The oral route of drug delivery is typically considered the most favorable and preferred route of drug administration in case of conscious and co-operating patients because of convenience, possibility of self administration and enhanced compliance. More than 60% of drugs are marketed in the form of oral products.

Conventional immediate release dosage forms are associated with fluctuations in plasma drug concentration; hence multiple dosing is required for maintaining a steady plasma level. Modified-release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration-time profiles of drugs that otherwise suffer from such limitations. Modified release dosage forms can be classified into single unit and multiple unit dosage forms. As compared to the conventional non-disintegrating single-unit modified-release dosage forms, **Multi Unit Particulate System (MUPS)** have gathered much more attention due to numerous advantages. However MUPS are generally available in capsule and tablet dosage form. These solid formulations are not always advantageous, especially in case of patients suffering from dysphagia. This problem is exacerbated when the drug administered is indicated for chronic therapy in which the patient has to take the medicine for longer duration of time, often leading to **patient inconvenience** and **non compliance** to therapy.

Metoprolol succinate (MS) and **Metformin hydrochloride (MH)** are indicated for hypertension and diabetes respectively (chronic disorders). Both these drugs have bioavailability approximately 50%. No new dosage form has been introduced for above drugs since many years. Moreover, till date neither MS nor MH is available in the form of **controlled release powder for reconstitution (CRPFR)** in the market. Hence current chronic therapies suffer from drawback of poor patient compliance and market competition due to prevalence of same solid dosage form since long years.

Hence, there is an **acute need to develop a drug delivery system which can combine the advantages of MUPS as well as are easy to swallow** like **controlled release powder for reconstitution (CRPFR)** for these drugs.

7.1 Aim

The present investigation was aimed at development of Multi Unit Particulate System for oral administration of Metoprolol succinate and Metformin hydrochloride and further formulating them into controlled release powder for reconstitution.

7.2 Preformulation

Authentication of MS and MH was done by identification tests like UV Visible spectroscopy, Fourier Transform Infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC) and Melting point determination. UV spectra showed wavelength maxima (λ_{max}) in 6.8 phosphate buffer at 274 nm and 233 nm for MS and MH respectively. Similar functional groups were obtained in the IR spectra as reported in USP monographs for both the drugs. DSC thermogram showed sharp endothermic peak at 137.33^{0}C and 232.67^{0}C for MS and MH respectively. The melting point of MS and MH was found to be in the range of 136-138^{0}C and 232-236^{0}C. Thus, the drugs were authenticated. Results of drug-excipients compatibility study using FTIR and DSC techniques indicated no interactions between the drug and excipients used in the present study.

7.3 Analytical Method Development

7.3.1 UV spectrophotometric methods

Rapid analytical methods for the quantitative estimation of MS and MH using UV spectrophotometry were successfully developed and validated. The spectrometric analysis of MS were carried out between 200 - 400 nm using four different solvents viz., 0.1N HCl, phosphate buffer pH 3.0, phosphate buffer pH 6.8 and distilled water. The UV absorption by the drug was observed at 274 nm λ_{max} for all four solvents. A strong linear correlation with $R^2 \geq 0.994$ in all four solvents was observed between the concentration of the drug and absorbance obtained for a concentration range of 4 to 20 µg/mL. The spectrometric analysis of MH were carried out between 200 - 400 nm using three different solvents viz., 0.1 N HCl, phosphate buffer (pH 6.8) and distilled water and the absorption maxima were found to be 230, 233 and 232 nm, respectively. A strong linear correlation with $R^2 \geq 0.995$ in all three solvents was observed between the concentration of the drug and absorbance obtained for a

concentration range of 2 to 10 µg/mL. The analytical methods for estimation of MS as well as MH were found to be precise and also depicted accuracy in measuring the additional drug concentrations spiked in standard drug solutions. The developed UV methods were found to be specific and showed no interference with other formulation components.

7.3.2 HPLC methods

HPLC methods for the quantitative estimation of MS and MH in plasma were also successfully developed and validated. The chromatographic separation of MS was carried out on a C18 column (Phenomenex) using a reported mobile phase. The flow rate was maintained at 1.4 mL/min. The UV absorption by the effluents was read at 280nm. Similarly, the chromatographic separation of MH was carried out on a C18 column (Phenomenex) using a reported mobile phase. The flow rate was maintained at 1 mL/min. The UV absorption by the effluents was read at 233 nm. The developed HPLC methods were found to be specific for both MS and MH. A strong linear correlation with an R^2 = 0.999 was observed between the concentration of the drugs and peak area obtained upon chromatographic extraction over a concentration range of 50 to 2000 ng/mL. The methods were found to measure the concentrations with significant precision and accuracy.

7.4 Formulation Development of MS and MH-MUPS

In order to establish a **platform technology** for the formulation of highly soluble drugs (MS and MH) into a controlled release dosage form suitable for patients unable/ not willing to swallow the available solid dosage forms; formulation development was carried out using **Quality by Design (QbD)** approach. MS and MH-MUPS were developed by fluid bed processor technique. A predefined Quality Target Product Profile (QTPP) was set as target for the product development and Critical Quality Attributes (CQAs) were identified. In the present study, initial risk assessment was evaluated with the help of FMEA tool, to identify the failure modes that have the greatest chance of causing product failure, i.e., not meeting the QTPP. The effect of formulation attributes (Core pellet size, Core pellet quantity, Drug layering technique, Extent of CR coating and Drug: Polymer) on the CQAs (Dissolution and Assay) was evaluated by Failure Mode and Effects Analysis (FMEA) (a risk assessment tool) for both the drugs.

The process and formulation parameters were optimized systematically. Celpheres were selected as the core material upon which successive drug layering was applied. Celphere CP 203 having size 150 -300µm was selected as the core pellet size. The initial load for drug loading was selected based upon movement of the bed, occupancy of Wurster column and flow pattern of the pellets. Considering all these parameters it was decided to use 40g as initial load for both the proposed formulations.

To achieve a balance between the size of the pellets and the final bulk of the product for both MS and MH, 50mg/unit of core pellets was selected on the basis of drug release study.

The CR polymer was selected on the basis of drug release study. The polymer which was able to sustain the drug release for longer period of time was selected for each drug. Thus Ethyl Cellulose and Eudragit® RS were selected as CR polymer for MS and MH respectively.

Similarly the drug layering technique was selected on the basis of drug release study, pellet size and the number of processing steps involved. Thus, the matrix technique was selected as it was better able to control the drug release and yielded pellets of smaller size as compared to reservoir technique. Moreover the matrix technique was a one step process while reservoir technique was a two step process.

The most critical part of the present MUPS formulation was CR coat, as it dictates the rate and extent to which the drug gets released from the formulation. So to establish a design space within which changes would yield similar results, optimization was performed using statistical tool- Design of Experiments (DoE). It was used to establish the optimized extent and coating composition of the drug+ CR coat [MS + (EC: HPC) (90:10)] and [MH + (Eudragit RS: Eudragit RL) (85:15)] required to prolong the release for 20h.

Optimization of controlled release coating was carried out using Face Centered Composite statistical design (CCF). Extent of coating (X_0) (%w/w) and ratio of drug: polymer (X_1) were chosen as independent variables while the drug release at 1h (Y_1), 4h (Y_2), 8h (Y_3) and 20h (Y_4) were selected as responses for MS and drug release at 1h (Y_1), 5h (Y_2), 12h (Y_3) and 20h (Y_4) were selected as responses for MH on the basis of pharmacopoeial

specification. Polynomial models including interaction and quadratic term were generated for all the four response variables using multiple linear regression for both MS and MH. Contour Plots and Response surface Plots were generated using Design Expert® software (Version 7.0.0, Suite, Minneapolis, USA). Based on the responses from CCF design, desired release for MS was achieved at 65% extent of coating and 1:0.8 ratio of Drug : Polymer, while that for MH was achieved with 70% extent of coating and 1:0.6 ratio of Drug : Polymer.

The risk mitigation and control strategy assured that quality was built into the product and not just tested. Formulation attributes (Core pellet size, Core pellet quantity and Drug layering technique) which had medium risk were addressed by design (development trials). For other formulation attributes (Extent of coating and ratio of drug: polymer) which had high risk, a Proven Acceptance Range was identified in final risk assessment.

7.4.1 Eudragit® E coated MUPS

Major challenge involved in formulation development of CRPFR is diffusion of drug into the suspending vehicle upon storage. In the present study, this difficulty was overcome by application of Eudragit® E coating over the optimized CR-MUPS to avoid the drug leaching upon reconstitution in water while ensuring its release once it comes in contact with the acidic pH of stomach, whereby the release would be solely controlled by the functionally coated pellets. Formulating such a convenient CRPFR dosage form can provide a novel means of overcoming the potential barriers associated with the administration of such controlled release systems. Moreover such functionally coated pellets can also be effectively used in orally disintegrating tablets, where there would be minimal release of drug into the alkaline buccal pH.

Suitable process parameters and solid content were selected for MS Eudragit® E coating stage. The optimized batches (MS-40 and MH-33) were evaluated for particle size distribution, morphology, micromeritic properties and *in vitro* drug release study.

The final Eudragit® E coated pellets appeared to be spherical in shape with smooth surface and no visible aggregation.

Results from particle size distribution study showed that the D_{90} value for MS MUPS was 500µ while that for MH MUPS was 600µ.

Scanning Electron Microphotographs showed that the thickness of drug+ CR polymer layer was 217-256µ and 151-159µ while that of Eudragit® E layer was found to be 33-46µ and 23-31µ for MH and MS MUPS respectively.

The bulk and tapped density were found to be 0.810± 0.052 g/mL, 0.895± 0.031 g/mL and 0.791± 0.054 g/mL, 0.872± 0.026g/mL for MS MUPS and MH MUPS respectively. The results for Hausner's ratio and compressibility index for MS Eudragit® E pellets was 1.105± 0.03, 10.53± 0.4 while that for MH Eudragit® E pellets was 1.103± 0.05 and 10.26± 0.2 respectively. Angle of repose for Eudragit® E coated pellets of the optimized batch MS-40 and MH-33 was 28.15±0.27° and 29.65±0.30° respectively. Results of micromeretics collectively indicated that pellets had excellent flow. The friability was found to be 0.03± 0.02% and 0.05± 0.02% for MS MUPS and MH MUPS respectively indicating that the pellets possessed sufficient mechanical strength to withstand the rigors and shocks encountered during production and transportation.

The drug release for MS Eudragit® E pellets at 1, 4, 8 and 20h was 17.6± 3.8, 31.9± 3.1, 48.9± 2.6 and 95.9± 1.1 % while that for MH Eudragit® E pellets at 1, 5, 12 and 20h was 27.7± 2.9, 48.1± 1.1, 73.4± 1.6 and 93.4± 1.4% respectively. This release profile met the USP specification of NMT 25% in 1h, 20-40% in 4h, 40-60% in 8h and NLT 80% in 20h for MS and 20-40% in 1h, 45-65% in 5h, 70-90% in 12h and NLT 85% in 20h for MH. The data obtained from *in vitro* drug release studies for both the drugs were fitted to various release models namely Zero order model, First order model and Higuchi model. The regression coefficient value for both the drugs was found to be highest (r^2 = 0.991 for MS and r^2 = 0.982 for MH) for zero order model. Thus the release of MS and MH from CR pellets followed zero order kinetics i.e. the drug was released at a constant rate, which is the ideal drug release profile to achieve a controlled pharmacological action.

The Eudragit® E coated pellets from the optimized batches were pursued further for formulation into suitable dosage form- CRPFR. The CRPFR was prepared by blending the

Eudragit® E coated pellets with suitable excipients like suspending agent, alkalizing agents, flavorant and colorant.

7.5 Formulation Development of CRPFR- MS and MH

The main challenge associated with the formulation development of CRPFR is diffusion of drug into the suspending vehicle after reconstitution. Suspending agents are used to control or minimize sedimentation and impart suitable viscosity to the final preparation. In the present study, considering the higher bulk density of the MS-Eudragit® E coated pellets (0.810± 0.052 g/mL) and MH- Eudragit® E coated pellets (0.791± 0.054 g/mL) it was anticipated that the pellets would settle down in suspension preparation. The reconstituted suspension was targeted to have sufficient viscosity that would be easily pourable as well as prevent formation of cake. For both the products (MS-CRPFR and MH-CRPFR), HPMC K15M was selected at a concentration of 0.75% along with 5% w/w of Avicel CL-611 as suspending agent.

To avoid drug leaching into the reconstituted suspension an alkaline microenvironment was created by adding an alkalizer in the final dosage form. Sodium carbonate was selected as alkalizer for both MS and MH-CRPFR. The pH of MS and MH reconstituted suspensions were found to be in the range of 7.1 to 7.4 and 7.3 to7.6 respectively.

Although the reconstituted suspension was meant to be used within 30 min of reconstitution the drug leaching was studied for 12h as an extreme condition. Due to the alkali resistance nature of the Eudragit® E polymer, only 3.4± 0.3% and 2.7± 0.6% drug leached out from MS and MH reconstituted suspension after 12h respectively.

Final reconstituted suspension was evaluated for organoleptic characteristics, sedimentation volume, redispersibility, viscosity and pH. Final suspension after reconstitution was slightly yellow colored with pleasant odor of vanilla. The sedimentation volume for MS and MH-CRPFR was found to be 0.90± 0.8 and 0.96±0.12 respectively. The ease of redispersion was found to be 93.33% and 96.66% for MS and MH-CRPFR respectively, indicating easy redispersibility. The MS and MH-reconstituted suspensions were easily pourable and had viscosity of 5426 to 5710 cps and 5548 to 5691cps respectively. The pH of MS and MH-

reconstituted suspension was found to be 7.1 to 7.4 and 7.3 to 7.6 respectively at which the Eudragit® E coating remained intact.

The final formulations of MS and MH CRPFR were stable for 3 months for the packaging material selected at 40^0C/75%RH and 25^0C/60%RH condition.

7.6 Formulation Development of CRODT- MS and MH

After formulation of CR PFR, in order to explore the possibility of alternate dosage form for drugs (MS and MH) used in chronic disorders, it was decided to develop a controlled release orally disintegrating tablets (CRODT) formulation. In the present study, Eudragit® E coated pellets from the optimized batches were pursued further for formulation into - CRODT.

Direct compression method of tabletting was utilized for fabrication of MS and MH CRODT. Compression was done using 12 mm round shaped punch on single rotary tablet compression machine. Lubricated blend for compression consisted of Eudragit® E coated pellets equivalent to 50mg MS and 50mg MH. The lubricated blend also comprised of excipients like diluents or fillers (Prosolv SMCC HD90 and Pearlitol SD 200) to make up the bulk of the tablet while superdisintegrants (Croscarmellose sodium in combination with Polyplasdone XL) were employed to achieve rapid disintegration. Glidant (Aerosil 200) was added to have a good flow while lubricant (Sodium stearyl fumarate) was added to avoid sticking of blend to die and punches. Rupture of functionally coated pellets is the most common problem associated with the compression of pellets; hence cushioning agents are incorporated to prevent this. In present work, Poly Ethylene Glycol 6000 was used as cushioning agent to prevent rupture of pellets. To increase palatability of tablet, sweetener (Aspartame) and flavor (Vanilla flavor) were added.

The final lubricated blend-ready for compression- was characterized for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index. Tablets thus prepared were evaluated for average weight, hardness, thickness, friability, disintegration time, drug content and drug release study. Transverse sections of tablets were checked for intactness of pellets using SEM.

Angle of repose for MS and MH lubricated blend was found to be 32.15± 0.42° and 33.21±0.37° respectively. The bulk and tapped density for MS and MH lubricated blend were found to be 0.625± 0.031 g/mL, 0.714± 0.022 g/mL and 0.652± 0.039 g/mL, 0.746± 0.032 g/mL respectively. Hausner's ratio (1.143 ± 0.031 and 1.114 ± 0.028) and compressibility index (14.29± 0.43 and 14.44± 0.37) indicated good flow of the lubricated blend for MS and MH respectively.

The optimized batch for MS and MH-CRODT exhibited average weight of 511.1± 12.8 mg and 559.3± 7.1 mg, thickness of 3.41± 0.13 mm and 3.56± 0.16 mm, hardness of 6-8 Kp and 7-8 Kp, Friability of 0.8% and 0.6%, disintegration time- 0.5-1 min and 0.6-1 min, drug content of 102.6± 1.1% and 101.1± 1.4% respectively. Dissolution profile was similar to that of Eudragit® E coated pellets for both MS and MH CRODT which indicated that there was no rupture of pellets after compression. Transverse section of tablets showed uniformly distributed intact pellets. The final formulations of MS and MH CRODT were stable for 3 months for the packaging material selected at 40^0C/75%RH and 25^0C/60%RH condition.

It would be acknowledged here that the CR ODT formulation for MH was not equivalent to indicated dose (500 mg). However the technology described here would serve as a platform for development of alternate dosage form (CR PFR) for highly soluble drugs with high dose required to be administered chronically. CR ODT for MH (and other drugs with higher doses) could be developed effectively with equipments with higher drug loading capacity (like GPCG 1.1 and Glatt 5 Pro), wherein smaller core pellets can be efficiently coated with higher extent of coating without facing the problem of agglomeration with the modus operandi used in present study.

7.7 Pharmacokinetic Studies

Pharmacokinetic studies were performed in rabbits in order to investigate the potential of developed formulation in mitigating the problems of dose fluctuation and dosing frequency through maintaining therapeutic plasma drug levels for prolonged period. The concentrations of MS and MH in blood plasma were estimated at different sampling time points after oral administration of plain drug solution as well as optimized pellets formulation. Mean plasma concentrations at various sampling time points were used to

generate pharmacokinetic parameters by AUC calculation method under non compartmental analysis for extra vascular administration using Kinetica software v5.0 (Thermo Scientific).

7.7.1 Metoprolol succinate

Rapid attainment of higher peak plasma drug concentration in case of plain drug solution (C_{max} 183.74 ± 31.19 ng/mL) could be attributed to rapid absorption of drug from its solution form. Rapid decline in plasma drug concentrations was also be seen in rabbits administered with plain drug solution. Optimized formulation showed significantly lower C_{max} (69.87 ± 10.68 ng/mL) as compared to plain drug solution ($p < 0.05$) and required significantly more time to reach C_{max} (t_{max} 3.0 h) as compared to plain drug solution (t_{max} 0.5 h). This could be due to a prolonged absorption at a slower rate which reflects controlled release behavior of the developed formulation after oral administration in rabbits.

The AUC_{last} and AUC_{total} values for optimized pellets formulation (902.64 and 1020.88 ng*h/mL, respectively) were significantly higher than the same for plain drug solution (533.19 and 548.09, respectively) advocating significant improvement in extent of drug absorption from optimized pellets formulation as compared to plain drug solution. An almost two fold rise in bioavailability ($F_{relative}$, 186.26 %) also reflected the improvement in extent of drug absorbed. A significant increase in MRT (12.35 h) and $t_{1/2}$ (7.97 h) of MS from optimized pellets formulation as compared to plain drug solution (MRT, 2.58 h; $t_{1/2}$, 1.41 h) further signified the maintenance of plasma drug levels for prolonged period of time.

7.7.2 Metformin hydrochloride

Early attainment of higher peak plasma drug concentration in case of plain drug solution (C_{max} 805.65 ± 125.61 ng/mL) could be attributed to faster absorption of drug from its solution form. Rapid decline in plasma drug concentrations was also be seen in rabbits administered with plain drug solution. Optimized formulation showed significantly lower C_{max} (489.36 ± 98.38 ng/mL) as compared to plain drug solution ($p < 0.05$) and required significantly more time to reach C_{max} (t_{max} 6.0 h) as compared to plain drug solution (t_{max} 3.0 h). This could be due to a prolonged absorption at a slower rate which reflects controlled release behavior of the developed formulation after oral administration in rabbits.

The AUC_{last} and AUC_{total} values for optimized pellets formulation (6287.25 and 7315.81 ng*h/mL, respectively) were significantly higher than the same for plain drug solution (4884.90 and 4893.43, respectively) advocating significant improvement in extent of drug absorption from optimized pellets formulation as compared to plain drug solution. An almost 1.5 fold rise in bioavailability ($F_{relative}$, 149.50 %) also reflected the improvement in extent of drug absorbed. A significant increase in MRT (13.82 h) and $t_{1/2}$ (7.7 h) of MS from optimized pellets formulation as compared to plain drug solution (MRT, 5.11 h; $t_{1/2}$, 1.8 h) further signified the maintenance of plasma drug levels for prolonged period of time.

7.8 Conclusions

In the present study, controlled release powders for reconstitution (CRPFR) and controlled release orally disintegrating tablets (CRODT) using Multi Unit Particulate System (MUPS) technology were prepared for drugs like metoprolol succinate and metformin hydrochloride which are used in chronic therapies. The optimized CRPFR and CRODT formulations were able to sustain the drug release upto 24 h. The reconstituted CRPFR exhibited negligible drug leaching upon reconstitution. The CRODT exhibited rapid disintegration. The final formulation thus prepared serves as an effective alternative to the existing solid dosage forms available in the market. Present platform technology holds importance for drugs which are required to be administered chronically, prevalent in solid dosage form and undergoing a decline phase of their product life cycle. This would extend product's profitable life, for available controlled release formulation in addition to increased patient compliance and other advantages including pharmaco economics of drug. From the results it was also evident that the developed CRPFR formulation of both MS and MH were able to sustain the drug release for 24 h *in vivo.* Hence, the developed CRPFR and CRODT formulations of MS and MH can be potentially useful in clinical treatment of hypertension and diabetes, respectively. Thus, these formulations hold promise as better alternative to the existing solid dosage forms. However, further examinations in human beings under clinical conditions are essential for their commercialization.

7.9 Future perspectives of present study

- Many drugs that are prevalent in the same dosage form and undergoing a decline phase of their product life cycle can be revitalized using proposed delivery system. It will add on to the existing product portfolio, extend product life and find new markets, thus giving financial advantages to pharmaceutical companies.
- Avoidance of costly and time-consuming clinical trials is, quite desirable for drug companies in the race to bring products to the marketplace before competition. A **505 (b) (2) application** offers an appealing alternate regulatory pathway. The 505(b) (2) approval route can be utilized for a product that represents changes in **formulation and dosage form**. This route permits companies to obtain FDA approval of new drug applications (NDAs) by relying, in part, on the agency's findings for a previously approved drug. The 505(b) (2) applicant may qualify for **3 or 5 years of market exclusivity** thus providing **quicker access to affordable medicines** for patients and financial benefits for the manufacturer by **keeping off generic competition**.
- Infusion of drugs used in chronic therapies into an enhanced delivery system would improve overall product life cycle and enhance patient compliance. Moreover it would set a **platform technology** for development of other drugs (belonging to BCS class I and III) used in such condition.