ (linear mixture) were found to be significant for all the studied responses. Where as the interaction factors X₁X₂, X₁X₃ and X₂X₃ were found to be significant for the responses Y₁ and Y₃ but, only X₂X₃ were significant for the response Y₂.

A positive sign of coefficient indicates a synergistic effect while a negative sign indicates antagonistic effect upon the responses. As depicted in Table 5.41, all the interaction factors exhibited a negative effect for response Y₃, and interaction factors X₁X₂ and X₂X₃ exhibited a negative
effect on the response $Y_1$. But in case of $Y_2$ only one interaction factor $X_1X_3$ showed a negative effect. The linear mixture for all the responses exhibited positive effect along with interaction factor $X_1X_3$ for response $Y_1$ and $X_1X_2, X_2X_3$ for the response $Y_2$. Among all, coefficient $X_3$ and $X_2$ was largest for responses $Y_1-Y_2$ and $Y_3$ respectively, indicating that the amount of Eudragit-S-100 plays an important role on the drug release, where as the lag time is totally dependent on the amount of GG.

The probable reason for such behavior can be studied with the help of data presented in **Table 5.37, Figures 5.29 & 5.30.**

A complete drug release at 8th hr of dissolution studies with lag time less than 4.2hr was observed in case of formulations containing E-S100 as an outer coating material (TPE4 and TPE11). Such a behavior may be attributed due to high solubility of Eudragit-S-100 above pH 7. In case of formulations TPE3 and TPE12 which contained HPC alone as an outer coating material exhibited a complete drug release at the end of dissolution studies with a lag time of around 6hr indicating a time controlled disintegration of outer coating material. But, in case of formulations TPE5 and TPE13 containing GG alone as an outer coating material which showed a least drug release even at the end of dissolution studies with a high lag time of around 11hr. This may be due to formation of high thick viscous gel around core tablet thus preventing the penetration of dissolution media through the matrix layer. In case of formulations TPE2 and TPE14 containing a combination of GG with Eudragit-S-100 which exhibited approximately 45% of drug release at 8th hr and complete drug release at the end of dissolution of studies with
a lag time of around 6.5hr, but such type of release properties were not seen in case of formulations containing either HPC-GG (TPE1) or HPC-E-S100 (TPE6) combinations. Such a behavior may be attributed due to the formation of thick viscous gel layer by HPC and GG thus preventing the diffusion of dissolution medium into the core tablet and hence, less release is observed. In case of formulations containing HPC and Eudragit-S-100 both exhibited a complete drug release at the end of 8hr of dissolution studies. This may be due to high solubility of Eudragit-S-100 at pH above 7 which causes destruction and rapid erosion of the gel layer formed by HPC leading to more drug release.

The data of pure error and lack of fit are summarized in Table 5.40, which can provide a mean response and an estimate of pure experimental uncertainty the residuals are the differences in the observed and predicted value. The computed F values were respectively less than the critical F value, which denotes non-significance of lack of fit.

6.3.3.5. Optimization

An oral chronotherapeutic drug delivery system must have an appropriate lag time with complete drug release in a specified time period. Therefore optimization of ternary mixture is required in developing such dosage forms. A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent (response) variables $Y_1 - Y_3$ and the optimal formula was arrived by restricting to $50\% \leq Y_1 \leq 75\%$; $80\% \leq Y_2 \leq 100\%$; $6\text{hr} \leq Y_3 \leq 7\text{hr}$ (Table 5.42). The optimal levels of factor $X_1$, $X_2$ and $X_3$ were 4.32, 45.37 and 50.31mg respectively.
with a maximum desirability value of 1 (Table 5.43). To gain the reliability of the mixture design model, new optimal formulation was prepared according to the predicted model and evaluated for the responses. The results in Table 5.44 showed good relationship between the experimental and predicted values, which confirms the practicability and validity of the model.

6.3.3.6. Stability studies

Stability studies were performed for optimal press/coated tablets as per ICH guidelines. The drug content and hardness was evaluated before and after 6 months of stability studies and was found to be 101.35 ± 1.70% and 97.71 ± 2.19%; 14.50 ± 0.28kg/cm² and 13.83 ± 0.44kg/cm² respectively (Table 5.45). The results thus obtained were subjected to statistical analysis by using t-test and based on the p-value (drug content- 0.2669 and hardness- 0.0672) and it was concluded that no significant differences were observed before and after stability studies. The in vitro drug release profiles of the optimal press/coated tablet before and after stability studies were presented in Figure 5.31. The release profiles appear to be almost super imposable and the calculated $f_2$ value is 72.66. These findings suggest that the developed press-coated tablets were found to be stable with similarity in release profile.

6.3.3.7. In vivo studies

For in vivo pharmacokinetic studies in rabbit, the optimal formula obtained from D-optimal design was reduced to half the quantity and compressed by using 7 and 9mm for core and press-coated tablets respectively. The mean concentration versus time profile curve for core
tablet and press-coated tablet are shown in Figure 5.32 and the pharmacokinetic parameters are presented in Table 5.46. The core tablet showed a high C\textsubscript{max} value than that of press-coated tablet and were found to be statistically significant (p<0.01). No statistically significance (p>0.05) was observed in case of half-life, K\textsubscript{e} and AUC\textsubscript{total} between core and press-coated tablet. The mean T\textsubscript{max} values for press-coated tablet (7.83 ± 0.29hr) were markedly delayed and exhibited a high statistically significant difference (p<0.001) as compared to that of core tablets (2.67 ± 0.29hr). The mean residence time for press-coated tablet was almost double the core tablet with high statistically significant difference (p<0.001) and the time point at which the theophylline first appeared in the plasma for core and press-coated tablets were 0.5hr and 6.25 ± 0.25hr respectively. Level A in vitro- in vivo correlation was performed by using the percent theophylline dissolved versus the percent theophylline absorbed data of press-coated tablet at the same point (Figure 5.33). A R\textsuperscript{2} value of 0.9282 indicated an appreciable linear regression relationship between the fraction dissolved and fraction absorbed. The results of in vivo studies depicted that the formula generated by using D-optimal design of experiment is reliable and also it may be concluded that the so developed optimal press-coated tablets exhibited a time, enzyme and pH controlled release profile of theophylline for chronotherapy.
6.3.4. Development of Controlled Release Tablets of Terbutaline Sulphate

6.3.4.1. Pre-compression parameters

The results of pre-compression parameters are presented in Table 5.47. The bulk density values are between 0.33 ± 0.05 to 0.64 ± 0.01g/cm³ and the tapped density values are between 0.37 ± 0.02 and 0.73 ± 0.02g/cm³. The flow property of the powder blend was evaluated by fixed funnel method and was between 21.13° ± 3.21° to 27.50° ± 1.34° which indicated a good flow property. The propensity of a powder blend to consolidate was calculated by using compressibility index and the values were between from 14.03 ± 2.45 to 17.45 ± 1.89% indicating a good to fairly passable flow properties.

6.3.4.2. Post-compression parameters

The average drug content for 11CR tablets were between from 94.12 ± 2.46 to 97.25 ± 1.73% of the theoretical value. The average percentage weight deviations for 20 CR tablets of all the formulations were found to be less than ±10%. The hardness was found to be within the fixed limit of 7 ± 0.5 Kg/cm² for all the tablets and the thickness of the tablets were between from 1.95 ± 0.02 to 3.22 ± 0.03mm. The friability was found to be less that 1% for all the formulations indicating good mechanical resistance for the tablets (Table 5.48).

6.3.4.3. Selection of best model fit

The first step of statistical analysis is to select the model that best fits the data was obtained by analyzing the results of sequential model. As seen from the Table 5.51, the quadratic model was found to be statistically
significant \( (p= 0.0010, 0.0002, <0.0001, <0.0001) \) with small standard deviation, high \( R^2 \) value and low PRESS value which adequately describe their suitability to fit in the data. Thus the quadratic model was deemed suitable for describing all the studied variables and it was further subjected for ANOVA studies.

6.3.4.4. Statistical analysis

The model term for \( Y_1 \) (% drug release at 1hr), \( Y_2 \) (% drug release at 12hr), \( Y_3 \) (Diffusion coefficient) and \( Y_4 \) (\( T_{50\%} \)) were found to be significant with an \( F \) value of 84.50 (< 0.0001), 53.39 (0.0002), 181.12 (< 0.0001) and 430.70 (<0.0001) respectively. Since the \( R^2 \) value for the studied variables were found to be high indicating the adequate fitting of quadratic model (Table 5.52).

Effect of formulation variables on % drug release at 1hr

In case of \( Y_1 \), both the studied variables along with its quadratic terms were found to be significant. As the amount of HPC and GG increased, the % drug release at 1hr decreased. Such a behavior of drug release may be attributed due to low hydration rate of polymers in acidic pH of 1.2.

Effect of formulation variables on % drug release at 8hr

In this case, only quadratic factor of HPC was found to be significant. As the amount of HPC in the tablet increased the formation of gel thickness also increases, leading to decreased diffusion of dissolution media which in turn decreases the drug release.

Effect of formulation variables on diffusion coefficient

In this case, all the studied factors along with its quadratic effect were found to be significant. The quadratic effects for both the variables were
found to be dominating in negative manner. As the amount of HPC and GG were simultaneously increased from lower level to higher level, the n value increases from 0.25 to 0.42. The probable reason for this may be due to increased polymer concentration in the delivery system and the system takes complete control over the release of the drug.

Effect of formulation variables on \( T_{50\%} \)

In this case, factor \( X_1 \), \( X_1^2 \), \( X_2^2 \) and interaction factor \( X_1 X_2 \) were found to be significant. The interaction effect can be studied with the help of Table 5.49. At low level of \( X_1 \), the \( T_{50\%} \) values decrease from 6.42 to 4.43 by increasing \( X_2 \) from lower level to higher level. Similar but opposite effect was observed by keeping \( X_1 \) at higher level and increasing the factor \( X_2 \) from lower to higher level. Such an increase in half life may be attributed due to increased amount of polymer concentration in the tablet which leads to formation of a thick viscous gel which in turn increases the diffusion path length for dissolution media thereby decreasing the drug release.

6.3.4.5. Release mechanism

In order to understand the mechanism of drug release from the CR tablets, the \textit{in vitro} drug release data was fitted to Korsmeyer-Peppas equation (Table 5.50). The ‘n’ value from the equation enlightens in understanding the release mechanism from the tablet. Formulations CR1, CR2, CR3, CR4 and CR7 showed Fickian diffusion mechanism because their ‘n’ value ranges from 0.35 to 0.43. In case of formulations CR5, CR6, CR8, CR9, CR10 and CR11 the ‘n’ value ranges from 0.46 to
0.66 indicating anomalous (non-Fickian transport) release mechanism from these dosage forms.

6.3.4.6. Optimization

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent (response) variables (Table 5.55) $Y_1 - Y_4$ and the optimal formula was arrived at by restricting to $21\% \leq Y_1 \leq 24\%;$ $75\% \leq Y_2 \leq 80\%;$ $0.5 \leq Y_3 \leq 0.66;$ $4\text{hr} \leq Y_3 \leq 5\text{hr}.$ The optimal levels of factor $X_1$ and $X_2$ were 63.44 and 94.69mg respectively with a maximum desirability value of 1 (Table 5.56). To gain the reliability of the mixture design model, new optimal formulation was prepared according to the predicted model and evaluated for the responses. The results in Table 5.57 showed good relationship between the experimental and predicted values, which confirms the practicability and validity of the model. With reference to Table 5.57 and Plate No. 5.4 the mechanism of drug release from optimal formulation was found to be anomalous (non-Fickian) release following first order.

6.3.4.7. Stability studies

Stability studies were performed for optimal controlled release tablets as per ICH guidelines. The drug content and hardness was evaluated before and after 6 months of stability studies and was found to be $99.66 \pm 2.45\%$ and $97.34 \pm 2.09\%;$ $8.10 \pm 0.56\text{kg/cm}^2$ and $7.93 \pm 0.13\text{kg/cm}^2$ respectively (Table 5.58). The results thus obtained were subjected to statistical analysis by using t-test and based on the p value (drug content- 0.0944 and hardness- 0.0596) it was concluded that no statistically significant differences were observed before and after stability
studies. The *in vitro* drug release profiles of the optimal CR tablets before and after stability studies are presented in Figure 5.37. The release profiles appear to be almost superimposable and the calculated $f_2$ value is 76.76. These findings suggest that the developed CR tablets were found to be stable with similarity in release profile. The release profile of optimal formulation was compared with marketed product and the calculated $f_2$ value was found to be 44.69 indicating non-similarity of release profile between them.

6.3.4.8. *In vivo studies*

For *in vivo* pharmacokinetic studies in rabbit, the optimal formula thus obtained from CCD was administered orally and at appropriate time intervals the blood samples were drawn from marginal ear vein. The amount of terbutaline was determined from serum samples by HPLC method. The mean concentration versus time profile curve for CR tablet is shown in Figure 5.39 and the pharmacokinetic parameters are presented in Table 5.60. The CR tablet showed $C_{\text{max}}$ value and $T_{\text{max}}$ of 4.27 ± 0.41 mcg/ml and 5.33 ± 0.94 respectively. The mean residence time and the half life were found to 13.83 ± 0.98 hr $^{-1}$ and 7.28 ± 0.58 hr respectively indicating a prolonged release profile of terbutaline. Level A *in vitro- in vivo* correlation was performed by using the percent terbutaline dissolved versus the percent terbutaline absorbed data of CR tablet at the same point (Figure 5.40). An $R^2$ value of 0.8649 indicated an appreciable linear regression relationship between the fraction dissolved and fraction absorbed. Based on the results of *in vivo* studies it is concluded that the optimal CR tablet obtained from CCD exhibited a controlled release profile of terbutaline for long period of time.