In the present research work an attempt has been made to optimize, formulate and evaluate fast dissolving tablet(s) of anti-emetic drugs (prochlorperazine maleate and promethazine theoclate) to achieve faster drug action in nausea and vomiting. Both drugs are specific anti-emetic drugs prescribed in all cases of nausea and vomiting. The whole research work presented in eight chapters such as introduction, literature review, analytical techniques & preformulation studies, development of preliminary tablet batches, development of prochlorperazine maleate and promethazine theoclate fast dissolving tablets, stability studies, in vivo studies and summary & conclusion.

In the preformulation studies prochlorperazine maleate and promethazine theoclate were characterized its physiochemical properties such as melting point, solubility, UV and FTIR.

UV spectrophotometric method was established for quantitative estimation of drugs in the formulations. 254 nm and 250 nm as the absorption maxima were found to be typical of prochlorperazine maleate and promethazine theoclate respectively. Linearity was observed in the range of 0-70 μg/ml for prochlorperazine maleate and 0-10 μg/ml for promethazine theoclate. Drug polymer interaction studies were carried out for 4 weeks at 40±5° and 75±5% RH. Samples were evaluated after every week for physical and chemical changes such as change in absorption maxima (λmax) and FTIR studies. There were no physical changes after 4 weeks and also no significant interaction of drug with polymers was observed in the UV and FTIR analysis. As the drug and polymer(s) were compatible and thus were found to be suitable for dosage form design.

The formulation of the tablet was divided into three steps.

In first step, preliminary trial batches were prepared to find out the three levels (low, medium and high) of the independent factors to be included in optimization technique. These tablets were evaluated for its blend characteristics and tablets properties like thickness, hardness, weight variation, friability, disintegration time and wetting time.
In second step, formulations were prepared according to the factorial design to know the effect of particular independent factors on dependent factors. The optimized amount of the independent factor was estimated for the desired values of dependent factors.

In third step, final formulations were prepared with the desired optimized amount of the independent factors was incorporated in the tablets. These tablets were also used as the check point of the regression analysis model.

During preliminary studies, drug free formulations were prepared by employing different concentrations of superdisintegrants (Ac-di-sol, sodium starch glycolate and crospovidone) (1-5% w/w), sublimating agents (camphor, thymol and menthol) (5-20% w/w) and effervescent agents (sodium bicarbonate and citric acid) (1-5% w/w). The pre-compression characterization of mixed blends was done for determination of mass volume relationship and flow properties. The results of bulk density, tapped density, Hausner’s ratio, compressibility index and angle of repose indicated good compressibility and flow characteristics of the formulated mixed blends.

After compression of powder blends, the tablets were evaluated for their post-compression properties like organoleptic (color, odor and taste), physical (size, shape and texture) and quality control parameters (diameter, thickness, hardness, friability, disintegration time, wetting time and dispersion time). The results indicated that disintegration of the tablet depends on nature and concentration of superdisintegrant used. Order of disintegration time according to technique was found as superdisintegrants < effervescent agents < pore forming agents. The similar results were obtained in case of measurement of in vitro wetting time and dispersion time of the tablets. The friability of all the formulations was found to be less than 1.0 % except those that contained higher concentration of subliming agents.

By evaluating these tablets, the levels for the optimization of the independent factors were determined. The three levels (-1; 0; +1) of different disintegrating agents were selected. The tablets with crospovidone showed the best results for all the characterization parameters and hence this was selected as one factor of the optimization of the fast dissolving tablets. After application of full factorial design and
with help of polynomial terms the optimized tablet was produced which have
disintegration time 30 sec, friability 0.6% and 90% of drug release of drug within 5
min. The optimized amount of the independent factors was incorporated in the tablet
which was also used as the check point of the regression analysis model.
In optimization of prochlorperazine maleate fast dissolving tablets, a $3^2$ factorial
design was employed. The optimization was carried out in different groups and each
group consists of 9 formulations. The prepared formulations were evaluated for
disintegration time and percent friability. The desirability of the models was found
very near to one, so, these models can be used to navigate the design space. The
amount of independent variables were calculated for DT 30 s and 0.6% friability. The
optimized amount of independent variables was obtained by software and these
amounts were incorporated in the check point batches.
In optimization of promethazine theoclate fast dissolving tablets, a $3^3$ randomized full
factorial design was used in the present study. In this design, 3 formulation
independent factors were evaluated, each at 3 levels (low, medium and high), and
experimental trials were performed for all 27 possible combinations. The amount of
independent factors ($X_1$, $X_2$, and $X_3$) was selected on preliminary batches. The
disintegration time (DT), percentage friability ($%F$) and drug release in five minute
($Q_5$) were selected as dependent variables. After application of full factorial design
and with the help of produced polynomial terms, amount of three formulation variable
was optimized. The desirability of the models was found very near to one, so, these
models can be used to navigate the design space. The amount of independent
variables were calculated for DT 30 s, friability 0.6% and 90% drug release after 5
min. The optimized amount of independent variables was obtained easily by software
and these amounts were incorporated in the check point batches.
The optimized tablets were prepared and evaluated for physiochemical properties.
The results of characterization of optimized tablet batch were found to be very near to
the expected values ($P \geq 0.05$). The result showed the validity of the statistical model
in the preparation of the fast dissolving tablets. The optimized formulations were
disintegrates within 30 sec and having friability less than 0.6%. The optimized
formulation showed 90% drug release in five min. The results indicated that the formulation satisfied all the criteria of the fast dissolving tablet.

The optimized formulations were selected for stability studies at 45±1⁰ and 75±5% RH for three months. No significant change in physical properties, drug content and drug release of the tablets were observed. The dissolution similarity factor (f2) was also calculated to compare before and after storage dissolution profile. The f2 value was found to be more than 50, indicating a close similarity between both the dissolution profiles.

A single dose bioavailability study was designed in albino rats under fasting conditions comparing with pure drug. 24 animals weighing 150-225 g of either sex were taken for study. Each animal received dose equivalent to 1 mg of both drugs orally. Blood samples were collected at a period of 5, 10, 15, 30, 60, 120, 180, 240 and 300 min after dosing. Washout period of 7 days was considered. The plasma was separated and drug content was carried out by HPLC method using RP-C18 column. Pharmacokinetic parameters including C\text{max}, T\text{max}, AUC\text{0-t}, AUC\text{0-∞}, t_{1/2} and MRT were determined from plasma profile for both drugs. For promethazine theoclate fast dissolving tablet C\text{max} was more than three times higher (8.03 ng/ml) and T\text{max} (30 min) than pure drug. The similar kinds of results were obtained in case of prochlorperazine maleate fast dissolving tablets.

The \textit{in vivo} efficacy of pure drugs and selected fast dissolving tablet formulations were studied by rat model because of rats react to emetic or nausea-producing stimuli, such as chemotherapeutic agents (cisplatin), rotational stimulation (motion sickness), with altered feeding habits, manifested by increased consumption of non-nutritive value foods like cloth, wood, charcoal and plaster refers to Pica. Thirty six albino rats weighing 150-225 g were taken for study in 6 groups (n=6). Throughout the experiment, all of the rats were housed in individual home cage and had free access to standard laboratory chow pellets (food), water and kaolin pellets.
Summary

Group I- Control group
Group II- Treated with cisplatin
Group III- Pre-treated with prochlorperazine maleate drug
Group IV- Pre-treated with prochlorperazine maleate fast dissolving tablet
Group V- Pre-treated with promethazine theoclate drug
Group VI- Pre-treated with promethazine theoclate fast dissolving tablet

Animals of Group III, IV, V, VI received one ml of drug/FDT solution (dose: 1 mg/kg) orally. Thirty minutes later, cisplatin (dose: 3 mg/kg) was injected to all the groups to induce pica except Group I (control). After treatment given to all rats they had free access to food and kaolin. Kaolin was collected after every hour, weighed and subtracted from the difference between the pre- and post- weight of kaolin. In this way, kaolin consumption during the six hour period immediately following treatment was determined for each subject. Obtained data were analyzed using analysis of variance (ANOVA) for turkey multiple comparisons P < 0.05 was considered statistically significant. The significant reduction in kaolin consumption was observed in the group having pre-treatment with fast dissolving tablets of promethazine theoclate and prochlorperazine maleate.