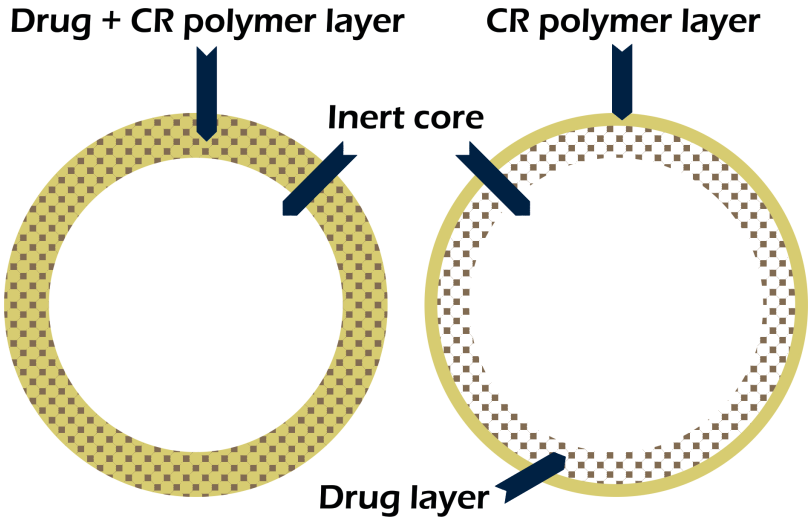
Formulation Development (MUPS)

Part A: Experimental



Chapter 4

4.1 Materials and Equipments

4.1.1 Materials

Metoprolol Succinate (MS) and Metformin HCl (MH) were received as gift samples from Alembic Research Centre, Vadodara, India. Celpheres were obtained as gift samples from Asahi Kasei Chemicals Corporation, Tokyo, Japan. Hydroxy propyl cellulose and Polyvinyl Pyrrolidone were obtained as gift samples from Ashland Pvt. Ltd., India. Eudragit® E, Eudragit® RS and Eudragit® RL were received as gift samples from Evonik Degussa, India. Ethyl Cellulose was received from Dow, USA, Tri Ethyl Citrate from Merck, Germany, Talc UM form Luzenac Pharma, USA, Acetone and Isopropyl alcohol were purchased from Merck Ltd, Mumbai, India.

4.1.2 Equipments

Following is the list of equipments and instruments used for the preparation of MUPS.

Table 4.1.1: List of Equipments and Instruments

Name of equipment/ Instrument	Model	Make
Fluid Bed Processor	Mini Glatt	Pam Glatt, India
Electronic weighing Balance	ELB300	Shimadzu, Japan
UV-visible double beam spectrophotometer	UV-1800	Shimadzu, Japan
USP dissolution apparatus Type II	TDT-06P	Electrolab, India
pH meter	PICO+	Lab. India, India
Centrifuge	CPR-30	Remi, India
Peristaltic Pump	PP-50V	Electrolab, India
USP Tapped Density Tester	ETD-1020	Electrolab, India
Tablet friability test apparatus	VFT-2D	Veego, India
Stability chamber	Tanco-PLT 258	S.R Lab Instruments, India
Magnetic stirrer	1MLH	Remi Motors, India
Microscope	DS-Fi2	Nikon Digital, Japan
Scanning Electron Microscope	JSM-5610LV	Jeol, Japan
Differential scanning calorimeter	DSC-60	Shimadzu, Japan
Melting point apparatus	VPM-PM	Veego, India
Fourier Transform Infrared spectrophotometer	IR Affinity-1	Shimadzu, Japan

4.2 Preformulation

4.2.1 Authentication of drugs: Metoprolol succinate and Metformin hydrochloride

4.2.1.1 UV Visible spectroscopy

Solutions containing 10 µg/mL of MS and MH were prepared in pH 6.8 Phosphate Buffer and scanned over the wavelength range of 200-400 nm against 6.8 Phosphate Buffer as blank using double beam UV-Visible spectrophotometer (UV-1800, Shimadzu Corporation, Japan). The UV absorption spectra were recorded.

4.2.1.2 Fourier Transform Infrared spectroscopy

Individual drugs (MS and MH) were triturated in mortar pestle to remove any lumps. A small amount of fine powder of each drug was kept in sample holder and the spectra were recorded by scanning in the wavelength region of 4000-600 cm^{-1} using FTIR spectrophotometer (IR Affinity-1, Shimadzu, Kyoto, Japan).The IR spectrum of individual drugs were compared with that of the reported spectra [1].

4.2.1.3 Differential scanning calorimetry

Differential scanning calorimeter (Shimadzu, Kyoto, Japan) equipped with an intra-cooler and a refrigerated cooling system was used to analyze the thermal behaviour of MS and MH in the range of 35 to 300ºC. Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50 mL/min and 100 mL/min through cooling unit.

4.2.1.4 Melting point determination

Melting point of both the drugs was determined by melting point apparatus (Veego-VPM-PM) using capillary method.

4.2.2 Drug-Excipients compatibility study

A compatibility study was carried out with potential formulation excipients to determine drug- excipients interaction. The drug-excipients compatibility study was carried out by visual observation and also by using FTIR spectroscopy. The excipients Celphere CP 203, Polyvinyl Pyrrolidone K30, Ethyl cellulose, hydroxy proyl cellulose were studied

with MS, while Celphere CP203, Polyvinyl Pyrrolidone K30, Eudragit® RS, Eudragit® RL, TEC, Talc UM were studied with MH.

4.2.2.1 Physical observation

Placebo blend of each drug and above mentioned excipients mixtures in 1:1 ratio were kept under compatibility study for 14 days at 40ºC±2ºC / 75%±5% RH in sealed glass vials and were observed visually.

4.2.2.2 Fourier Transform Infrared spectroscopy

Placebo blend for MS was prepared by mixing together the individual excipients (Celphere CP 203, Polyvinyl Pyrrolidone K30, Ethyl cellulose, hydroxy proyl cellulose, Eudragit® E) while that for MH was prepared by mixing together Celphere CP203, Polyvinyl Pyrrolidone K30, Eudragit® RS, Eudragit® RL, TEC, Talc UM, Eudragit® E. Samples of individual drug with respective placebo blend in 1:1 ratio were kept for 14 days at 40ºC±2ºC/75%±5% RH in sealed glass vials and were analyzed by FTIR spectrophotometer.

4.2.2.3 Differential Scanning Calorimetry (DSC)

Samples of individual drug with respective placebo blend (similar to section 4.2.2.2) were studied for Drug-Excipients compatibility study for both MS and MH. DSC procedure used was similar to section 4.2.1.3

4.3 Formulation Development

Roadmap for formulation development

To develop multiple unit sustained release drug delivery system, several studies were necessary to identify the process (load, air flow, atomization air, product temperature etc.) and formulation variables (selection of core material, core pellet quantity per unit, CR polymer and extent of CR coating etc.) yielding a product meeting quality target product profile. Preliminary batches were taken to select working ranges for these variables within which a process capable of yielding reproducible results could be set.

Roadmap of process undertaken for formulation development is shown in Figure 4.3.1.

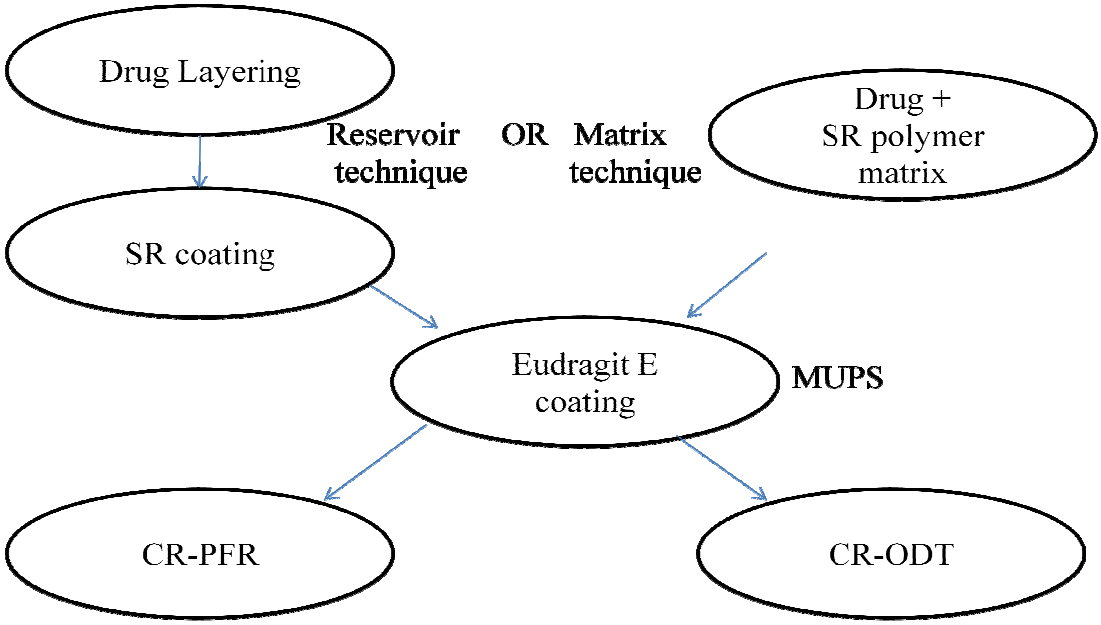


Figure. 4.3.1. Roadmap for process development

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 to/ not willing to swallow the available solid dosage forms; formulation development was carried out using **Quality by Design (QbD)** approach.

QbD, as defined by the ICH, is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and control, based on sound science and quality risk management [2]. It is a modern, science and risk based approach used to formulation development.

4.3.1 Quality Target Product Profile (QTPP)

QTPP can be regarded as a set of elements that defines the drug product. It acts as a guide to the product development, setting the target or goal in advance [2]. QTPP set as the target for MS and MH controlled release pellets is shown in Table 4.3.1. Only difference for MS and MH was in terms of drug release (Table 4.3.2). From the QTPP, drug release and assay were identified as Critical Quality Attributes (CQA) for use in risk assessment. The criteria for inclusion in the list of CQA were that, these attributes had the potential to be altered by process parameters or formulation variables and also impact TPP. Since both the drugs are highly soluble in water, and the desired MUPS formulation is meant for once a day therapy, similar QTPP was set for both the drugs differing only in target drug release profile.

Table 4.3.1: QTPP for MS and MH controlled release pellets

QTPP element	Target	Justification
Route of administration	Oral	Dosage form designed to be administered orally
Dosage form	MUPS (Multi unit particulate system)	Uniform distribution in the GIT
Assay	90-110%	Regulatory requirement
Stability	Stable for 3 months at accelerated and controlled room temperature	Minimum time period decided to study stability of final formulation
Packaging	Suitable for storage of dosage form	To maintain product integrity and quality upon storage

Table 4.3.2: Drug release as QTPP element for MS and MH controlled release pellets

QTPP element	Target	Justification
Drug release for MS	NMT 25% in 1h, 20-40% in 4h, 40-60% in 8h, NLT 80% in 20h	USP specifications for once daily controlled release formulation
Drug release for MH	20-40% in 1h , 45-65% in 5h, 70-90% in 12h, NLT 85% in 20h	

4.3.2 Initial Risk assessment by Failure Mode and Effects Analysis (FMEA)

Risk is defined as the combination of the severity and the probability of occurrence of harm. The concept of quality risk management (QRM) was introduced by the ICH in the year 2005 through its Q9 guidance document. It describes systematic processes for the assessment, control and review of quality risks. The effect of formulation attributes over the CQA can be evaluated by various risk assessment tools like FMEA, Fault tree analysis, Ishikawa diagram, Pareto diagram, Hazard Operability Analysis etc. 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 relative risk that each formulation attributes presents was ranked (prioritized) according to risk priority number (RPN) for corrective action. The severity of each failure effect (S), the likelihood of occurrence (O) and the likelihood of prior detection (D) for each cause of failure was rated. In short,

$$RPN = S \times O \times D$$

In case of hazardous severity without warning the severity (S) was ranked 10; while that in case of inoperable system with minor damage: 6; and in case of operable system with minimal or no interference: 1. In case of inevitable failure i.e. probability (O) of 1 in 2 chances was ranked 10; while that in case of occasional failures i.e.1 in 80 chances was ranked 6; and in case of relatively low probability of failure i.e. 1 in 1,50,000 chances was ranked 2. Similarly if the likelihood of detection by design control was absolutely uncertain then the detection (D) was ranked as 10, while that in case of moderate and almost certain it were ranked as 6 and 2 respectively.

The FMEA lays down the foundation for initial risk assessment, where the nature of risk is considered as high (marked in red color) in case of RPN score 295-1000, medium (marked in yellow color) for a score 96-294 and low (marked in green color) for 1-95 (Table 4.3.3) [3]. The formulation attributes which had high impact on the CQA were studied in detail whereas those which had low impact were not investigated further.

Table 4.3.3: Initial Formulation Risk Assessment for MS and MH MUPS

Drug Product CQA	Formulation attribute					
	API particle size	Core pellet size	Core pellet quantity	Drug layering technique	Extent of CR coating	Drug: Polymer
Dissolution	Low	Medium	Medium	Medium	High	High
Assay	Low	Low	Low	Low	Low	Low
Initial strategy	No investigation	Investigate	Investigate	Investigate	Optimize by DoE	Optimize by DoE

4.3.3 Selection of core material

Core material constitutes the substrate upon which drug layering and other release modifying coatings are applied. Inert starters are traditionally prepared from

pharmaceutically acceptable substances, such as lactose, sucrose and starch (e.g., Suglets®, Nu-Pareil PG®). While sugar spheres are constituted of sucrose and starch [4], Celphere represents 100% pure MCC spheres or seed cores [5]. Microcrystalline cellulose (MCC) starters (e.g., Celphere®, Cellets®) are routinely used commercially [6]. Selection of core material requires careful consideration, since it affects the drug release profile owing to its water solubility and osmotic activity. Hence, various core materials were investigated.

4.3.4 Selection of load

Preliminary batches were taken to identify suitable working load (Table 4.3.4). Accordingly, Batches MS-1, MS-2, MS-3, MS-4 and MS-5 were taken by loading 20, 40, 80, 120, 160 g Celphere® respectively in the product container of the Fluid Bed Processor (FBP) (MiniGlatt, Glatt Gmbh, Germany) and allowed to fluidize at a constant air flow (0.35 bar). Load selected in case of MS was also used in MH.

Table 4.3.4: Selection of load

Batch no.	Load (g)
MS-1	20
MS-2	40
MS-3	80
MS-4	120
MS-5	160

4.3.5 Drug loading

The drug layering or drug loading process comprises the deposition of successive layers of drug solution or drug dispersion over inert core pellets. It can be accomplished by bottom spray (suspension layering) [7, 8] or tangential spray (powder layering) techniques. Suspension layering can be executed in Wurster (bottom spray) assembly into which functional (extended or delayed release) coating, the next very step, can be performed. On the other hand, powder layering is a convenient way of drug loading but requires a separate rotor (tangential spray) assembly. Of the two techniques, the former is more widely used in pharmaceutical industry due to its ease of operation. Hence, in the present study, bottom spray technique was used for drug (MS as well as MH) loading [9-11].

Procedure for MS loading

The solvent system (IPA: Water) (6:4) was taken into beaker and stirred to form a vortex using magnetic stirrer (Remi, India). PVP-K30 was added to it and stirred for 30 min. MS was added into the solution thus prepared and stirred for 15 min. The inert core pellets (CelPhere) were loaded in the product container of the FBP (MiniGlatt, Glatt Gmbh, Germany) and the drug loading solution was sprayed over it.

Procedure for MH loading

The solvent system (IPA: Water) (3:7) was taken into beaker and stirred to form a vortex using magnetic stirrer (Remi, India). PVP-K30 was added to it and stirred for 30 min. MH was added into the solution thus prepared and stirred for 15 min. The inert core pellets (CelPhere) were loaded in the product container of the FBP (MiniGlatt, Glatt Gmbh, Germany) and the drug loading solution was sprayed over it.

4.3.5.1 Process parameters

In order to execute the process smoothly, the process parameters were optimized.

Selection of process parameters for MS loading

Using same formula (Table 4.3.5), preliminary feasibility batches (Batch MS-6, MS-7, MS-8 and MS-9) were taken to set the processing parameters (Table 4.3.6) for drug loading stage

Table 4.3.5: Composition used for selection of MS loading process parameters

Sr. No.	**Ingredients**	mg/unit
1	Celphere (CP203)	50.00
2	MS	11.25
3	PVP-K30	1.25
4	Iso Propyl Alcohol	q.s.
5	Distilled Water	q.s.
	Total	62.50

Table 4.3.6: Selection of process parameters for MS loading

Parameter	Batch MS-6	Batch MS-7	Batch MS-8	Batch MS-9
Inlet temperature (°C)	30-33	30-34	35-45	45-50
Product temperature (°C)	24-26	24-27	28-34	38-40
Air flow (cfm)	0.15 -0.30	0.15 -0.30	0.15-0.30	0.15 -0.30
Atomization (bar)	0.10- 0.25	0.30- 0.55	0.30- 0.55	0.30- 0.55
Spray rate (g/min)	1.2- 1.5	1.2- 1.5	0.25- 1.00	0.25- 1.00

In case of both the drugs, after completion of drug loading, the pellets were sifted through sieve no. # 60 and # 24 to remove fines and agglomerates (if any) respectively, and stored in tightly closed containers, until further experimentation.

Selection of process parameters for MH loading

Using same formula (Table 4.3.7) following preliminary feasibility batches (Batch MH-1, MH-2 and MH-3) were taken to set the processing parameters (Table 4.3.8) for drug loading stage.

Table 4.3.7: Composition used for selection of MH loading process parameters

Sr. No.	Ingredients	mg/unit
1	Celphere (CP203)	50.00
2	MH	11.25
3	PVP-K30	1.25
4	Iso Propyl Alcohol	q.s.
5	Distilled Water	q.s.
	Total	62.50

Table 4.3.8: Selection of process parameters for MH loading

Parameter	Batch MH-1	Batch MH-2	Batch MH-3
Inlet temperature (^{0}C)	31-37	38-48	45-50
Product temperature (^{0}C)	27-29	30-36	38-40
Air flow (cfm)	0.15 -0.30	0.15-0.35	0.15 -0.35
Atomization (bar)	0.30- 0.55	0.35- 0.65	0.35- 0.65
Spray rate (g/min)	1.2- 1.5	0.25- 0.80	0.25- 1.00

Evaluation of drug loaded pellets

The process parameters for drug layering were selected on the basis of percentage yield. Percentage yield reflects the efficiency of the process being employed. Higher the yield, better the process is. Yield above 90% was considered to be satisfactory. Reduction in yield generally occurs due to retention of the agglomerates upon the coarser mesh (sieve no. #24 in present study) or passage of fines from the fine mesh (sieve no. #60 in present study) during sifting of coated pellets. The percentage yield was calculated from the following formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

4.3.5.2 Solvent system

Solvent system acts as a vehicle by which the drug or any other polymer can be layered over the substrate. The drug or the polymer can be either dissolved or dispersed into the solvent. The solvent systems can be classified into aqueous, non- aqueous (organic solvent) and hydro-alcoholic systems. Choice of solvent system affects the processing conditions. Therefore selection of appropriate solvent is critical.

4.3.5.3 Solid content

Solid content of the coating solution/dispersion dictates the ease with which it can be sprayed onto the substrate. The solid content for drug (MS and MH) loading solution was selected on the basis of percentage yield. Solid content at which highest yield was achieved was selected for further trails.

Selection of solid content for MS loading

The most appropriate solid content for the drug loading stage was selected by taking trials (MS-10, MS-11 and MS-12) at three different levels viz. 10, 15 and 20% w/w respectively for MS (Table 4.3.9). The drug (MS) loading solution was prepared by procedure mentioned in section 4.3.5 and sprayed over Celphere under optimized process parameters which were used for batch MS-8. After completion of drug loading, the pellets were sifted through sieve #60 and #24 to remove fines and agglomerates (if any) respectively.

Table 4.3.9: Selection of solid content for MS loading solution

Sr. No.	Ingredients	Batch MS-10	Batch MS-11	Batch MS-12
		mg/unit	mg/unit	mg/unit
1	Celphere (CP203)	50.0	50.0	50.0
2	MS	11.25	11.25	11.25
3	PVP-K30	1.25	1.25	1.25
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	Total	62.5	62.5	62.5
	Solid content	10 %	15 %	20 %

Selection of solid content for MH loading

The most appropriate solid content for the drug (MH) loading stage was selected by taking trials (Batch MH-4, MH-5 and MH-6) at three different levels viz. 30, 20 and 10% w/w respectively (Table 4.3.10).

The drug (MH) loading solution was prepared by procedure mentioned in section 4.3.5 and sprayed over Celphere under optimized process parameters of batch MH-2. After completion of drug loading, the pellets were sifted through sieve #60 and #24 to remove fines and agglomerates (if any) respectively.

Table 4.3.10: Selection of solid content for MH loading solution

Sr. No.	Ingredients	Batch MH-4	Batch MH- 5	Batch MH- 6
		mg/unit	mg/unit	mg/unit
1	Celphere (CP203)	50.0	50.0	50.0
2	MH	11.25	11.25	11.25
3	PVP-K30	1.25	1.25	1.25
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	Total	62.5	62.5	62.5
	Solid Content	30 %	20 %	10 %

4.3.5.4 Binder selection

In order to increase the binding efficiency of the drug with the core pellet, suitable binder is required to be incorporated into the drug loading solution. Various binders such as hydroxypropyl methyl cellulose (HPMC 3cps and HPMC 5cps) and Poly vinyl pyrrolidone (PVP-K30 and PVP-K90) were evaluated for both the drugs.

Binder selection in MS loading

Batches MS-13, MS-14, MS-15 and MS-16 were taken with HPMC 3cps, HPMC 5cps, PVP-K30 and PVP-K90 respectively (Table 4.3.11). Process parameters used in Batch MS-8 were followed for below batches.

Table 4.3.11: Selection of binder in MS loading stage

Sr. No.	Ingredients	**Batch MS-13**	**Batch MS-14**	**Batch MS-15**	**Batch MS-16**
		mg/ unit	mg/ unit	mg/ unit	mg/ unit
1	Celphere CP 203	50.0	50.0	50.0	50.0
2	MS	11.25	11.25	11.25	11.25
3	HPMC 3cps	1.25	0.0	0.0	0.0
4	HPMC 5cps	0.0	1.25	0.0	0.0
5	PVP-K30	0.0	0.0	1.25	0.0
6	PVP-K90	0.0	0.0	0.0	1.25
7	Iso Propyl Alcohol	q.s.	q.s.	q.s.	q.s.
8	Distilled water	q.s.	q.s.	q.s.	q.s.
	Total	62.5	62.5	62.5	62.5

Binder selection in MH loading stage

Batches MH-7, MH-8, MH-9 and MH-10 were taken with HPMC 3cps, HPMC 5cps, PVP-K30 and PVP-K90 respectively (Table 4.3.12). Process parameters used in Batch MH-2 were followed for below batches.

Table 4.3.12: Selection of binder in MH loading stage

Sr. No.	Ingredients	**Batch MH-7**	**Batch MH-8**	**Batch MH-9**	**Batch MH-10**
		mg/ unit	mg/ unit	mg/ unit	mg/ unit
1	Celphere CP 203	50.0	50.0	50.0	50.0
2	MH	11.25	11.25	11.25	11.25
3	HPMC 3cps	1.25	0.0	0.0	0.0
4	HPMC 5cps	0.0	1.25	0.0	0.0
5	PVP-K30	0.0	0.0	1.25	0.0
6	PVP-K90	0.0	0.0	0.0	1.25
7	Iso Propyl Alcohol	q.s.	q.s.	q.s.	q.s.
8	Distilled Water	q.s.	q.s.	q.s.	q.s.
	Total	62.5	62.5	62.5	62.5

Evaluation

Suitable binder was selected on the basis of percentage yield and drug content of the drug loaded pellets. Binder which gave highest yield and drug content was selected.

Drug content (MS)

MS content was determined by method as described in the US Pharmacopoeia-30, NF25, with some modifications. Accurately weighed quantity of pellets (5g) was finely crushed into the mortar and quantity equivalent to 25mg drug was transferred in a 25 mL volumetric flask. 5 mL distilled water was added in the volumetric flask and shaken manually for 5 min. 7.5 mL methanol was added and the volumetric flask was shaken for 30 min (Rotary shaker). 0.1N HCl was added upto the mark and shaking continued for 30 min. 0.5mL solution was pipetted out in 10mL volumetric flask and volume was made upto the mark by pH 3.0 phosphate buffer. The contents of the volumetric flask were filtered by Whatman filter paper number 44 and analyzed spectrophotometrically for MS content at 274 nm.

Drug content (MH)

MH content was determined by reported method with some modifications [12]. Accurately weighed quantity of pellets (5g) was finely crushed into the mortar and quantity equivalent to 25 mg drug was transferred in a 25 mL volumetric flask. 5mL distilled water was added in the volumetric flask and shaken manually for 5 min. 7.5 mL methanol was added and the volumetric flask was shaken for 30 min (Rotary shaker).

Distilled water was added upto the mark and shaking continued for 30 min. 0.5mL solution was pipetted out in 10mL volumetric flask and volume was made upto the mark by distilled water. The contents of the volumetric flask were filtered by Whatman filter paper number 44 and analyzed spectrophotometrically for MH content at 233 nm.

4.3.5.5 Binder concentration

Binder concentration should be selected aptly so as to achieve proper film formation and minimize the production of fines and agglomerates during coating.

Selection of binder concentration in MS loading stage

To select the level at which PVP-K30 is most efficient, three trials (Batch MS-17, MS-18 and MS-19) were taken at different concentrations (Table 4.3.13) employing process parameters used in Batch MS-8.

Table 4.3.13: Optimization of binder concentration in MS loading stage

Sr. No.	Ingredients	**Batch MS-17**	**Batch MS-18**	**Batch MS-19**
		mg/unit	mg/unit	mg/unit
1	Celphere CP 203	50.00	50.00	50.00
2	MS	11.25	11.25	11.25
3	PVP-K30	1.25	1.50	1.75
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	Total	62.50	62.75	63.00

Selection of binder concentration in MH loading stage

To select the level at which PVP-K30 is most efficient, three trials (Batch MH-11, MH-12 and MH-13) were taken at different concentrations (Table 4.3.14). Process parameters used in Batch MH-2 were followed for below batches.

Table 4.3.14: Optimization of binder concentration in MH loading stage

Sr. No.	Ingredients	**Batch MH-11**	**Batch MH-12**	**Batch MH-13**
		mg/unit	mg/unit	mg/unit
1	Celphere CP 203	50.00	50.00	50.00
2	MH	11.25	11.25	11.25
3	PVP-K30	1.25	1.50	1.75
4	Distilled Water	q.s.	q.s.	q.s.
5	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	62.50	62.75	63.00

Evaluation

The binder concentration for both the drugs was selected on the basis of percentage yield and drug content. The concentration at which higher percentage yield and drug content was achieved, was used for further trials for both the drugs.

4.3.6 Controlled release (CR) coating

CR coating was applied over the drug loaded pellets to sustain the drug release. Batches (MS-20 and MS-21) (Table 4.3.15) were taken to set the process parameters (Table 4.3.16) for MS-CR coating step while batches (MH-14 and MH-15) (Table 4.3.17) were taken to set the process parameters (Table 4.3.18) for the MH-CR coating step.

4.3.6.1 Process parameters

Preparation of CR coating solution

Iso Propyl Alcohol was stirred using magnetic stirrer (Remi, India) to form a vortex. Hydroxy Propyl Cellulose EXF (HPC) was added in it and stirring continued for 15 min. After dissolution of HPC, Ethyl cellulose (EC) was added and stirring continued for 30 min. The CR coating solution thus prepared was sprayed over MS and MH drug layered pellets under parameters as mentioned in Table 4.3.16 and 4.3.18 respectively.

Table 4.3.15: Composition for selection of MS-CR coating process parameters

Sr. No.	Ingredients	Batch MS-20	Batch MS-21
		mg/unit	mg/unit
1	MS loaded pellets	62.75	62.75
2	Ethyl Cellulose 10 cps	9.41	9.41
3	Hydroxy Propyl Cellulose EXF	6.28	6.28
4	Iso Propyl Alcohol	q.s.	q.s.
	Total	78.44	78.44

Table 4.3.16: Selection of processing variables for MS-CR coating stage

Parameter	Batch MS-20	Batch MS-21
Inlet temperature (^{0}C)	36-42	35-40
Product temperature (^{0}C)	28-33	28-32
Air flow (cfm)	0.15-0.30	0.18-0.35
Atomization (bar)	0.20- 0.40	0.20- 0.40
Spray rate (g/min)	0.25- 1.00	0.20- 0.75

Table 4.3.17: Composition for selection of MH-CR coating process parameters

Sr. No.	Ingredients	Batch MH-14	Batch MH-15
		mg/unit	mg/unit
1	MH loaded pellets	63.00	63.00
2	Ethyl Cellulose 10 cps	9.45	9.45
3	Hydroxy Propyl Cellulose EXF	6.30	6.30
4	Iso Propyl Alcohol	q.s.	q.s.
	Total	78.75	78.75

Table 4.3.18: Selection of processing variables for MH-CR coating stage

Parameter	Batch MH-14	Batch MH-15
Inlet temperature (^{0}C)	37-41	34-38
Product temperature (^{0}C)	28-31	27-30
Air flow (cfm)	0.15-0.30	0.18-0.45
Atomization (bar)	0.20- 0.40	0.20- 0.45
Spray rate (g/min)	0.25- 1.00	0.20- 0.80

Evaluation

Processing variables for CR coating stage were selected on the basis of percentage yield.

4.3.6.2 Solvent system

Ethyl Cellulose readily dissolves into Iso Propyl Alcohol, Acetone and Methylene chloride [13] Considering the environmental safety aspect, use of Acetone and Methylene chloride was precluded. Hence, Iso Propyl Alcohol was chosen as solvent system for CR coating considering wide industrial applicability.

4.3.6.3 Solid content

To select a suitable solid content for the CR coating stage, trials were taken at 4 and 6 % w/w solid content. Accordingly, batches MS-22 and MS-23 (Table 4.3.19) were taken using processing parameters similar to batch MS-21, to determine the solid content for MS- CR coating solution while batches MH-16 and MH**-**17 (Table 4.3.20) were taken using processing parameters similar to batch MH-15 to determine the solid content for MH- CR coating solution.

Table 4.3.19: Selection of solid content for MS-CR coating stage

Sr. No.	Ingredients	Batch MS-22	Batch MS-23
		mg/unit	mg/unit
1	**MS** loaded pellets	62.75	62.75
2	Ethyl Cellulose 10 cps	9.41	9.41
3	Hydroxy Propyl Cellulose EXF	6.28	6.28
4	Iso Propyl Alcohol	q.s.	q.s.
	Total	78.44	78.44
	Solid content	4 %	6 %

Table 4.3.20: Selection of solid content for MH-CR coating stage

Sr. No.	Ingredients	Batch MH-16	Batch MH-17
		mg/unit	mg/unit
1	MH loaded pellets	63.00	63.00
2	Ethyl Cellulose 10 cps	9.45	9.45
3	Hydroxy Propyl Cellulose EXF	6.30	6.30
4	Iso Propyl Alcohol	q.s.	q.s.
	Total	78.75	78.75
	Solid content	4 %	6 %

Evaluation

Solid content for both the CR coating solutions were selected on the basis of percentage yield.

4.3.7 Selection of core pellet size

Celphere is available in various grades depending upon its particle size like Celphere CP-102 (106- 212 µm), Celphere CP-203 (150- 300µm), Celphere CP-305 (300- 500 µm) etc [5]. Selection of particle size is critical since it directly affects the drug release particularly in case of CR MUPS [14]. Based on this, it was decided to evaluate Celphere CP-102, CP-203 and CP305 for formulation development of both the drugs.

Batches MS-24, MS-25 and MS-26 were taken using Celphere grades- CP 102, CP 203 and CP 305 as the core material respectively (Table 4.3.21). The core pellets were layered (25.5% w/w) with MS using Polyvinyl Pyrrolidone (PVP- K30) as a binder and iso propyl alcohol: water (6:4) as solvent system. The drug loaded pellets thus prepared were further coated with ethyl cellulose + hydroxy propyl cellulose (3:2) (25% w/w).

Table 4.3.21: Selection of core pellet size for MS

Sr. No.	Ingredients	Batch MS-24	Batch MS-25	Batch MS-26
		mg/unit	mg/unit	mg/unit
	Drug layering			
1	Celphere	50 (CP102)	50 (CP203)	50 (CP305)
2	MS	11.25	11.25	11.25
3	PVP-K30	1.50	1.50	1.50
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	CR Coating			
6	Ethyl Cellulose 10 cps	9.41	9.41	9.41
7	Hydroxy Propyl Cellulose EXF	6.28	6.28	6.28
8	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	78.44	78.44	78.44

Batches MH-18, MH-19 and MH-20 were taken using Celphere grades- CP 102, CP 203 and CP 305 as the core material respectively (Table 4.3.22). The core pellets were layered (26.0 % w/w) with MH using Polyvinyl Pyrrolidone (PVP- K30) as a binder and iso propyl alcohol: water (3:7) as solvent system. The drug loaded pellets thus prepared were further coated with ethyl cellulose + hydroxy propyl cellulose (3:2) (25% w/w).

Table 4.3.22: Selection of core pellet size for MH

Sr. No.	Ingredients	Batch MH-18	Batch MH-19	Batch MH-20
		mg/unit	mg/unit	mg/unit
	Drug layering			
1	Celphere	50 (CP102)	50 (CP203)	50 (CP305)
2	MH	11.25	11.25	11.25
3	PVP-K30	1.75	1.75	1.75
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	CR Coating			
6	Ethyl Cellulose 10 cps	9.45	9.45	9.45
7	Hydroxy Propyl Cellulose EXF	6.30	6.30	6.30
8	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	78.75	78.75	78.75

Evaluation of pellets

The core pellet size for both the drugs was selected on the basis of percentage yield and drug release study.

Drug release study

The cumulative percent drug (MS and MH) released was determined using method described in US Pharmacopoeia-30, NF25 with slight modification. In the present study Eudragit E coating has been applied over drug+ polymer matrix. Eudragit E is an alkali resistant polymer which dissolves below pH 5. Hence an acid stage was incorporated to check the drug release after solubilization of Eudragit E layer. The drug release study was carried out using USP type II apparatus (Electrolab TDT 06P, USP XXIII) at 37± 0.5°C.

Acid stage: The pellets were evaluated by dissolution testing in 0.1N HCl (500 mL for MS and 1000mL for MH) at 37^0C at a paddle speed of 50 rpm. Accurately weighed pellets (n= 3) equivalent to 200 mg of each drug were introduced in the dissolution medium. After 1h, sample aliquots (5mL) were collected from the vessel, passed through 45µ filter membrane and analyzed spectrophotometrically at 274 nm for MS and 233 nm for MH. Equal volume of dissolution media was added to maintain the sink condition.

Buffer stage: Acidic medium was decanted, replaced with equal volume of phosphate buffer (pH 6.8) in each case, and the dissolution testing was continued upto 24h. At specified time intervals sample aliquots (5mL) were collected from the vessel, passed through 45µ filter membrane and analyzed spectrophotometrically at 274 nm for MS and 233 nm for MH. Equal volume of dissolution media was added to maintain the sink condition.

4.3.8 Selection of core pellet quantity per unit

After selection of core pellet size, the next formulation factor which affected the CQAs was quantity per unit of core pellet. To strike off a balance between the size of the pellets and the final bulk of the product, trials (MS-27, MS-25 and MS-28) (Table 4.3.23) were taken at a constant load of 40g in product chamber of Miniglatt, but at three levels viz. 25, 50 and 75 mg/unit of core pellets and the impact on drug release was studied.

Similar trials were taken for MH at three levels viz. 25, 50 and 75 mg/unit of core pellets (MH-21, MH-19 and MH-22) (Table 4.3.24) and the impact on drug release was studied.

Table 4.3.23: Selection of core pellet quantity per unit for MS

Sr. No.	Ingredients	Batch MS-27	Batch MS-25	Batch MS-28
		mg/unit	mg/unit	mg/unit
	Drug layering			
1	Celphere CP203	25.0	50.0	75.0
2	MS	11.25	11.25	11.25
3	PVP-K30	1.50	1.50	1.50
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	Total	37.75	62.75	87.75
	CR Coating (25% w/w)			
6	Ethyl Cellulose 10 cps	5.66	9.41	13.16
7	Hydroxy Propyl Cellulose EXF	3.78	6.28	8.78
8	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	47.19	78.44	109.69

Table 4.3.24: Selection of core pellet quantity per unit for MH

Sr. No.	Ingredients	Batch MH-21	Batch MH-19	Batch MH-22
		mg/unit	mg/unit	mg/unit
	Drug layering			
1	Celphere CP203	25.0	50.0	75.0
2	MH	11.25	11.25	11.25
3	PVP-K30	1.75	1.75	1.75
4	Iso Propyl Alcohol	q.s.	q.s.	q.s.
5	Distilled Water	q.s.	q.s.	q.s.
	Total	38.00	63.00	88.00
	CR Coating (25% w/w)			
6	Ethyl Cellulose 10 cps	5.70	9.45	13.20
7	Hydroxy Propyl Cellulose EXF	3.80	6.30	8.80
8	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	47.50	78.75	110.00

Evaluation

The core pellet size for both the drugs was selected on the basis of percentage yield, drug content and drug release study.

4.3.9 Selection of controlled release (CR) polymer

Prior to assessing the extent of CR coating and drug: polymer ratio, there is a prerequisite for selection of controlled release polymer. Various pH independent cellulosic and acrylic polymers like Ethyl cellulose, Eudragit® RS, Eudragit® RL which release drug independent of pH, enzyme concentration or contents of GIT, are widely used in the pharmaceutical industry. Batches were taken at a constant weight gain of 25% w/w for above mentioned polymers followed by drug release study (Table 4.3.25 and Table 4.3.26). These polymers were evaluated based on their ability to control the drug release at constant 25%. The level of functional polymer was kept constant at 9.41mg/unit for comparative evaluation. For the purpose of proper binding, Hydroxy Propyl Cellulose EXF was used along with Ethyl Cellulose in batch MS-25 and MH-19. In case of batch MS-29, MS-30, MH-23 and MH-24, Talc UM was used as detackifier as Eudragits cannot be sprayed alone due to their tacky property [15].

Table 4.3.25: Selection of CR polymer for MS

Sr. No.	Ingredients	**Batch MS-25**	**Batch MS-29**	**Batch MS-30**
		mg/unit	mg/unit	mg/unit
	Drug loading			
1	Celphere CP 203	50.0	50.0	50.0
2	MS	11.25	11.25	11.25
3	PVP-K30	1.5	1.5	1.5
4	Distilled Water	q.s.	q.s.	q.s.
5	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	62.75	62.75	62.75
	CR Coating			
6	Ethyl Cellulose 10 cps	9.41	0	0
7	Eudragit RS	0	9.41	0
8	Eudragit RL	0	0	9.41
9	Hydroxy Propyl Cellulose EXF	6.28	0	0
10	Talc UM	0	6.28	6.28
11	Iso Propyl Alcohol	q. s.	q. s.	q. s.
	Total	**78.44**	**78.44**	**78.44**

Table 4.3.26: Selection of CR polymer for MH

Sr. No.	Ingredients	Batch MH-19	Batch MH-23	Batch MH-24
		mg/unit	mg/unit	mg/unit
	Drug loading			
1	Celphere CP 203	50.0	50.0	50.0
2	MH	11.25	11.25	11.25
3	PVP-K30	1.75	1.75	1.75
4	Distilled Water	q.s.	q.s.	q.s.
5	Iso Propyl Alcohol	q.s.	q.s.	q.s.
	Total	63.00	63.00	63.00
	CR Coating (25% w/w)			
6	Ethyl Cellulose 10 cps	9.45	0.0	0.0
7	Hydroxy Propyl Cellulose EXF	6.30	0.0	0.0
8	Eudragit® RS	0.0	9.45	0.0
9	Eudragit® RL	0.0	0	9.45
10	Talc UM	0.0	6.30	6.30
11	Iso Propyl Alcohol	q. s.	q. s.	q. s.
	Total	**78.75**	**78.75**	**78.75**

Evaluation of pellets

The CR polymer was selected on the basis of percentage yield, drug content and drug release study.

4.3.10 Reservoir Vs Matrix technique

Drug loading by using bottom spray assembly of MiniGlatt (Glatt GmbH, Germany) with a Wurster insert, was performed using two different approaches, viz. reservoir and matrix technique.

4.3.10.1 Reservoir technique

Reservoir technique for MS- Drug layering (25.5% w/w) followed by CR coating (25% w/w) was carried out on Celphere CP 203 as core pellet (Table 4.3.27) using process parameters as mentioned in Table 4.3.28. The drug loading and CR coating solution were prepared as mentioned in section 4.3.5 and 4.3.6.1 respectively.

Table 4.3.27: Drug loading by reservoir technique for MS

Sr. No.	Ingredients	Batch MS-25
		mg/unit
	Drug loading	
1	Celphere CP 203	50.0
2	MS	11.25
3	PVP-K30	1.5
4	Distilled Water	q.s.
5	Iso Propyl Alcohol	q.s.
	CR Coating	
6	Ethyl Cellulose 10 cps	9.41
7	Hydroxy Propyl Cellulose EXF	6.28
8	Iso Propyl Alcohol	q. s.
	Total	**78.44**

Table 4.3.28: Process parameters for reservoir technique (Batch MS-25)

Parameter	Drug layering	CR coating
Inlet temperature (^{0}C)	38-47	35-40
Product temperature (^{0}C)	30-36	28-32
Air flow (bar)	0.15-0.30	0.18-0.35
Atomization (bar)	0.30- 0.55	0.20- 0.40
Spray rate (g/min)	0.25- 1.00	0.20- 0.75

Reservoir technique for MH- Drug layering (26% w/w) followed by CR coating (25% w/w) was carried out on Celphere CP 203 as core pellet (Table 4.3.29) using process parameters as mentioned in Table 4.3.30. The drug loading and CR coating solution were prepared as mentioned in section 4.3.5 and 4.3.6.1 respectively.

Table 4.3.29: Drug loading by reservoir technique for MH

Sr. No.	Ingredients	Batch MH-23
		mg/unit
	Drug loading	
1	Celphere CP 203	50.0
2	MH	11.25
3	PVP-K30	1.75
4	Distilled Water	q.s.
5	Iso Propyl Alcohol	q.s.
	CR Coating	
6	Eudragit® RS	9.45
7	Eudragit® RL	0.50
8	Talc UM	5.80
9	Iso Propyl Alcohol	q. s.
10	Distilled Water	q.s.
	Total	**78.75**

Table 4.3.30: Process parameters for reservoir technique (Batch MH-23)

Parameter	Drug layering	CR coating
Inlet temperature (^{0}C)	38-48	34-38
Product temperature (^{0}C)	30-36	27-30
Air flow (bar)	0.15-0.35	0.18-0.45
Atomization (bar)	0.35- 0.65	0.20- 0.45
Spray rate (g/min)	0.25- 0.80	0.20- 0.80

Evaluation of pellets prepared by reservoir technique

The pellets prepared by reservoir technique were evaluated on the basis of percentage yield, drug content, drug release study and pellet size.

Optical microscopy

The pellet size was determined using optical microscopy technique (Nikon Digital Sight DS-Fi2, Japan). Pellets were placed on a glass slide and observed under 4X magnification.

4.3.10.2 Matrix technique

Batch MS-31 and MH-25 were prepared by matrix technique (Table 4.3.31 and Table 4.3.33 respectively). For comparative evaluation, the amount of drug (MS) and the polymers (EC+HPC) in batch MS-31was kept same as that of batch MS-30 (reservoir technique). Similarly, the amount of drug (MH) and the CR polymer (Eudragit® RS) in batch MH-25 was kept same as that of batch MH-23 (reservoir technique).

Preparation of drug+ CR polymer (MS+ EC and HPC) solution: IPA was taken into beaker and stirred using magnetic stirrer (Remi, India) to form a vortex. Hydroxy propyl cellulose (HPC) was added in it and stirred for 20 min. Ethyl cellulose was then added into the HPC solution thus prepared and stirred for 30 min. Water was taken into another beaker and stirred using magnetic stirrer (Remi, India) to form a vortex. MS was added into it and stirring continued for 20 min. The drug (MS) solution was added into the polymer solution and stirred for 20 min.

Preparation of drug+ CR polymer (MH +Eudragit® RS) solution: IPA was taken into beaker and stirred using magnetic stirrer (Remi, India) to form a vortex. Eudragit® RS was added in it and stirred for 20 min. Talc UM was then added into the Eudragit solution thus prepared and stirred for 30 min. Water was taken into another beaker and stirred using magnetic stirrer (Remi, India) to form a vortex. MH was added into it and stirring continued for 20 min. The drug (MH) solution was added into the polymer solution and stirred for 20 min.

Celphere were loaded in the product container of the FBP (MiniGlatt, Glatt Gmbh, Germany) and the drug+ CR coating solution was sprayed over it to achieve weight gain of 53.88% w/w under process parameters as mentioned in Table 4.3.32 for MS and Table 4.3.34 for MH.

Table 4.3.31: MS loading by matrix technique

Sr. No.	Ingredients	Batch MS-31
		mg/unit
	Drug+ CR coating	
1	Celphere CP 203	50.0
2	MS	11.25
3	Ethyl Cellulose 10 cps	9.41
4	Hydroxy Propyl Cellulose EXF	6.28
5	Iso Propyl Alcohol	q. s.
7	Distilled water	q. s.
	Total	**76.94**

Table 4.3.32: Process parameters for matrix technique (Batch MS-31)

Process Parameters	Experimental values
Inlet temperature (^{0}C)	35-40
Product temperature (^{0}C)	28-32
Air flow (bar)	0.20 -0.45
Atomization (bar)	0.35- 0.55
Spray rate (g/min)	0.20- 0.75

Table 4.3.33: MH loading by matrix technique

Sr. No.	Ingredients	Batch MH-25
		mg/unit
	Drug+ CR coating	
1	Celphere CP 203	50.0
2	MH	11.25
3	PVP-K30	1.75
4	Eudragit® RS	9.45
5	Eudragit® RL	0.5
6	Talc UM	5.80
7	Iso Propyl Alcohol	q. s.
8	Distilled water	q. s.
	Total	**78.75**

Table 4.3.34: Process parameters for matrix technique (Batch MH-25)

Process Parameters	Experimental values
Inlet temperature (^{0}C)	35-40
Product temperature (^{0}C)	28-32
Air flow (bar)	0.20 -0.55
Atomization (bar)	0.30- 0.60
Spray rate (g/min)	0.20- 0.70

Evaluation of pellets prepared by matrix technique

The pellets prepared by matrix technique were evaluated on the basis of percentage yield, drug content, drug release study and pellet size.

4.3.11 Optimization of drug + CR polymer coating solution solid content

Optimization of drug (MS) + CR polymer (EC and HPC) coating solution solid content

Solid content of the coating solution/dispersion dictates the ease with which it can be sprayed onto the substrate. The most appropriate solid content for the drug+ CR polymer coating stage was selected by checking the percentage yield at two different levels viz 6 and 8% w/w. Accordingly, batches MS-31, MS-32 and MS-33 were taken with same composition (Table 4.3.31) but with 5, 7.5 and 10% solid content respectively.

Optimization of drug (MH) + CR polymer (Eudragit® RS) coating solution solid content

The most appropriate solid content for the drug (MH)+ CR polymer (Eudragit® RS) coating stage was selected by checking the percentage yield at two different levels viz. 6 and 8% w/w. Accordingly batches MH-25 and MH-26 were taken with same composition (Table 4.3.33) but with 6 and 8% solid content respectively.

Evaluation

The solid content for drug + CR polymer coating solution was selected on the basis of percentage yield.

4.3.12 Extent of CR coating and drug: polymer ratio in matrix system

After selection of pH independent controlled release polymer, MS-loaded controlled release pellets were prepared. The most critical component in case of any controlled release systems is the release controlling component.

MS matrix system

Procedure for drug (MS) + CR polymer (EC+HPC) solution preparation was same as mentioned in section 4.3.10.2. Process parameters used for the coating are mentioned in Table 4.3.36. The target dissolution profile for MS-CR pellets was set as: NMT 25% in 1h, 20-40% in 4h, 40-60% in 8h and NLT 80% in 20h [1]. Following trials (Table 4.3.35) were taken to prepare MS CR pellets exhibiting above drug release profile.

Table 4.3.35: Optimization for extent of CR coating and drug: polymer ratio for MS matrix system

Sr. No.	Ingredients	Batch MS-31	Batch MS-34	Batch MS-35	Batch MS-36	Batch MS-37
	Coating extent %	53.88	53.88	53.88	60.0	70.0
	Drug : polymer	1:1.4	1:1.4	1:1.4	1:1	1:1
1	Celphere CP 203	50.0	50.0	50.0	50.0	50.0
2	MS	11.25	11.25	11.25	40.0	42.50
3	Ethyl Cellulose 10 cps	9.41	12.55	15.69	36.0	38.25
4	Hydroxy Propyl Cellulose EXF	6.28	3.14	0.0	4.0	4.25
5	Iso Propyl Alcohol	q. s.	q. s.	q. s.	q. s.	q. s.
6	Distilled water	q. s.	q. s.	q. s.	q. s.	q. s.
	Total	78.44	78.44	78.44	80.0	85.0

Table 4.3.36: Process parameters for optimization for extent of CR coating and drug: polymer ratio for MS matrix system

Process Parameters	Experimental values
Inlet temperature (°C)	35-40
Product temperature (°C)	28-32
Air flow (bar)	0.20 -0.45
Atomization (bar)	0.35- 0.55
Spray rate (g/min)	0.20- 0.75

MH matrix system

Procedure for drug (MH) + CR polymer (Eudragit® RS) solution preparation was same as mentioned in section 4.3.10.2. Process parameters used for the coating are mentioned in Table 4.3.38. The target dissolution profile for MH-CR pellets was set as: 20-40% in 1h, 45-65% in 5h, 70-90% in 12h and NLT 85% in 20h [1]. Following trials (Table 4.3.37) were taken to prepare MH CR pellets exhibiting above drug release profile.

Table 4.3.37: Optimization for extent of CR coating and drug: polymer ratio for MH matrix system

Sr. No.	Ingredients	Batch MH- 25	Batch MH- 27	Batch MH- 28	Batch MH- 29	Batch MH- 30
	Coating extent %	57.50	65.0	65.0	65.0	65.0
	Drug : polymer	1:0.87	1:0.87	1:0.87	1:0.8	1:0.7
1	Celphere CP 203	50.0	50.0	50.0	50.0	50.0
2	MH	11.25	13.29	13.29	15.04	15.93
3	PVP K30	1.75	1.75	1.75	1.75	1.75
4	Eudragit® RS	9.45	11.16	10.05	10.23	9.48
5	Eudragit® RL	0.5	0.5	1.12	1.81	1.67
6	TEC	0.0	0.0	1.12	1.12	1.12
7	Talc UM	5.8	5.8	5.17	2.55	2.55
8	Iso Propyl Alcohol	q. s.	q. s.	q. s.	q. s.	q. s.
9	Distilled water	q. s.	q. s.	q. s.	q. s.	q. s.
	Total	78.75	82.5	82.5	82.5	82.5

Table 4.3.38: Process parameters for optimization of extent of CR coating and drug: polymer ratio for MH matrix system

Process Parameters	Experimental values
Inlet temperature (^{0}C)	35-40
Product temperature (^{0}C)	28-32
Air flow (bar)	0.20 -0.55
Atomization (bar)	0.30- 0.60
Spray rate (g/min)	0.20- 0.70

Evaluation

The pellets prepared to achieve target dissolution profile were evaluated on the basis of percentage yield drug content and drug release study.

4.3.13 Curing time

Stability study is important for pharmaceutical dosage forms and official guidelines [16] require stability testing at elevated (40°C/75% RH) as well as controlled room conditions. Changes in release profile during stability testing due to improper curing have been reported [17]. In order to avoid any changes in the dissolution profile at these conditions the functionally coated pellets must be cured properly. The importance of curing has been reported widely in the literature [18, 19].

Curing can be performed either under static conditions (ex. trays in hot air oven), or under dynamic conditions, (ex. Fluidized bed processor). The major drawback of static curing is that it is generally cumbersome to transfer the coated dosage forms into an oven and often requires prolonged time. Dynamic curing, on the other hand, can be performed in the same equipment as that of coating process, thereby avoiding transfer step as well as reduced curing time as compared to static curing [20]. In the present study, the MS-CR polymer layered pellets from batch MS-36 and MH- CR polymer layered pellets from batch MH-30 were cured at 40^0C in the fluid bed coater itself at low air flow (0.05-0.10 bar) and low atomization (0.05-0.10 bar) for 10 min (Batch MS-36A and MH-30A), 20 min (Batch MS-36B and MH-30B) and 30 min (Batch MS-36C and MH-30C). A sample quantity of 5g was withdrawn at each time point and subjected to drug release study.

Evaluation

The batches prepared for studying the effect of curing time were evaluated on the basis of percentage yield, drug content and drug release study.

4.3.14 Design of Experiment

The most critical part of the present 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 design (CCF), which is a routinely used statistical tool for optimization purpose [21]. It predicts all the interactions, especially the second order- quadratic ones between the variables and the responses. Extent of coating (X_0) (%w/w) and ratio of drug: polymer (X_1) were chosen as independent variables while the responses of drug release at 1h (Y_1), 4h (Y_2), 8h (Y_3) and 20h (Y_4) were selected for MS and responses of drug release at 1h (Y_1), 5h (Y_2), 12h (Y_3) and 20h (Y_4) for MH on the basis of pharmacopoeial specification . Based on the results of drug-release studies observed in preliminary experiments, the lower, middle and upper levels of each factor were set as depicted in Table 4.3.39 and Table 4.3.40 for MS and MH respectively. Contour Plots and Response surface Plots were generated using Design Expert® software (Version 7.0.0, Suite, Minneapolis, USA).

Table 4.3.39: Independent variables (factors) and their levels for MS-FCCD

Variables (Factors)	Levels		
	−1	0	1
X0: Extent of coating (%w/w)	55	60	65
X1: Ratio of drug: polymer	1:0.8	1:0.9	1:1

Table 4.3.40: Independent variables (factors) and their levels for MH-FCCD

Variables (Factors)	Levels		
	−1	0	1
X0: Extent of coating (%w/w)	60	65	70
X1: Ratio of drug: polymer	1:0.6	1:0.7	1:0.8

4.3.15 Risk mitigation and control strategy

The risk mitigation and control strategy demonstrates product knowledge of the current process and assures that quality is built into the product and not just tested- the objective of QbD. As seen in the initial risk assessment, the formulation attribute like API particle

size had least chances of affecting dissolution (CQA). Hence it was not further investigated and marked as low risk (green color) in risk control strategy. In case of other formulation attributes which had medium to high risk, the Proven Acceptance Range (PAR) was identified.

4.3.16 Eudragit® E coating

Prototype Eudragit® E coated pellets were prepared by layering Eudragit® E (pH dependent polymer) over the controlled release pellets using fluid bed coater.

4.3.16.1 Selection of process parameters for Eudragit® E coating

Preparation of Eudragit E coating solution: A mixture of Acetone: IPA (4:6) was taken in a beaker and stirred using magnetic stirrer (Remi, India) to form a vortex. Eudragit® E was added to it and stirring continued for 30 min. Talc UM was added and stirring continued for 15min. The solution thus prepared was sprayed over the controlled release pellets to achieve a weight gain of 10% w/w.

Trials were taken to optimize the process parameters used for preparing Eudragit® E coated pellets. Accordingly, batches MS-38 and MS-39 were prepared with same composition (Table 4.3.41) and different spray rates (Table 4.3.42) for MS. Similarly batches MH-31 and MH-32 were prepared with same composition (Table 4.3.43) and different spray rates (Table 4.3.44) for MH.

Table 4.3.41: Composition for selection of process parameters for MS-Eudragit® E coating

Sr. No.	Ingredients	Batch MS-38 and MS-39
		mg/unit
1	Celphere CP 203	50.00
2	MS	18.06
3	Ethyl cellulose 10 cps	13.00
4	Hydroxy propyl cellulose EXF	1.44
5	Distilled Water	q.s.
6	Iso Propyl Alcohol	q.s.
	Total	82.50
7	Eudragit® E	7.01
8	Talc-UM	1.24
9	Acetone	q.s.
10	Iso Propyl Alcohol	q.s.
	Total	90.75

Table 4.3.42: Process parameters for MS-Eudragit® E coating

Process Parameters	Batch MS-38	Batch MS-39
Inlet temperature (^{0}C)	29-33	28-32
Product temperature (^{0}C)	26-29	26-28
Air flow (bar)	0.15- 0.20	0.15- 0.20
Atomization (bar)	0.40- 0.55	0.40- 0.55
Spray rate (g/min)	0.20- 0.60	0.50- 0.90

Table 4.3.43: Composition for selection of process parameters for MH-Eudragit® E coating

Sr. No.	Ingredients	Batch MH-31 and MH-32
		mg/unit
1	Celphere CP 203	50.00
2	MH	16.85
3	PVP K30	1.75
4	Eudragit® RS	8.59
5	Eudragit® RL	1.52
6	TEC	1.12
7	Talc UM	5.17
8	Distilled Water	q.s.
9	Iso Propyl Alcohol	q.s.
	Total	85.00
10	Eudragit® E	7.23
11	Talc-UM	1.28
12	Acetone	q.s.
13	Iso Propyl Alcohol	q.s.
	Total	93.50

Table 4.3.44: Process parameters for MH-Eudragit® E coating

Process Parameters	Batch MH-31	Batch MH-32
Inlet temperature (^{0}C)	27-32	27-33
Product temperature (^{0}C)	26-29	26-28
Air flow (bar)	0.15- 0.20	0.15- 0.20
Atomization (bar)	0.40- 0.55	0.40- 0.55
Spray rate (g/min)	0.20- 0.60	0.50- 0.90

4.3.16.2 Solid content

Trials were taken to optimize the solid content of the Eudragit® E layering solution. Accordingly, trials were taken with 6 % and 8% w/w solid content for MS (Batch MS-40 and MS-41) (Table 4.3.45) and MH (Batch MH-33 and MH-34) (Table 4.3.46) using optimized process parameters of batch MS-38 and MH-31 respectively.

Table 4.3.45: Selection of solid content for MS-Eudragit® E coating

Sr. No.	Ingredients	Batch MS-40	Batch MS-41
		mg/unit	mg/unit
1	Celphere CP 203	50.00	50.00
2	MS	18.06	18.06
3	Ethyl cellulose 10 cps	13.00	13.00
4	Hydroxy propyl cellulose EXF	1.44	1.44
5	Distilled Water	q.s.	q.s.
6	Iso Propyl Alcohol	q.s.	q.s.
	Total	82.50	82.50
7	Eudragit® E	8.25	8.25
8	Talc-UM	1.24	1.24
9	Acetone	q.s.	q.s.
10	Iso Propyl Alcohol	q.s.	q.s.
	Total	90.75	90.75
	Solid content	6 %	8 %

Table 4.3.46: Selection of solid content for MH-Eudragit® E coating

Sr. No.	Ingredients	Batch MH-33	Batch MH-34
		mg/unit	mg/unit
1	Celphere CP 203	50.00	50.00
2	MH	16.85	16.85
3	PVP K30	1.75	1.75
4	Eudragit® RS	8.59	8.59
5	Eudragit® RL	1.52	1.52
6	TEC	1.12	1.12
7	Talc UM	5.17	5.17
8	Distilled Water	q.s.	q.s.
9	Iso Propyl Alcohol	q.s.	q.s.
	Total	85.00	85.00
10	Eudragit® E	7.23	7.23
11	Talc-UM	1.28	1.28
12	Acetone	q.s.	q.s.
13	Iso Propyl Alcohol	q.s.	q.s.
	Total	93.50	93.50
	Solid content	6 %	8 %

Evaluation of Eudragit® E coated pellets

The Eudragit® E coated pellets from optimized batches **MS-40** and **MH-33** were evaluated on the basis of percentage yield, drug content, micromeritic properties, DSC and drug release study.

Particle size distribution

The particle size distribution was determined by a sieve analysis method [22]. A sample quantity of 10g pellets was placed on the sieve nest comprising ASTM standards sieve numbers 30, 35, 40, 60 and pan arranged in sequential order. The assembly was placed over the sieve shaker and operated for 10 min. The weight of pellets retained on each sieve was determined.

Morphology

The surface morphology of the final optimized pellets was analyzed by Scanning Electron Microscopy (SEM) (JSM 5610 LV, Jeol, Tokyo, Japan). Samples were prepared by placing the pellets on a double adhesive carbon tape, which was stuck to a copper stub and the photomicrographs were taken at acceleration voltage of 20 kV, chamber pressure of 0.6 mm Hg with original magnification of 100 and 550X [23].

Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded (procedure similar to section 4.2.1.3) to check crystallanity for both the drugs in final pellets.

Micromeritic properties

Bulk density

Apparent bulk density was determined by placing pellets into graduated 25mL measuring cylinder and measuring the bulk volume and weight on as is basis [24]. Bulk density was calculated by following formula:

$$\text{Bulk density (g/mL)} = \frac{\text{Weight (g)}}{\text{Bulk volume (mL)}}$$

Tapped density

Tapped density was evaluated using tap density apparatus (Electrolab, India). Tapped density was determined by placing the same graduated cylinder filled with the pellets used for bulk density determination, into the tapped density tester. Initially the cylinder was tapped for 500 times and the tapped volume measured, to the nearest graduated unit, V_a. The tapping was repeated for an additional 750 times and the tapped volume was measured to the nearest graduated unit, V_b. If the difference between the two volumes is less than 2%, V_b is the final tapped volume, V_f. The taps were repeated in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. The tapped density was calculated by following formula [1]

$$\text{Tapped density (g/mL)} = \frac{\text{Weight (g)}}{\text{Tapped volume } V_f \text{ (mL)}}$$

Hausner's ratio

The Hausner's ratio is used to measure the degree of densification which could result

from vibration of the feed hopper[24]. Hausner's ratio (Table 4.3.48) was calculated from the ratio of bulk density and tapped density using following formula:

$$\text{Hausner's ratio} = \frac{\text{Bulk density (g/mL)}}{\text{Tapped density (g/mL)}}$$

Compressibility Index

Compressibility index measures of the propensity of a powder to be compressed. As such, it is a measure of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index (Table 4.3.47). Compressibility Index was calculated by following formula:

$$\text{Compressibility Index} = 100 \times \frac{V_0 - V_f}{V_0}$$

Table 4.3.47: Scale of flowability

Compressibility Index (%)	Flow Character	Hausner's Ratio
10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
> 38	Very, very poor	> 1.60

Angle of repose

The flowability of pellets was determined by calculating angle of repose (Table 4.3.48) by funnel method. A funnel (inner diameter of stem=10 mm) was fixed at a height of 2 cm over the platform. Sample quantity of 10 g was slowly passed along the wall of the funnel till the tip of the pile formed, just touches the stem of the funnel. A circle was drawn around the base of the pile and the radius of the powder cone was measured [24]. Angle of repose was calculated from the average radius using the following formula:

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose, h = height of the pile, r = average radius of the powder cone.

Table 4.3.48: Flow properties and corresponding angle of repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair- aid not needed	36–40
Passable- may hang up	41–45
Poor- must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	> 66

Mechanical strength

The pellets must possess sufficient mechanical strength so as to withstand the mechanical shocks encountered during various operating stages like coating in the FBP, filling into capsules or sachets and during transportation. The friability test was performed by using friability test apparatus (Electrolab, India) [25]. In this test accurately weighed quantity of pellets (6 g) was placed in the friability tester and rotated at the speed of 25 rpm for 10 min. After completion of test the pellets were placed on sieve number 100 to remove fine powder (if any) and the final weight was determined. Friability was calculated using following formula:

$$\text{Friability } (\%) = \frac{(\text{Initial weight - Final weight})}{\text{Initial weight}} \times 100$$

Drug release studies

Procedure described in section 4.3.7 was used to determine the drug release for MS and MH respectively.

To identify the mechanism and kinetics of drug release, various release models viz zero order (Eq. 4.3.1), first order (Eq. 4.3.2), and Higuchi model (Eq. 4.3.3) were applied. Regression coefficient (r^2) was calculated to identify the best-fit model.

Zero Order equation

$$Q_t = Q_0 + K_0 t \qquad \text{(Eq. 4.3.1)}$$

First Order equation

$$\ln Q_t = \ln Q_0 + K_1 t \qquad \text{(Eq. 4.3.2)}$$

Higuchi model

$$Q_t = K_H\sqrt{t} \quad \text{(Eq. 4.3.3)}$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_0 is the zero order release constant, K_1 is the first order release constant, K_H is Higuchi dissolution constant [26].

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Formulation Development (MUPS)

Part B: Results & Discussion

Chapter 4

4.4 Preformulation

4.4.1 Authentication of drugs: Metoprolol Succinate and Metformin HCl

4.4.1.1 UV spectroscopy

The solutions containing 10µg/mL MS and MH in pH 6.8 Phosphate Buffer were scanned and wavelength maxima (λ_{max}) were found to be 274 nm and 233 nm respectively, (Figure. 4.4.1 and 4.4.2) which were found to be similar to the reported values [1].

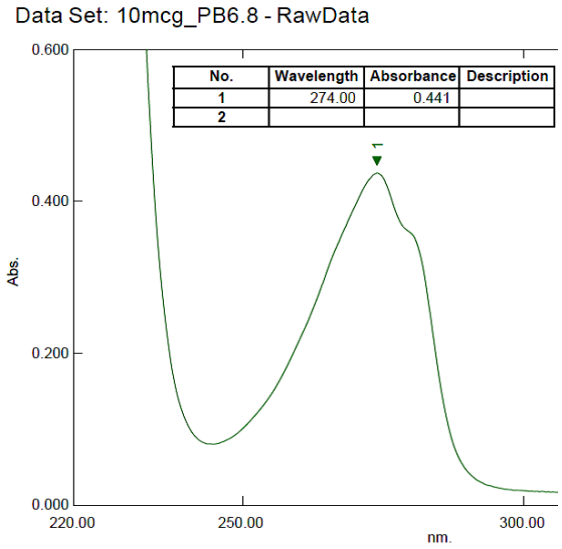

Figure 4.4.1: UV spectrum of Metoprolol succinate

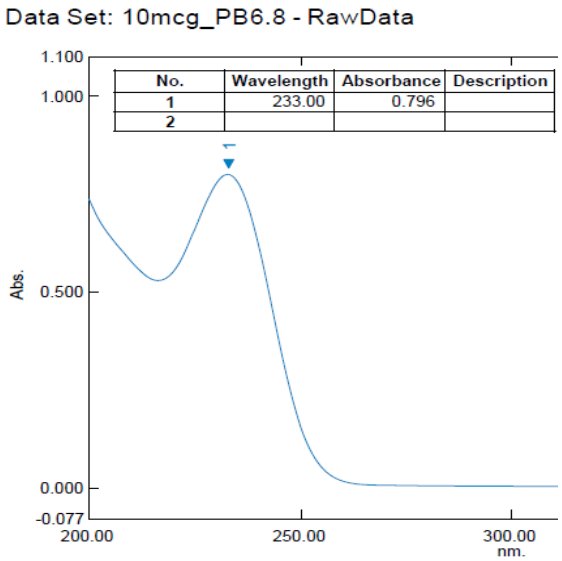

Figure 4.4.2: UV spectrum of Metformin Hydrochloride

4.4.1.3 Fourier transform infrared (FTIR) spectroscopy

The IR spectra of both the drugs were recorded (Figure 4.4.3 and 4.4.4) and the functional groups were interpreted as per the reported chemical structure of the drugs [1].

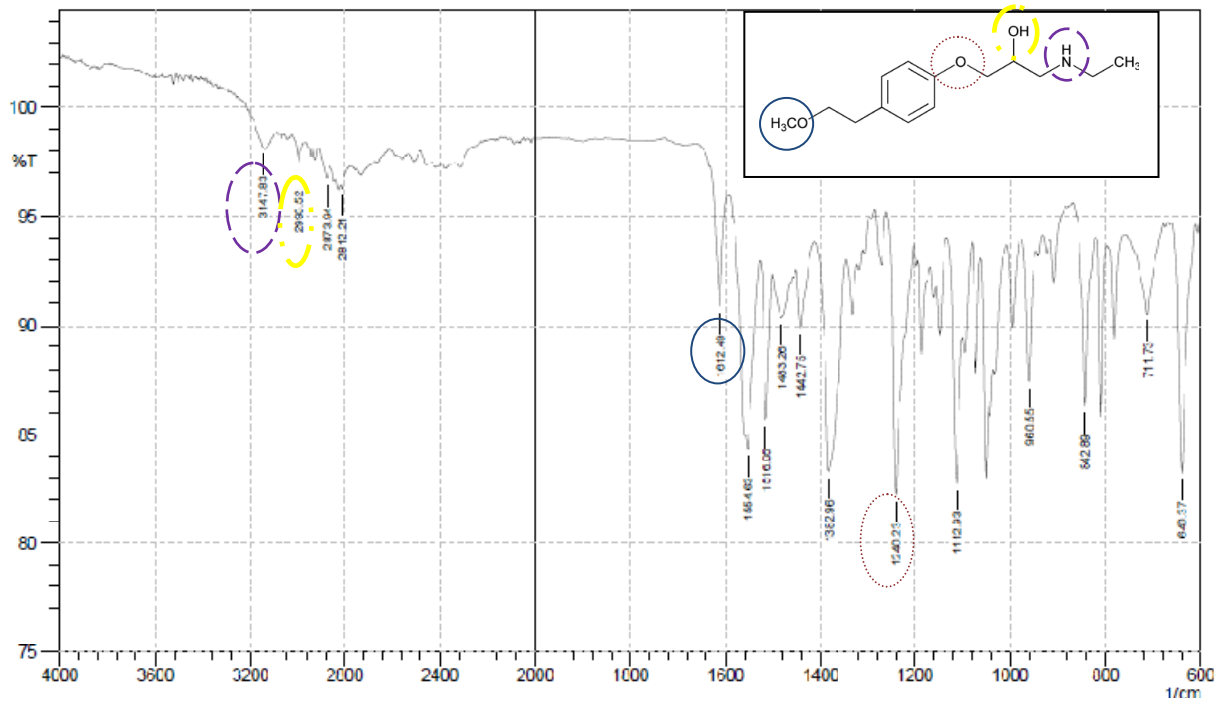

Figure 4.4.3: IR spectrum of Metoprolol succinate

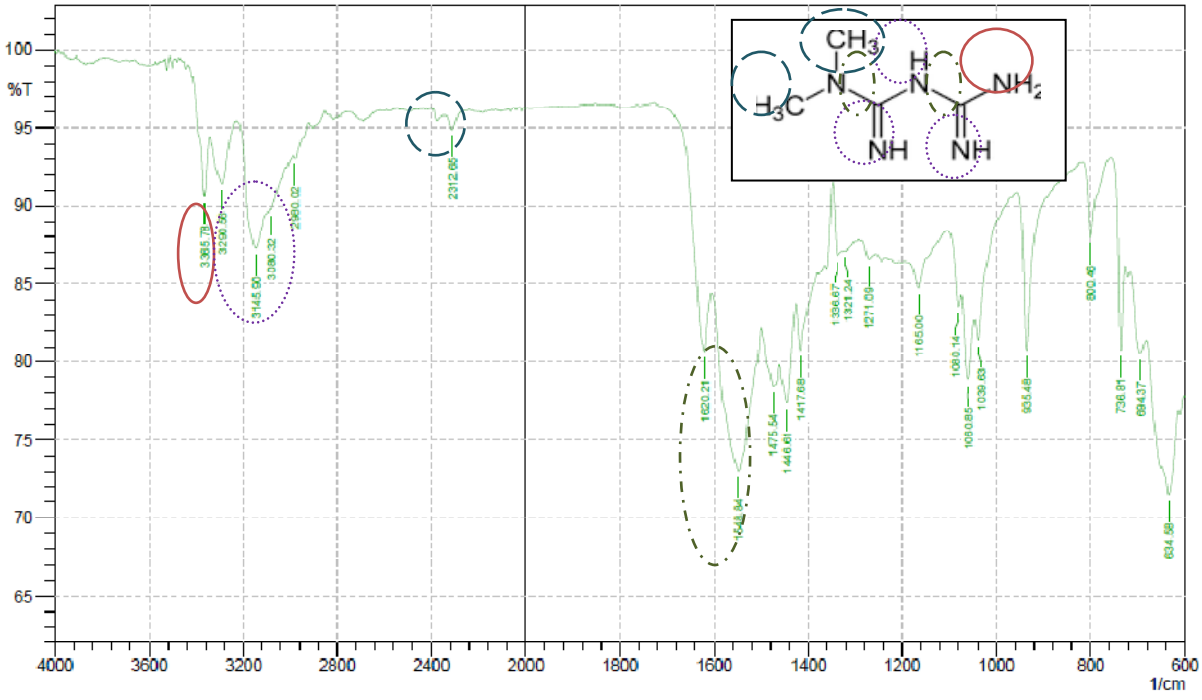

Figure 4.4.4: IR spectrum of Metformin hydrochloride

Principal peaks obtained in the IR spectra of MS and MH along with their corresponding functional groups at their respective wave numbers [1] are as shown in Table 4.4.1 and 4.4.2 respectively. Similar functional groups are reported in USP monographs [1] (Metoprolol succinate- (isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate), (Metformin hydrochloride- N, N-dimethylimidodicarbonimidic diamide). Hence, confirming the structure of MS and MH.

Table 4.4.1: Functional groups along with their wave numbers for MS

Functional Groups	Wave number (cm^{-1})
-NH (Primary amine)	3147
-OH	2993
-OCH3	1612
-O- (ether)	1240

Table 4.4.2 Functional groups along with their wave numbers for MH

Functional Groups	Wave number (cm^{-1})
Primary amine (-NH2)	3385
Secondary amine (-NH)	3290-3080
C=N (s)	1620 and 1548
-CH3	2312

4.4.1.3 Differential scanning calorimetry (DSC)

DSC thermograms (Figure 4.4.5 and 4.4.6) showed sharp endothermic peaks at 137.33^0C and 232.67^0C for MS and MH respectively which corresponds to their melting point similar to the reported value [2].

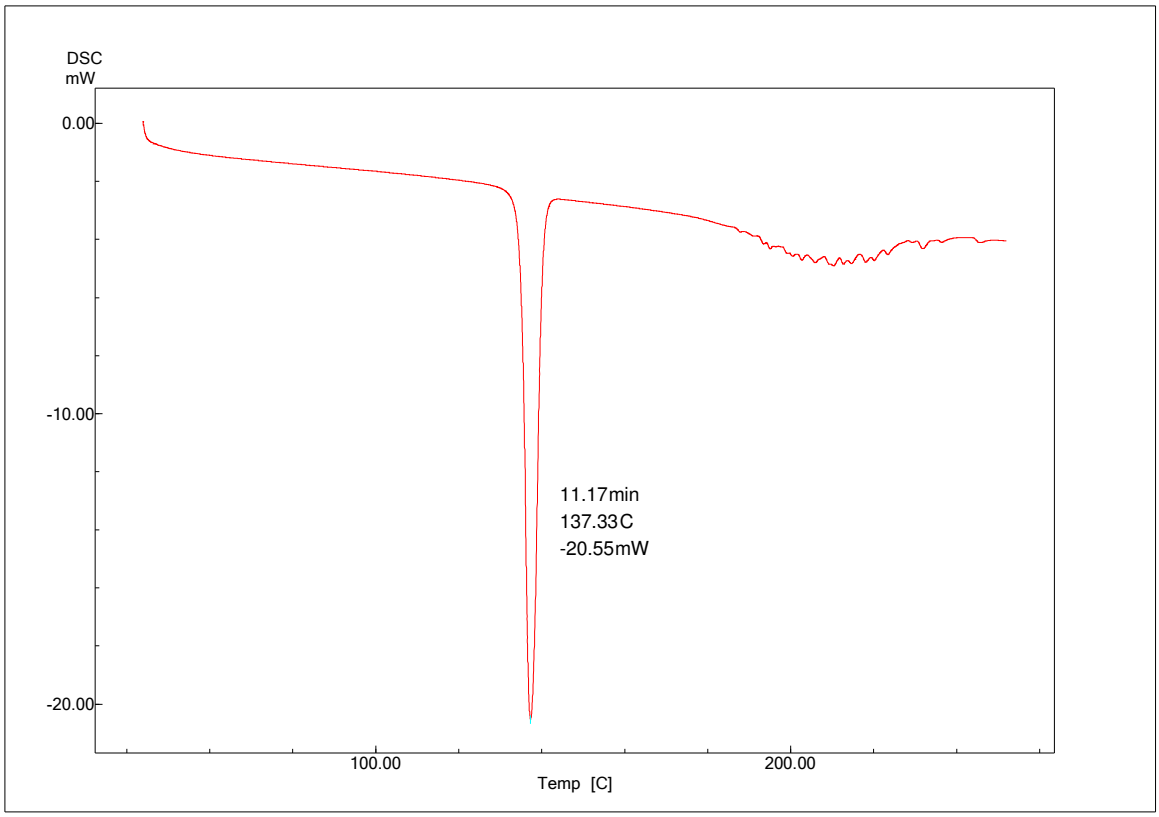

Figure 4.4.5: DSC thermogram of Metoprolol succinate

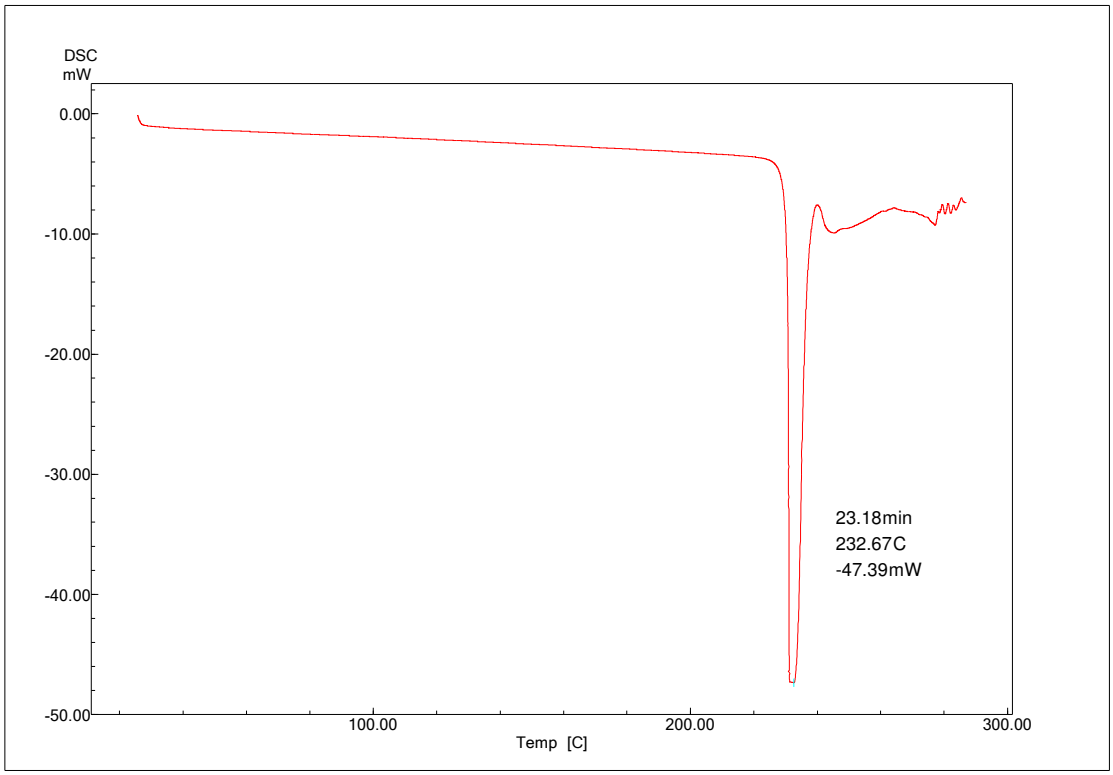

Figure 4.4.6: DSC thermogram of Metformin hydrochloride

4.4.1.4 Melting point determination

The melting points of MS and MH were found to be in the range of 136-138^{0}C and 232-236^{0}C respectively which matched with their reported value [2].

4.4.2 Drug-Excipients compatibility study

4.4.2.1 Physical observation

No physical change was observed for the placebo blend of MS with excipients (mentioned in Table 4.4.3) and MH with excipients (mentioned in Table 4.4.4) which were kept for compatibility study. Therefore it was concluded that both the drugs and their respective excipients were physically compatible with each other.

Sr. No.	Physical mixture	Visual observation	
		Initial	After 14 days
1	Metoprolol succinate+ Celphere	White to off white powder	No change
2	Metoprolol succinate + PVP K 90	White to off white powder	No change
3	Metoprolol succinate + Ethyl Cellulose 10 cps	White to off white powder	No change
4	Metoprolol succinate + Hydroxyproyl Cellulose EXF	White to off white powder	No change
5	Metoprolol succinate + Eudragit® E	White to off white powder	No change

Table 4.4.4: Physical compatibility study of MH with excipients

Sr. No.	Physical mixture	Visual observation	
		Initial	After 14 days
1	Metformin hydrochloride+ Celphere	White to off white powder	No change
2	Metformin hydrochloride + Eudragit® RS 100	White to off white powder	No change
3	Metformin hydrochloride + Eudragit® RL 100	White to off white powder	No change
4	Metformin hydrochloride + Triethyl Citrate	White to off white lumps	No change
5	Metformin hydrochloride + Eudragit® E	White to off white powder	No change
6	Metformin hydrochloride + Talc UM	White to off white powder	No change

4.4.2.2 Fourier Transform Infrared spectroscopy

Individual IR spectra of MS, placebo blend and MS + Placebo blend are shown in figures 4.4.7, 4.4.8, and 4.4.9 respectively. Similarly, IR spectra of MH, placebo blend and MH + Placebo blend are shown in figures 4.4.10, 4.4.11, and 4.4.12 respectively. It was observed that the principal peaks of MS and MH as shown in Table 4.4.1 and 4.4.2 respectively, were present in the spectra of pure drugs, placebo blend are not changed in MS + placebo blend and MH + placebo blend (Table 4.4.5 and Table 4.4.6) respectively, thereby suggesting the absence of any significant interaction between the drug and excipients used in the formulations.

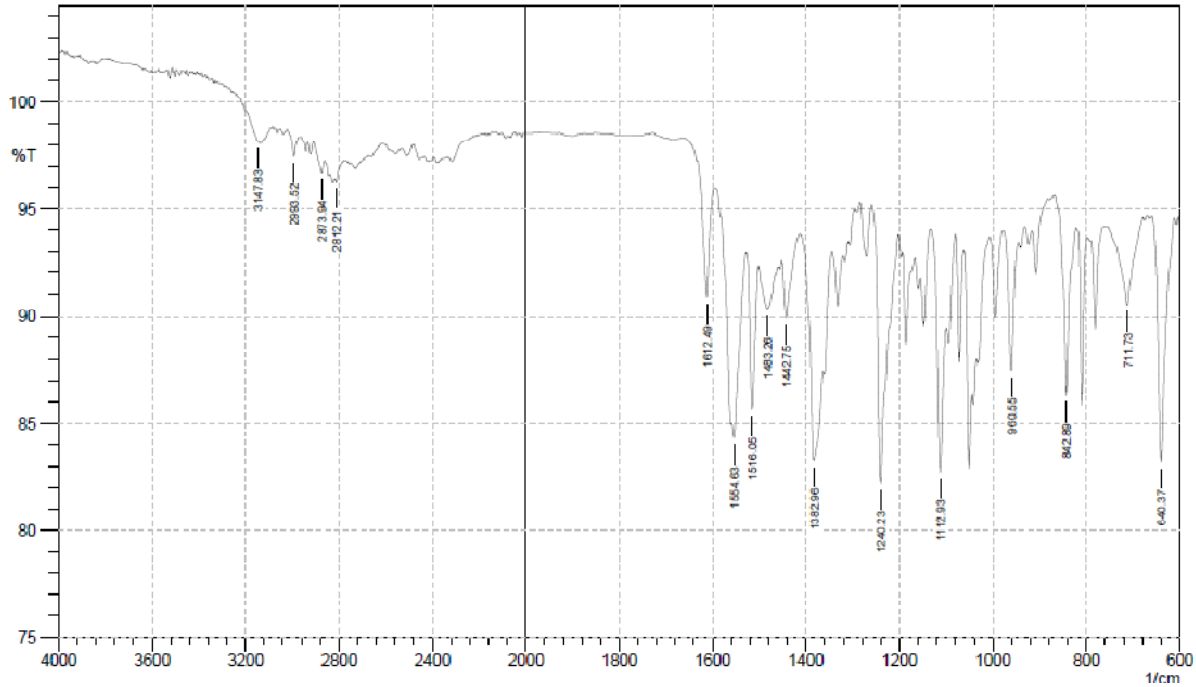

Figure 4.4.7: IR spectrum of Metoprolol succinate

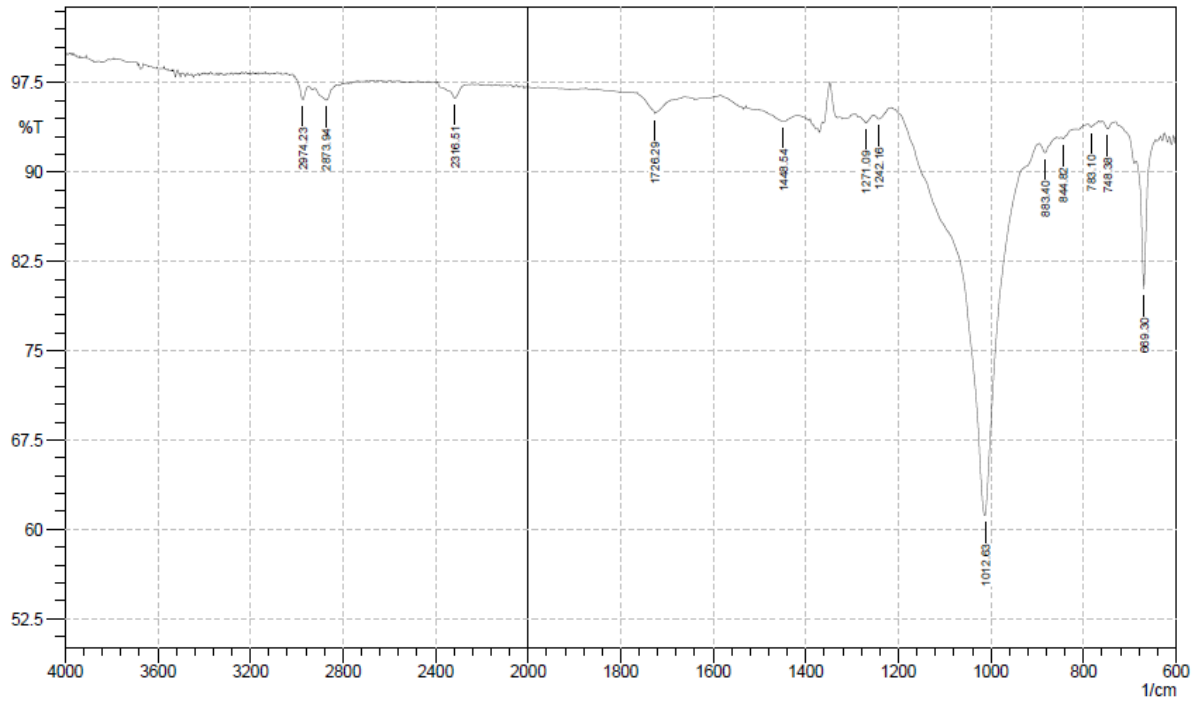

Figure 4.4.8: IR spectrum of placebo blend

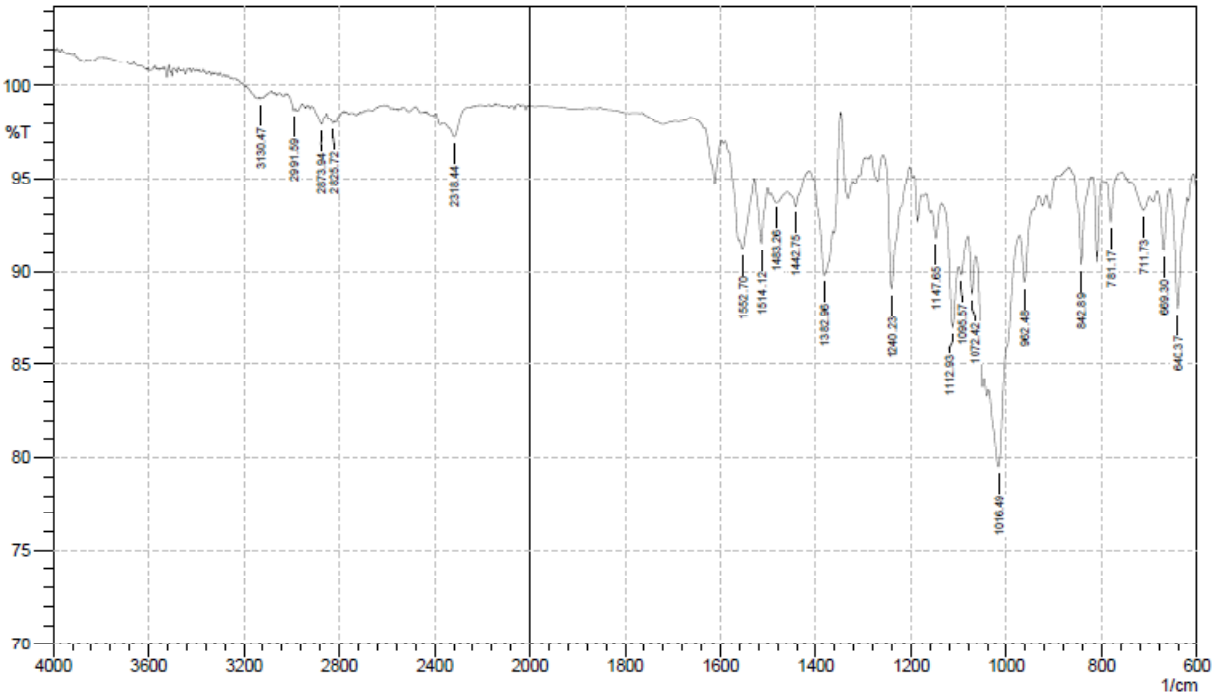

Figure 4.4.9: IR spectrum of Metoprolol succinate + placebo blend

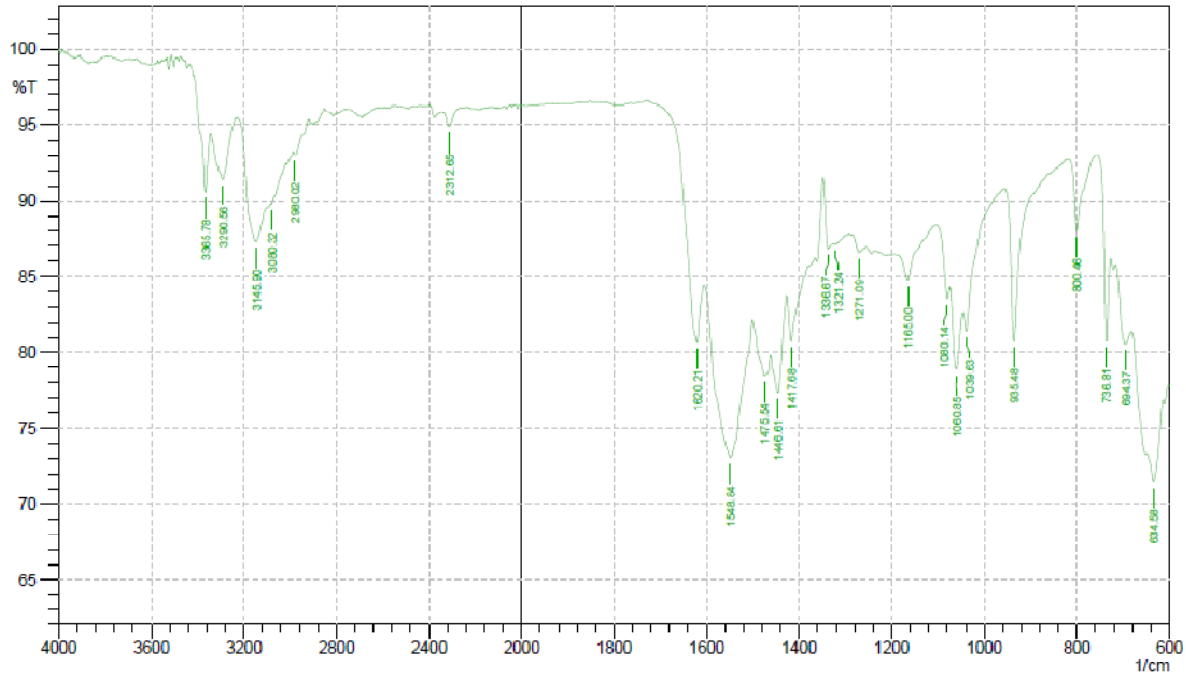

Figure 4.4.10: IR spectrum of Metformin HCl

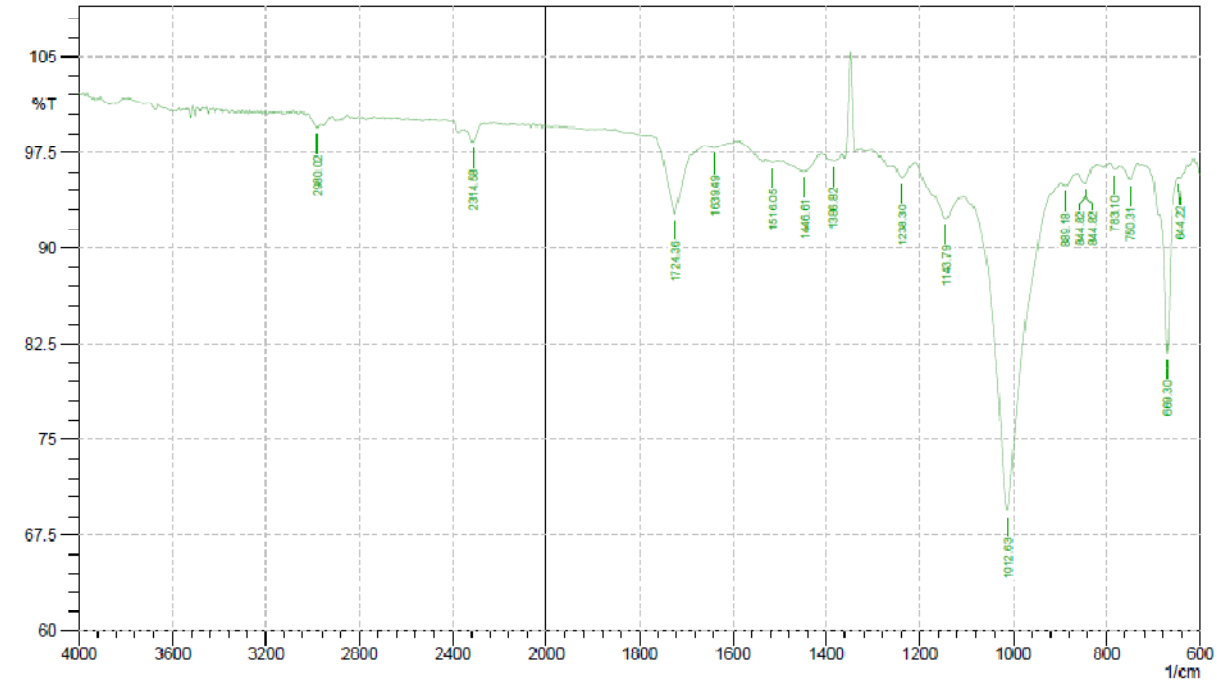

Figure 4.4.11: IR spectrum of placebo blend

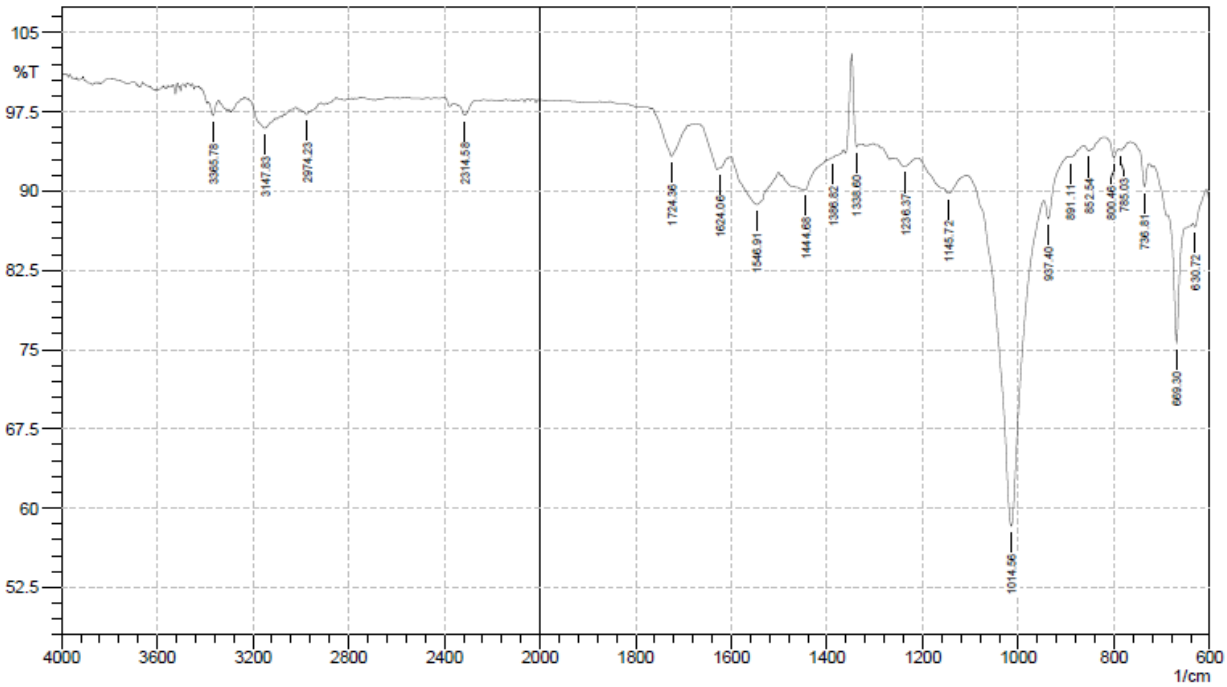

Figure 4.4.12: IR spectra of Metformin HCl + placebo blend

Table 4.4.5: Principal Peaks in IR spectra (MS)

Sample	**Wave No. (cm^{-1})**
Metoprolol succinate	3147, 2993, 1612, and 1240
Placebo blend	2318, 1240 and 1016
MS + Placebo blend	3130, 2991 and 1240

Table 4.4.6: Principal peaks in IR spectra (MH)

Sample	**Wave numbers (cm^{-1})**
Metformin hydrochloride	3385, 2312 and 1548
Placebo blend	1726, 1234 and 1014
MH + Placebo blend	3365, 1624 and 1548

4.4.2.3 Differential Scanning Calorimetry (DSC)

Sharp endothermic peaks at 137.76°C and 233.13°C were observed for both MS and MH in Drug + Placebo blend (Figure 4.4.13 and Figure 4.4.14) respectively. There were no significant changes in melting point, peak shape, area and peak location with that of individual pure drugs (Figure 4.4.5 and Figure 4.4.6). Hence, it can be confirmed that there is no incompatibility among respective drugs and Excipients.

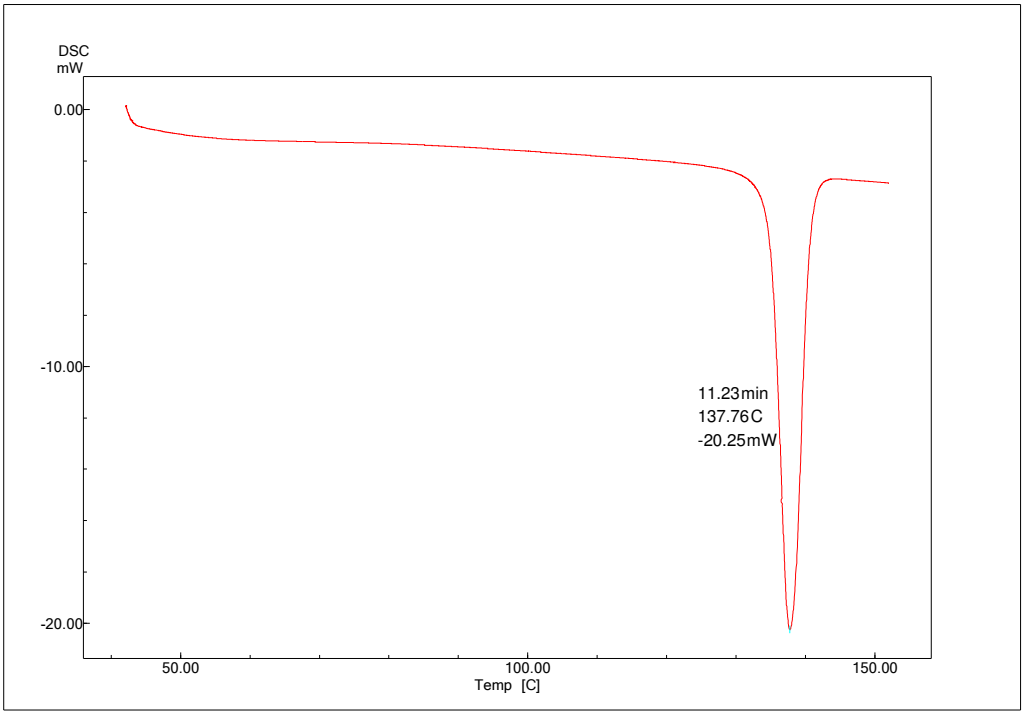

Figure 4.4.13: DSC thermogram of Metoprolol succinate and placebo blend

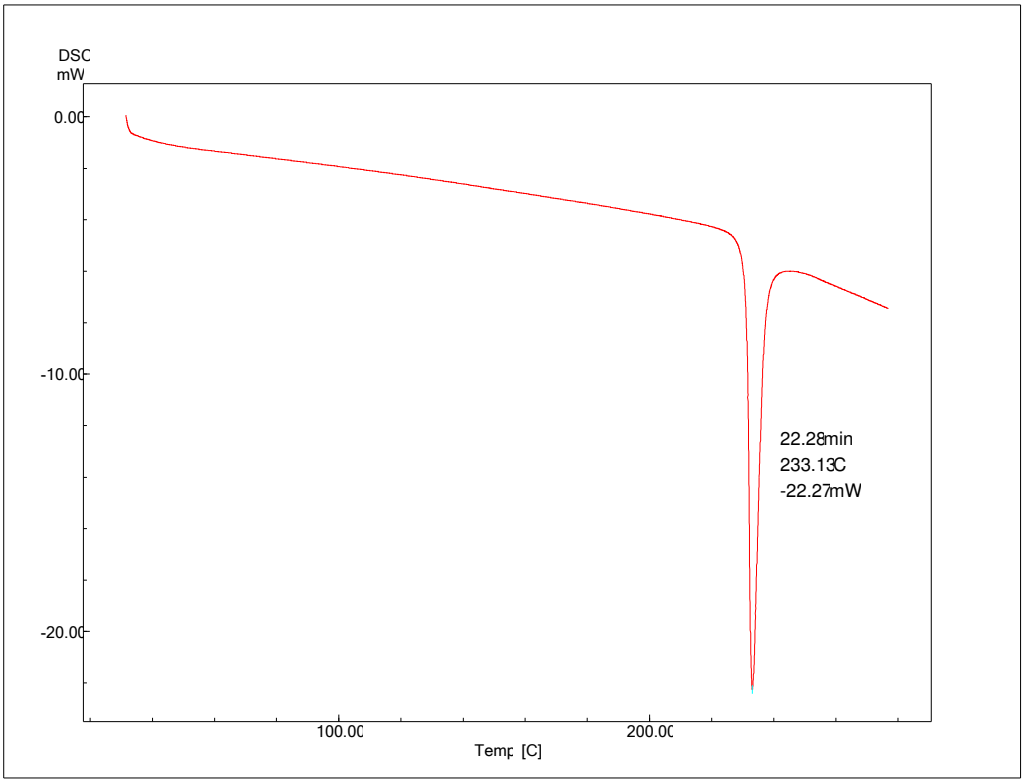

Figure 4.4.14: DSC thermogram of Metformin HCl and placebo blend

4.5 Formulation Development

4.5.1 Quality Target Product Profile (QTPP)

The QTPP provided a target for formulation development of MS and MH MUPS meeting all the quality attributes as mentioned in Table 4.3.1 and Table 4.3.2 and the FMEA analysis described the effect of formulation attributes upon the CQAs.

4.5.2 Failure Mode and Effects Analysis (FMEA)

Based upon FMEA analysis, RPN (Table 4.5.1) for extent of CR coating and Drug: Polymer was found to be highest (RPN-392) for both the drugs. Hence these were thoroughly investigated and optimized by using DoE tool. Also it was found that the core pellet size, core pellet quantity and the drug layering technique had medium impact upon the CQA (RPN 144-224) and hence were investigated by taking different trials. The API particle size had the least RPN (RPN 5) and hence was not investigated further.

Table 4.5.1: Risk assessment by FMEA analysis to identify criticality of failure modes

Formulation component	Failure mode	Failure effects	S	Potential causes or root of failure	O	Detectability method or control	D	RPN
API particle size	Higher particle size	Drug release	1	Availability	1	Dissolution	5	5
Core pellet size	Incorrect grade chosen	Drug release	8	Labeling error	4	Dissolution	7	224
Core pellet quantity	Incorrect quantity dispensed	Drug release, Assay	8	Operator's error	4	Dissolution, Assay	7	224
Drug layering technique	Incorrect technique chosen	Drug release	8	Operator's error, Wrong manufacturing instruction	3	Dissolution, Assay	6	144
Extent of CR coating	Incorrect extent	Drug release, Assay	8	Operator's error, machine failure	7	Dissolution, Assay	7	392
Drug: Polymer	Incorrect concentration	Drug release, Assay	8	Operator's error	7	Dissolution, Assay	7	392

4.5.3 Selection of core material

Various core materials were shortlisted for preparation of the pellets. Sugar spheres have greater water solubility which leads to changes in drug release and coating hydration due to the strong osmotic activity [3]. This results in faster and higher water uptake which consequently increases the tensile stress of the membrane and dilute the drug concentration inside the pellets [4]. After the sugar is released, the fluid filled channels also show a higher sensitivity to mechanical stress which is not desirable for sustained release products [3] Moreover, intake of sucrose is not desired in most medical cases like diabetes, cardio vascular disorders and so on.

On the other hand, MCC is insoluble in water. Use of MCC spheres could be advantageous especially in case of aqueous or hydro-alcoholic coatings. Celphere enables greater accuracy and consistency in drug layering and coating as it is highly spherical with narrow particle size distribution. Moreover, it's high mechanical strength and low friability allows it to withstand the rigors of Wurster coating process. Hence it

was decided to use microcrystalline cellulose spheres- Celphere, as inert carrier in the proposed formulations for both the drugs.

4.5.4 Selection of load

Initial load affects the efficiency of the coating process. When the inlet air velocity exceeds the settling velocity of the bed, pellets start to fluidize [5]. A sub optimal load would lead to deposition of the coating droplets on the Wurster column thereby leading to sticking of pellets on it, thereby lowering the overall process efficiency. A load above optimum capacity would be difficult to fluidize and coat. Thus initial load plays a crucial role in formulation development of products prepared by fluid bed technology.

As mentioned in table 4.5.2 different results were observed for different loads at same fluidized air volume. In the present study, the initial substrate would be layered with drug, CR polymer and Eudragit® E polymer. These coating operations would increase the weight of initial substrate. Thus load selected should be such that it would be suitable to execute all the stages of coating. Hence it was decided to use 40g as initial load for fabrication of MUPS for both the drugs.

Table 4.5.2: Selection of load for MUPS

Batch no.	Load (g)	Observation
MS-1	20	Vibrant movement of the bed. Wurster column was not completely filled with pellets. Pellets touched the filters present at the top of the assembly.
MS-2	40	Good movement of the bed. Wurster column was filled with the pellets adequately. Fountain pattern was observed.
MS-3	80	Good movement of the bed. Wurster column was completely filled with the pellets. Fountain pattern was observed.
MS-4	120	Slight movement of the bed. No fountain pattern was observed.
MS-5	160	Very slight movement of the bed.

4.5.5 Drug Loading

In the present study, bottom spray technique was used for drug (MS as well as MH) loading. For efficient drug loading process, suitable process parameters, solid content, binder and binder concentration were selected and optimized.

4.5.5.1 Selection of process parameters

As the drug solution is sprayed onto the product bed, the droplets get deposited on the core pellets. If the drying conditions and fluid dynamics are favourable, these droplets spread evenly on the surface. This is followed by the drying phase which allows the dissolved materials to crystallize and form solid bridges between the core and initial drug layer as well as among the successive layers which depends on the selection of process parameters [6].

MS process parameters

In case of Batch MS-6, agglomeration was observed during the coating process. This might be due to the low atomization air pressure and low product temperature, which together caused inefficient drying. Agglomeration was also observed in batch MS-7 taken with increased atomization air pressure, which might be due low product temperature. Hence batch MS-8 was prepared with increased product temperature and decreased spray rate. No agglomeration was observed. In order to further investigate the effect of product temperature on the process efficiency, batch MS-9 was taken with increased product temperature. White colored fine powder were observed in the final yield (Table 4.5.3). This might be due to rapid drying of the solvent due to increased product temperature. Hence process parameters used in Batch MS-8 (Table 4.3.6) were considered to be optimized and selected for further drug layering batches for MS.

Table 4.5.3: Selection of process parameters for MS loading

Batch	**Batch MS- 6**	**Batch MS- 7**	**Batch MS- 8**	**Batch MS-9**
Percentage yield (%)	37.2± 4.7	42.1± 3.6	84.1± 2.7	67.6± 2.5
Observation	Agglomeration	Agglomeration	No Agglomeration	Fines

MH Process parameters

Agglomeration was observed during the coating process of batch MH- 1. This might be due to the high spray rate and low product temperature, which together caused inefficient drying. The low product temperature may have led to formation of liquid bridges instead of solid bridges between the core and coating droplets, which caused agglomeration, resulting in low yield [5]. No agglomeration was observed in batch MH-2 (Table 4.5.4) prepared with decreased spray rate and increased atomization air pressure, air flow, inlet and product temperature.

In order to further investigate the effect of product temperature on the process efficiency, Batch MH-3 was taken with increased inlet temperature. White colored fine powder was observed in the final yield. This might be due to rapid drying of the solvent due to increased product temperature. Low yield was due to rejection of fines that passed through the lower mesh size (ASTM 60 mesh) upon sifting of pellets after completion of coating. Hence process parameters used in batch MH-2 (Table 4.3.8) were considered to be optimized and selected for further drug loading batches for MH.

Table 4.5.4: Selection of process parameters for MH loading

Batch	**Batch MH- 1**	**Batch MH- 2**	**Batch MH- 3**
Percentage yield (%)	40.8± 2.3	89.6± 2.8	61.1± 3.9
Observation	Agglomeration	No Agglomeration	Agglomeration

4.5.5.2 Solvent System

Organic solvents offer the advantages like solvation of most of the drugs and faster spray rate. However use of complete organic solvents cause deterioration of the environment and generate static charge (particularly in dry conditions) due to continuous attrition during coating process. Since the drugs (MS and MH) and binder (PVP) are readily soluble in water, aqueous drug loading becomes the primary choice. Use of aqueous based coating is preferred for its minimal damage to the environment, but sticking may be observed in humid conditions [7]. To combine the advantages offered by each system while overcoming their limitations, it was decided to go further with a hydroalcoholic solvent system- IPA: Water for both the drug (MS and MH) loading processes.

4.5.5.3 Solid content

Solid content of the coating solution/dispersion dictates the ease with which it can be sprayed onto the substrate. In case of low solid content, lengthening of process time occurs while higher solid content may lead to agglomeration. Hence, to identify the solid content at which smooth process occurs, trials were taken at different levels of solid content.

Selection of solid content for MS loading

In batches MS-10, MS-11 and MS-12 the solid content of drug loading solution was kept at 10, 15 and 20% w/w respectively. In batch MS-10 no agglomeration occurred, but fine white powder was observed over the pellet bed after completion of coating due to rapid evaporation of the solvent leading to lower yield (63.9± 2.6%). Also, use of dilute (low solid content) solutions is discouraged due to lengthening of process time.

Hence it was decided to increase the solid content to 15 % w/w in Batch MS-11. No fine powder was observed, which suggested that the processing conditions and the solid content of the drug loading solution selected were appropriate (Yield achieved = 81.8± 2.1%).

In order to check whether these conditions can be improved further, batch MS-12 with higher solid content (20% w/w) was prepared, but the resultant solution was difficult to spray and agglomeration occurred during the process. This might be due to the increase in viscosity of the solution. Lower yield (49.4± 4.0%) was achieved due to rejection of agglomerates retained on the upper mesh size (ASTM 24 mesh). Considering higher yield and ease of processing (process without agglomeration and fines), solid content of 15 % w/w was selected for MS loading solution.

Table 4.5.5: Selection of solid content for MS loading solution

Batch	**Batch MS-10**	**Batch MS-11**	**Batch MS-12**
Percentage yield (%)	63.9± 2.6	81.8± 2.1	49.4± 4.0
Observation	Fines	No Agglomeration	Agglomeration

Selection of solid content for MH loading

In Batches MH-4, MH-5 and MH-6 the solid content of drug loading solution was kept at 30, 20 and 10% respectively. In batch MH-4 the drug loading solution was difficult to spray due to recurrence of agglomeration. So batch MH-5 was taken with 20% solid content but still agglomeration persisted. The agglomeration in these two batches might be due to high viscosity of the drug solution.

No agglomeration was observed in Batch MH-6, taken with 10% solid content. Satisfactory yield of 90.2± 2.1% was achieved. Hence a solid content of 10 % w/w was selected for drug loading solution.

Table 4.5.6: Results for selection of solid content for MH loading solution

Batch	**Batch MH-4**	**Batch MH-5**	**Batch MH-6**
Percentage yield (%)	13.4± 3.5	21.8± 2.2	90.2± 2.1
Observation	Agglomeration	Agglomeration	No Agglomeration

4.5.5.4 Binder selection

In order to increase the binding efficiency of the drug with the core pellet, different binders were evaluated for both the drug loading solutions.

Binder selection in MS loading

Batches MS-13, MS-14, MS-15 and MS-16 were taken with HPMC 3cps, HPMC 5cps, PVP-K30 and PVP K90 respectively. In case of Batch MS-13, MS-14 and MS-15 no agglomeration or fines were observed. It was observed that as the viscosity of HPMC increased from 3 to 5 cps, binding efficiency of the drug increased, which was also reflected in the percentage yield as well as assay value (Table 4.5.7). In case of batch MS-16 with PVP K-90, agglomeration occurred due to higher viscosity of the coating solution. Highest yield (90.9± 2.3%) and drug content (93.3± 2.1%) was achieved in batch MS-15 containing PVP K30. Hence PVP-K30 was selected as the binder for drug (MS) loading stage.

Table 4.5.7: Results for binder selection batches for MS

	Batch MS-13	**Batch MS-14**	**Batch MS-15**	**Batch MS-16**
Percentage yield (%)	83.1± 2.4	86.1± 2.1	90.9± 2.3	29.7± 3.8
Assay (%)	82.6 ± 1.9	88.2 ± 1.5	93.3 ± 2.1	26.5± 1.8
Observation	No Agglomeration	No Agglomeration	No Agglomeration	Agglomeration

Binder selection in MH loading

Batches MH-7, MH-8, MH-9 and MH-10 were taken with HPMC 3cps, HPMC 5cps, PVP-K30 and PVP K90 respectively. In case of Batch MH-7, MH-8 and MH-9 with HPMC 3cps, HPMC 5cps and PVP-K30 respectively, no agglomeration or fines were observed. It was observed that as the viscosity of HPMC increased from 3 to 5 cps, binding efficiency of the drug increased, which was also reflected in the percentage yield as well as assay value (Table 4.5.8). In case of Batch MH-10 with PVP K-90, agglomeration occurred due to higher viscosity of the coating solution. Highest yield (90.2± 1.9%) and drug content (92.9± 1.1%) was achieved in Batch MH-9 containing PVP K30. Hence PVP-K30 was selected as the binder for drug (MH) loading stage.

Table 4.5.8: Results for binder selection batches for MH

	Batch MH-7	**Batch MH-8**	**Batch MH-9**	**Batch MH-10**
Percentage yield (%)	80.3± 2.3	85.6± 2.7	90.2± 1.9	34.4± 4.3
Assay (%)	81.6 ± 1.8	86.2 ± 1.6	92.9 ± 1.1	36.5± 0.8
Observation	No Agglomeration	No Agglomeration	No Agglomeration	Agglomeration

4.5.5.5 Selection of binder concentration

To select the level at which PVP-K30 is most efficient, various trials were taken at different PVP concentrations.

Selection of binder concentration for MS

For Batches MS-17 and MS-18 taken with 1.25 and 1.5mg PVP K30, the assay values were 93.3± 2.1% and 98.2 ±1.4% respectively. This suggests that the binding efficiency of MS increased with increase in concentration of the binder. This was also reflected from the percentage yield values which increased from 90.9% to 94.2% from batch MS-17 to batch MS-18. However, in case of Batch MS-19 with 1.75mg PVP K30, agglomeration occurred. This might be due to the higher viscosity of the MS solution. As no agglomeration or fines generation occurred and highest drug content (%) and percentage yield was achieved, 1.50 mg PVP K30 was selected as optimum level of binder.

Table 4.5.9: Results for optimization of binder concentration for MS MUPS

	Batch MS-17	**Batch MS-18**	**Batch MS-19**
Percentage yield (%)	90.9± 2.3	94.2± 2.4	31.1± 3.2
Assay (%)	93.3± 2.1	98.2± 1.4	29.9± 3.4
Observation	No Agglomeration	No Agglomeration	Agglomeration

Selection of binder concentration for MH

Batches MH-11 and MH-12 were taken with 1.25 and 1.5mg PVP K30 showed percentage yield values of 87.9± 2.3% and 90.2± 1.9% respectively. This suggests that the binding efficiency of MH increased with increase in concentration of the binder. This was also reflected from the assay values which increased from 88.3± 1.1% to 92.9 ±1.1% from batch MH-11 to batch MH- 12. In Batch MH-13 with 1.75mg PVP K30, the percentage yield and assay value were 96.1± 2.1 and 94.8± 2.4 respectively (Table 4.5.10). As no agglomeration or fines generation occurred and highest drug content (%) and percentage yield was achieved, 1.75mg PVP K30 was selected as optimum level of binder.

Table 4.5.10: Results for optimization of binder concentration for MH

	Batch MH-11	Batch MH-12	Batch MH-13
Percentage yield (%)	87.9± 2.3	90.2± 1.9	96.1± 2.1
Assay (%)	88.3± 1.1	92.9 ± 1.1	94.8± 2.4
Observation	No Agglomeration	No Agglomeration	No Agglomeration

4.5.6 Controlled release coating

4.5.6.1 Process Parameters

The coating process involves the deposition of successive layers over the substrate. As the coating solution is sprayed onto the product bed, the droplets deposit on the substrate and spread evenly, provided that the drying conditions and fluid dynamics are favorable. This is followed by the drying phase which allows dissolved materials to crystallize and form solid bridges between the substrate and successive layers. As the air flow increases the rate of drying increases and vice versa [6]. Hence different process parameters were studied.

Selection of process parameters for MS MUPS

In case of Batch MS-20, agglomeration was observed which might be due to high spray rate and low air flow which prevented the formation of solid bridges. This led to lower yield (27.9± 4.5%) due to retention of these agglomerates on the ASTM 24 sieve. Therefore batch MS-21 was taken with decreased spray rate and increased air flow in which no agglomeration was observed. The yield achieved was 89.6± 2.6%. The processing parameters (spray rate and air flow) were adequate to create the solid bridges between the successive coating droplets and layers. Hence it was decided to have the processing parameters of batch MS-21 (Table 4.3.16) in further Batches for CR coating stage of MS.

Table 4.5.11: Results for percentage yield for CR coating stage of MS MUPS

	Batch MS-20	Batch MS-21
Percentage yield (%)	27.9± 4.5	89.6± 2.6
Observation	Agglomeration	No Agglomeration

Selection of process parameters for MH MUPS

In batch MH-14, agglomeration was observed due to high spray rate, low air flow and atomization air pressure which prevented the formation of solid bridges and led to lower yield (32.6± 4.6%). Therefore batch MH-15 was taken with reduced spray rate, increased air flow and atomization air pressure in which no agglomeration was observed. The yield achieved was 87.1± 2.8%. The processing parameters (spray rate, air flow and atomization air pressure) were adequate to create the solid bridges between the successive coating droplets and layers. Hence it was decided to have the processing parameters of Batch MH-15 (Table 4.3.18) in further Batches for CR coating stage of MH.

Table 4.5.12: Results for percentage yield for CR coating stage of MH MUPS

	Batch MH-14	**Batch MH-15**
Percentage yield (%)	32.6± 4.6	87.1± 2.8
Observation	Agglomeration	No Agglomeration

4.5.6.2 Solid content

Selection of Solid content for MS

In case of batch MS-22 with 4 % w/w solid content, no agglomeration was observed which suggested that the processing conditions and the solid content of the CR coating solution selected were appropriate (Yield= 87.9± 2.8%). In order to check whether these conditions could be improved further, batch MS-23 with 6% w/w solid content was prepared, but agglomeration occurred during the process leading to lower yield (34.6± 3.4%). This agglomeration might be due to increase in viscosity due to increased solid content which rendered the solution difficult to spray. Hence a solid content of 4 % w/w was selected for CR coating on the basis of better yield and smooth processing (without any agglomeration and fines generation).

Table 4.5.13: Results for selection of solid content for CR coating stage of MS

	Batch MS-22	**Batch MS-23**
Percentage yield (%)	87.9± 2.8	34.6± 3.4
Observation	No Agglomeration	Agglomeration

Selection of Solid content for MH

In batch MH-16 with 4% w/w solid content, no agglomeration was observed which suggested that the processing conditions and the solid content of the CR coating solution selected were appropriate (Yield= 86.9± 3.2%). In order to check whether these conditions could be improved further, batch MH-17 with 6% w/w solid content was carried out, but agglomeration occurred during the process leading to decreased yield (32.5± 3.9%). This agglomeration might be due to increase in viscosity due to increased solid content which rendered the solution difficult to spray. Hence a solid content of 4 % w/w was selected for CR coating on the basis of better yield and smooth processing (without any agglomeration and fines generation).

Table 4.5.14: Results for selection of solid content for CR coating stage of MH MUPS

	Batch MH-16	**Batch MH-17**
Percentage yield (%)	86.9± 3.2	32.5± 3.9
Observation	No Agglomeration	Agglomeration

4.5.7 Selection of core pellet size

Selection of particle size is critical since it directly affects the drug release particularly in case of CR MUPS [8]. Based on this, it was decided to evaluate Celphere CP-102, CP-203 and CP305 for formulation development of both the drugs.

Selection of core pellet size for MS

Batches MS-24, MS-25 and MS-26 were taken with Celphere CP102, Celphere CP203 and Celphere CP305 respectively. In batch MS-24, processing of Celphere CP102 led to recurrent agglomeration during drug loading and CR coating while processing with Celphere CP 203 and Celphere CP 305 did not show such problems in batch MS-25 and MS-26 respectively. It was observed that during dissolution, the drug release (Table 4.5.15) was faster in case of CP 102 (100.1± 2.1 within 4h) as compared to CP 203 (101.5± 1.6 within 8h) (Figure 4.5.1). This was attributed to the greater surface area offered by the smaller sized particles of Celphere CP102 along with uneven coating (25%w/w) due to recurrent agglomeration during processing. The drug release was observed to be slower and sustained in case of Celphere CP 305 (100.3± 1.1% within 8h), but owing to its higher particle size, which might increase the rate of sedimentation

in case of controlled release powder for reconstitution or rupture of pellets in case of compression of controlled release orally disintegrating tablet (final dosage form for MUPS), it was decided to go further with Celphere CP 203.

Table 4.5.15: Results for selection of core pellet size for MS MUPS

	Batch MS-24	**Batch MS-25**	**Batch MS-26**
Percentage yield (%)	54.5± 3.3	94.9± 2.6	93.7± 2.1
Assay (%)	53.9± 3.4	98.9± 1.2	99.7± 1.7
Time (h)	Cumulative drug release (%)		
0.5	21.2± 3.9	26.4± 3.5	24.3± 3.4
1.0	69.4± 5.1	36.1± 3.7	30.3± 4.1
1.5	87.2± 3.2	49.2± 2.1	41.4± 2.7
2.0	99.4± 1.2	79.4± 2.1	55.2± 2.6
3.0	99.7± 1.5	86.1± 2.4	66.1± 2.4
4.0	100.1± 2.1	98.9± 2.3	82.5± 2.8
6.0	--	99.7± 2.4	90.2± 1.9
8.0	--	101.5± 1.6	100.3± 1.1

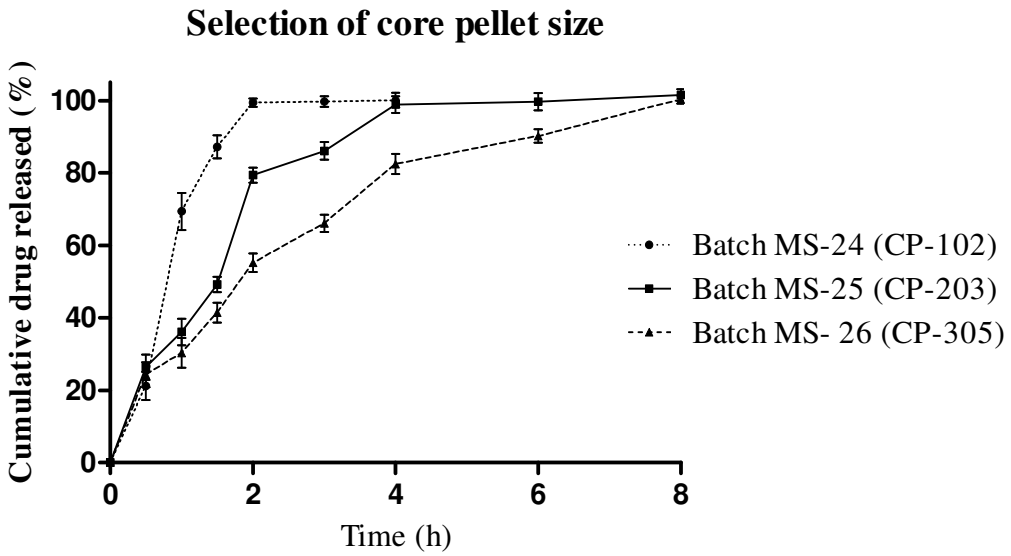

Figure 4.5.1: Cumulative drug released (%) Vs Time (h) for selection of core pellet size for MS MUPS

Selection of core pellet size for MH MUPS

Similar results (Table 4.5.16) were achieved for MH in which the drug release was faster in case of CP-102 (101.2± 1.1 within 3h) (Batch MH-18) as compared to CP-203 (101.4± 1.3 within 8h) (Batch MH-19). The drug release was observed to be slower and sustained in case of Celphere CP-305 (100.5± 1.2% within 8h) (Batch MH-20) (Figure 4.5.2).

The particle size of Celphere CP-102, Celphere CP-203 and Celphere CP-305 was 106-212, 150 -300 and 300- 500 μm respectively [9]. As the particle size decreases, the total surface area increases. Thus Celphere CP-203 and CP-305 can be regarded as having greatest and lowest surface area respectively, amongst the core pellets studied in present work. As the same amount of coating was applied to all the batches, a thinner film coat would be obtained for smaller pellets (Celphere CP-102), having a greater surface area and vice-versa. Therefore, drug release was fastest from MH-18 batch and slowest for MH-20 batch. This implies that as the surface area increases, the amount (extent) of CR coating required to control (retard) the drug release will also increase [10]. Similar impact upon drug release for different size of pellets was also reported [11].

Table 4.5.16: Results for selection of core pellet size for MH MUPS

	Batch MH-18	**Batch MH-19**	**Batch MH-20**
Percentage yield (%)	58.2± 3.1	96.1± 2.2	97.2± 2.5
Assay (%)	56.9± 2.9	94.8± 2.4	95.7± 1.7
Time (h)	Cumulative drug release (%)		
0.5	23.6± 2.9	21.3± 2.3	18.6± 2.1
1.0	61.3± 2.7	29.5± 2.1	26.8± 2.3
1.5	82.5± 2.5	41.4± 1.6	36.2± 1.0
2.0	93.6± 2.3	62.5± 1.8	48.5± 1.6
3.0	101.2± 1.1	84.6± 2.0	64.4± 1.8
4.0	--	91.9± 1.8	79.3± 2.0
6.0	--	98.1± 1.4	91.2± 1.4
8.0	--	101.4± 1.3	100.5± 1.2

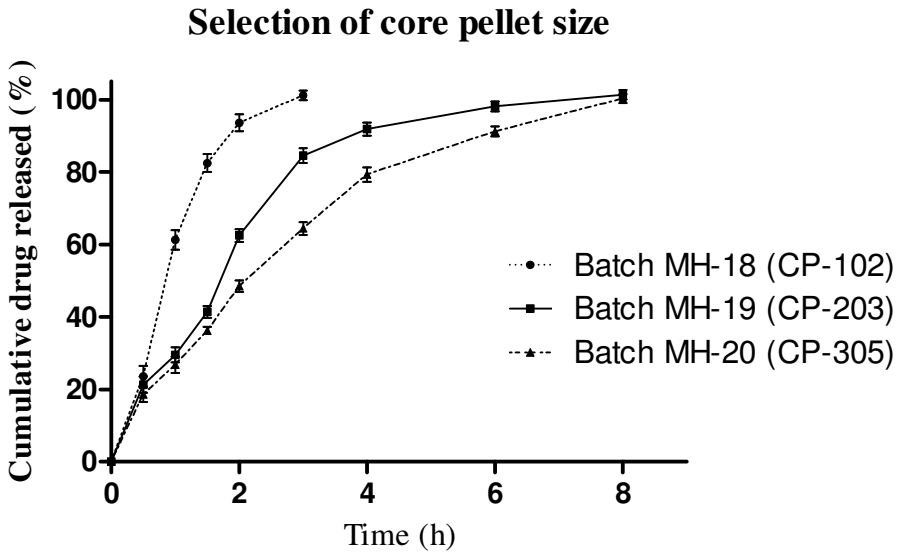

Figure 4.5.2: Cumulative drug released (%) Vs Time (h) for selection of core pellet size for MH MUPS

4.5.8 Selection of core pellet quantity per unit

At constant load, the impact of change in core pellet quantity per unit upon drug release was studied by taking trials at 25, 50 and 75mg for both the drugs.

Selection of core pellet quantity per unit for MS

Batches MS-27, MS-25 and MS-28 were taken with 25, 50 and 75mg core pellet per unit. Satisfactory yield (93.8± 1.9 to 96.2± 2.6%) and assay values (97.7± 1.4 to 99.1± 2.3%) were achieved in these trials (Table 4.5.17). The drug release was fastest in case of batch MS-28 (101.3± 1.1% in 8h) and slowest for batch MS-27 (Figure 4.5.3).

Table 4.5.17: Results for selection of core pellet quantity per unit for MS

	Batch MS-27	**Batch MS-25**	**Batch MS-28**
Percentage yield (%)	93.8± 1.9	94.9± 2.3	96.2± 2.6
Assay (%)	97.7± 1.4	98.9± 1.2	99.1± 2.3
Time (h)	Cumulative drug release (%)		
0.5	5.3± 2.9	26.4± 3.5	25.6± 3.4
1.0	25.1± 2.3	36.1± 3.7	53.2± 2.1
1.5	29.8± 2.2	49.2± 2.1	67.3± 3.7
2.0	48.7± 4.2	79.4± 2.1	77.2± 4.6
3.0	61.2± 2.5	86.1± 2.4	98.1± 2.4
4.0	76.1± 3.1	98.9± 2.3	99.1± 1.8
6.0	87.3± 2.9	99.7± 2.4	99.9± 1.9
8.0	92.4± 1.4	101.5± 1.6	101.3± 1.1
10.0	98.5± 1.3	--	--

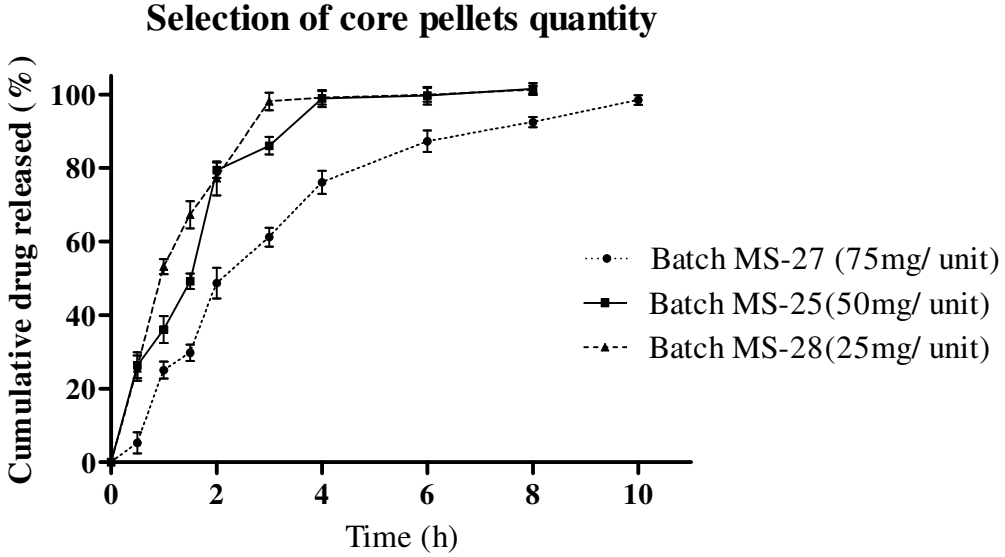

Figure 4.5.3: Cumulative drug released (%) Vs Time (h) for selection of core pellet quantity for MS MUPS

Selection of core pellet quantity per unit for MH

Similar results (Table 4.5.18) were achieved for MH in which satisfactory yield (94.4± 2.3 to 96.2± 2.2%) and assay values (94.8± 2.4 to 98.1± 1.8%) were achieved for batches

MH-21, MH-19 and MH-22. The drug release was fastest from batch MH-22 (100.2± 1.9% in 6h) and slowest from batch MH-21 (100.1± 1.1% in 10h) (Figure 4.5.4).

These differences were mainly attributed to the fact that as the number of core pellets per unit increased, the surface area also increased. Greater number of core pellets would require higher extent of sustained release coating to control the drug release, thereby increasing the process time and the product cost. However for lesser number of core pellets, the final size of the pellet would be higher, thereby increasing the sedimentation rate in case of powder for reconstitution (final dosage form). Thus at a constant level of CR coating (25%), formulation with 75 mg will receive lesser amount of CR polymer per pellet as compared to 50 mg, which would further receive lesser amount of CR polymer per pellet as compared to formulation with 25 mg core pellets.

Hence 50mg/unit of core pellets was selected to achieve a balance between the size of the pellets and the final bulk of the product for both MS and MH.

Table 4.5.18: Results for selection of core pellets quantity per unit for MH

	Batch MH-21	**Batch MH-19**	**Batch MH-22**
Percentage yield (%)	94.4± 2.3	96.1± 2.7	96.2± 2.2
Assay (%)	96.7± 1.2	94.8± 2.4	98.1± 1.8
Time (h)	Cumulative drug release (%)		
0.5	16.2± 2.7	21.3± 2.3	27.6± 3.4
1.0	23.1± 2.6	29.5± 2.1	46.2± 2.5
1.5	33.8± 2.1	41.4± 1.6	53.3± 1.7
2.0	53.2± 3.2	62.5± 1.8	68.2± 2.6
3.0	65.3± 2.5	84.6± 2.0	87.1± 1.4
4.0	78.1± 3.1	91.9± 1.8	94.1± 1.8
6.0	87.3± 2.7	98.1± 1.4	100.2± 1.9
8.0	96.4± 1.3	101.4± 1.3	--
10.0	100.1± 1.1	--	--

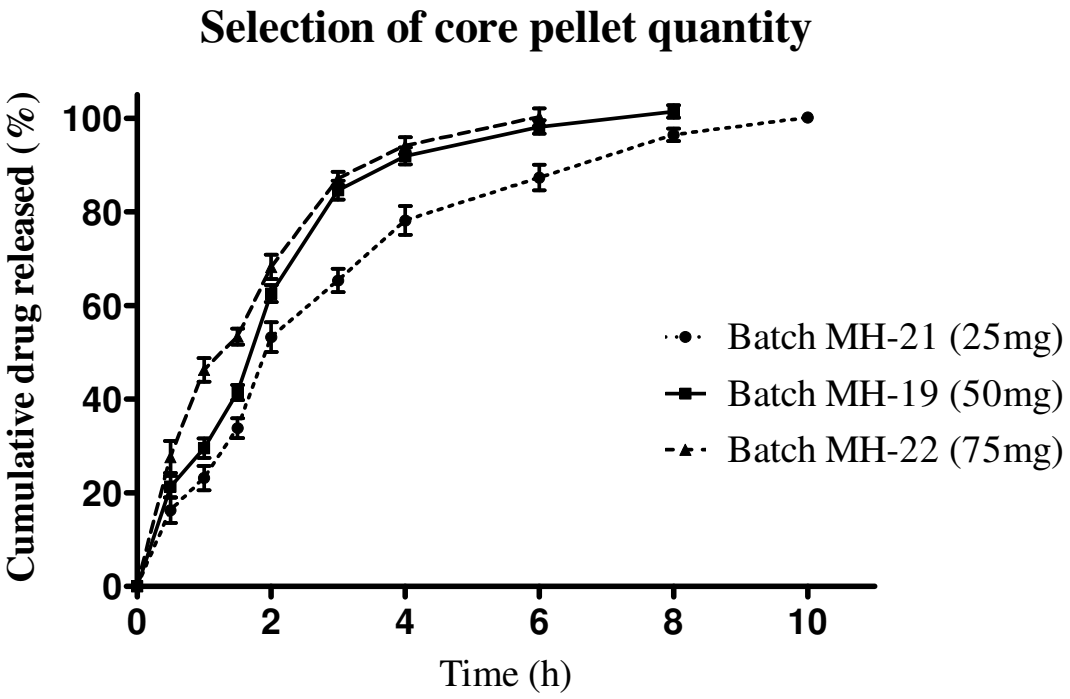

Figure 4.5.4: Cumulative drug released (%) Vs Time (h) for selection of core pellet quantity for MH MUPS

4.5.9 Selection of controlled release (CR) polymer

Developing oral controlled release dosage form for BCS class I and class III drugs like MS and MH respectively has always been a challenge for the pharmaceutical scientists [12, 13]. Selection of CR polymer is a prerequisite for a controlled release dosage form. In the present study, the impact of various pH independent CR polymers upon drug release was studied.

Selection of CR polymer for MS

Batches MS-25, MS-29 and MS-30 were prepared with Ethyl cellulose, Eudragit® RS and Eudragit® RL respectively. Satisfactory yield (94.2±1.7- 95.8±2.8%) and assay values (97.9±1.1- 99.2±3.6%) were achieved in these trials (Table 4.5.19). Formulation with Eudragit® RL released 100.5± 1.8% drug in 4h, while that with Eudragit® RS and Ethyl cellulose released 101.1± 2.4% and 99.7± 2.4% drug in 6h respectively (Figure 4.5.5). The difference in release profile of Eudragit® RS and Eudragit® RL can be attributed to the difference in quaternary ammonium groups they contain. Eudragit® RS and Eudragit® RL contain 5% and 10% of functional quaternary ammonium groups respectively which give rise to permeability of the polymers [14]. Out of these various

pH independent controlled release polymers, Ethyl cellulose was selected since it controlled the drug release for more time as compared to the other two polymers.

Table 4.5.19: Results for selection of CR polymer batches for MS

	Batch MS-25	**Batch MS-29**	**Batch MS-30**
Percentage yield (%)	94.9± 2.1	95.8± 2.8	94.2± 1.7
Assay (%)	98.9± 1.2	99.2± 3.6	97.9± 1.1
Time (h)	Cumulative drug release (%)		
0.5	26.4± 3.5	35.4± 2.9	45.6± 3.4
1.0	36.1± 3.7	41.1± 3.2	55.2± 4.1
1.5	49.2± 2.1	56.3± 1.5	76.3± 2.4
2.0	79.4± 2.1	79.4± 2.1	94.2± 4.6
3.0	86.1± 2.4	98.6± 1.3	99.1± 2.4
4.0	98.9± 2.3	99.9± 1.8	100.5± 1.8
6.0	99.7± 2.4	101.1± 2.2	--

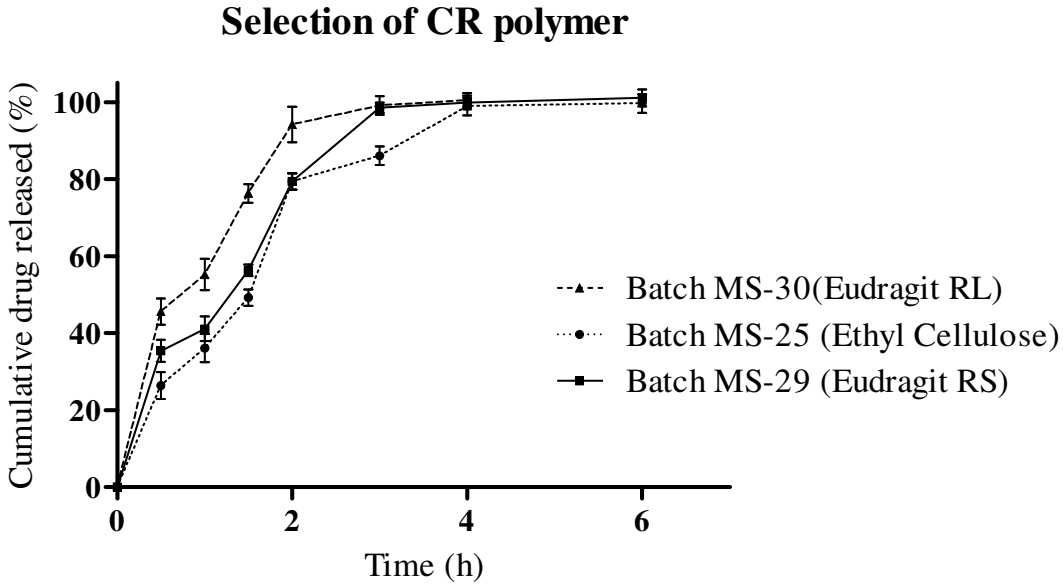

Figure 4.5.5: Selection of CR polymer for MS MUPS

Selection of CR polymer for MH

Batches MH-19, MH-23 and MH-24 were taken with Ethyl cellulose, Eudragit® RS and Eudragit® RL respectively. Satisfactory yield (90.2± 3.3-96.1± 2.7%) and assay values (92.9± 1.1- 97.2± 1.6%) were achieved in these trials (Table 4.5.20). Fastest drug release

was observed with Eudragit® RL (batch MH-24), which released 100.9± 1.6% drug in 4h. Batch MH-23 and MH-19 with Eudragit® RS and Ethyl cellulose released 101.3± 1.9% and 101.4± 1.3% drug in 8h respectively (Figure 4.5.6). Out of these various pH independent controlled release polymers, Eudragit® RS was selected since it exhibited a slower drug release profile than the other two polymers.

Table 4.5.20: Results for selection of CR polymer batches for MH

	Batch MH-19	**Batch MH-23**	**Batch MH-24**
Percentage yield (%)	96.1± 2.7	95.1± 2.1	90.2± 3.2
Assay (%)	94.8± 2.4	97.2± 1.6	92.9± 1.1
Time (h)	Cumulative drug release (%)		
0.5	21.3± 2.3	20.4± 2.5	25.6± 2.4
1.0	29.5± 2.1	25.4± 2.7	42.1± 3.1
1.5	41.4± 1.6	39.5± 1.6	67.1± 2.7
2.0	62.5± 1.8	54.1± 2.3	84.2± 3.6
3.0	86.6± 2.0	78.2± 2.1	93.5± 1.7
4.0	92.9± 1.8	84.9± 2.5	100.9± 1.6
6.0	98.1± 1.4	91.1± 2.7	--
8.0	101.4± 1.3	101.3± 1.9	--

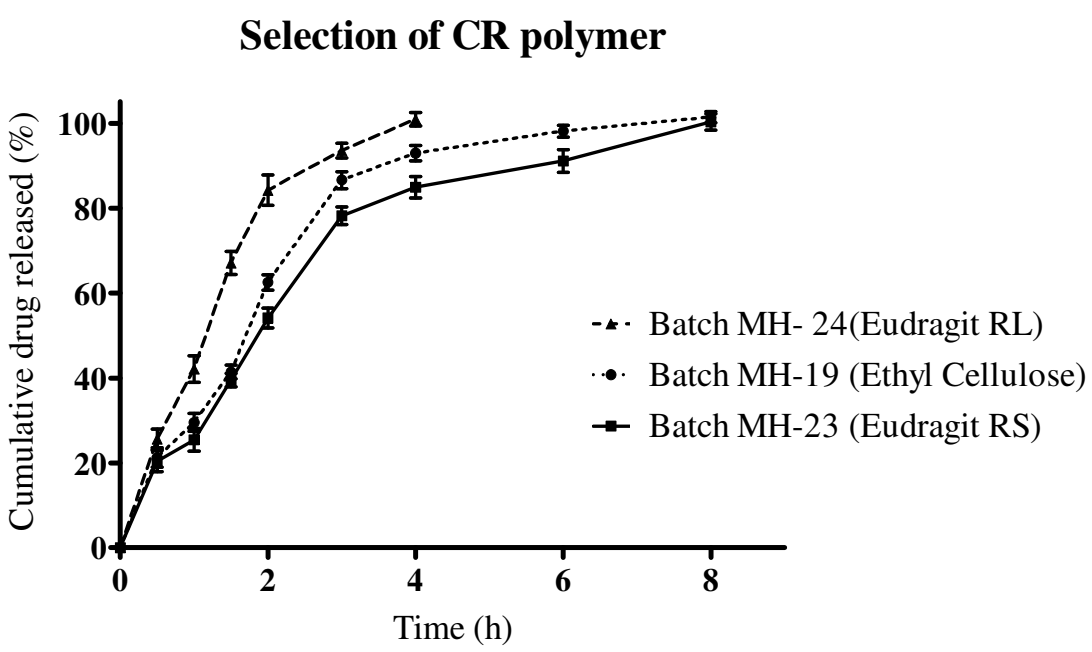

Figure 4.5.6: Selection of CR polymer for MH MUPS

4.5.10 Reservoir Vs Matrix techniques

Controlled release dosage forms are generally prepared by polymeric drug delivery systems in which the functionality of the system is predominantly determined by the polymer properties. These systems can be differentiated into- matrix systems (where the drug is embedded within the polymer) or reservoir systems (where a drug core is surrounded by a polymeric film). In the present study, both the approaches were evaluated for formulation of MS and MH-CR MUPS.

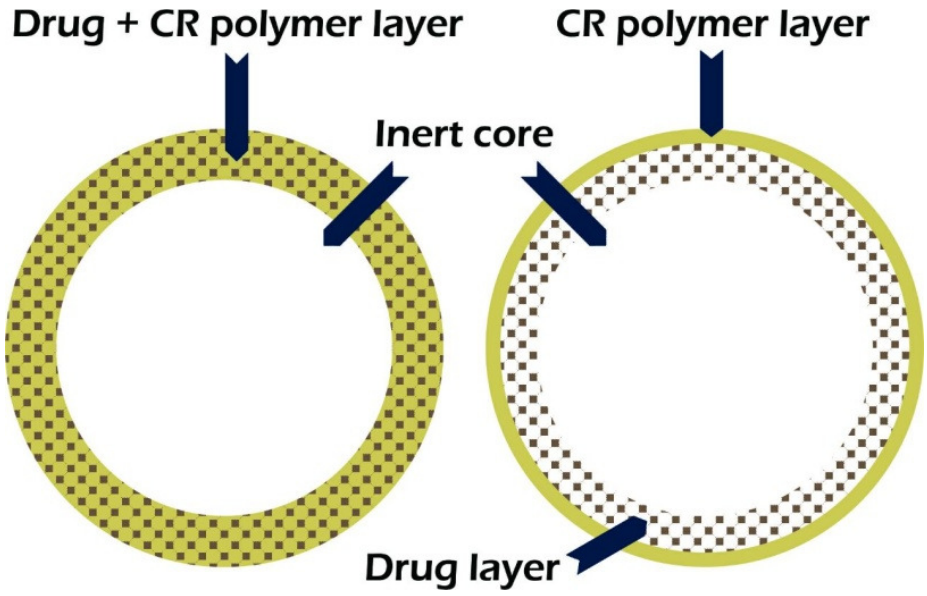

Figure 4.5.7: Schematic presentation of: matrix-coated pellets and reservoir pellets (black: drug; grey: release-controlling polymer; white: other excipients)

Reservoir Vs Matrix techniques for MS and MH

Batches MS-25, MS-31 and MH-19, MH-25 were formulated using reservoir and matrix technique respectively. For comparison purpose, the amount of drug (MS and MH) and CR polymer (EC and Eudragit® RS) were kept constant in all the trials.

In case of reservoir formulation, drug layering (25.5% w/w) followed by CR coating (25% w/w) was carried out on Celphere CP 203, while in case of matrix formulation, the Celphere CP 203 were sprayed with drug+ CR coating solution (53.88% w/w). All the batches were processed without any agglomeration and satisfactory yield (94.9± 2.1 to 96.8± 2.9%), (96.1± 2.7 to 95.3± 2.2%) and assay values (98.9± 1.2 to 99.6± 2.2%), (94.8± 2.4 to 98.4± 2.1%) were achieved respectively (Table 4.5.21 and 4.5.22). For batches MS-25 and MH-19, 101.5± 1.6% and 101.4± 2.6% drug was released at 8h

respectively. In case of batches MS-31 and MH-25, only 79.1± 1.5% and 100.3±1.2% drug was released after 10h respectively (Figure 4.5.8 and 4.5.9).

In reservoir systems, the drug release occurs by diffusion through a) the intact polymeric film, b) through channels made by pore formers and c) through medium filled channels / pores [15]. Due to higher concentration of hydrophilic polymer (HPC) in rate controlling membrane, more number of pores would be created leading to increased drug diffusion across the membrane into the dissolution media or gastrointestinal fluid. Thus, the thickness of membrane (extent of CR coating) mediates the diffusion of drug, i.e. greater the thickness of the membrane, more the prolongation of drug release would occur. In case of trial MS-25 and MH-19, the extent of CR coating (25% w/w) was able to sustain the drug release for 8h only (Table 4.5.21 and 4.5.22)

In matrix systems, MS and MH are uniformly dispersed into the polymer system comprising a blend of hydrophobic and hydrophilic polymers (EC and HPC for MS, Eudragit® RS and Eudragit® RL for MH). EC and Eudragit® RS being hydrophobic polymers create an impermeable structure while HPC and Eudragit® RL being hydrophilic polymers create a permeable passage for the dissolved drug. The drug release mainly occurs through porous matrix created by dissolution of highly soluble drug (MS and MH), along with permeation/diffusion through the permeable passage created by HPC and Eudragit® RL respectively to some extent. With passage of time, the distance that a drug molecule needs to travel from deep inside the matrix to the surface also increases, thereby sustaining the drug release.

Thus at constant amount of EC and Eudragit® RS, the drug release was more retarded from matrix system as compared to corresponding batches with reservoir system. Hence MS and MH-MUPS matrix formulation was selected over reservoir, considering better control of drug release and less number of processing steps involved.

Table 4.5.21: Batches prepared with Reservoir and Matrix techniques-MS

	Batch MS-25	**Batch MS-31**
Percentage yield (%)	94.9± 2.1	96.8± 2.9
Assay (%)	98.9± 1.2	99.6± 2.2
Time (h)	Cumulative drug release (%)	
0.5	26.4± 3.5	5.4± 2.7
1.0	36.1± 3.7	9.1± 3.1
1.5	49.2± 2.1	21.3± 1.1
2.0	79.4± 2.1	29.4± 2.4
3.0	86.1± 2.4	40.6± 2.1
4.0	98.9± 2.3	61.9± 1.9
6.0	99.7± 2.4	66.1± 2.3
8.0	101.5± 1.6	75.4± 1.8
10.0	--	79.1± 1.5

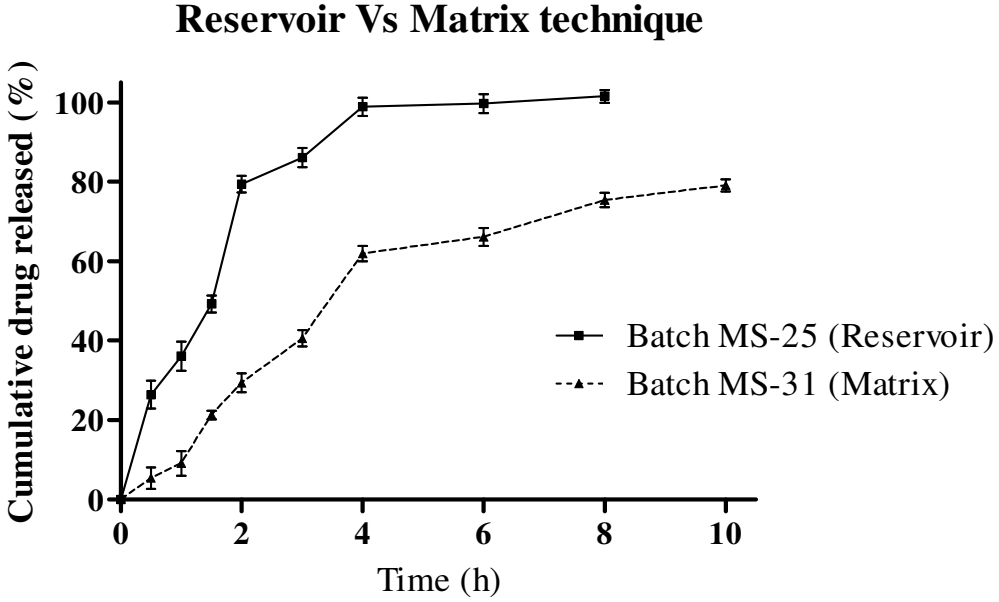

Figure 4.5.8: Reservoir and matrix techniques for MS loading

Table 4.5.22: Batches prepared with Reservoir and Matrix techniques- MH

	Batch MH-**19**	**Batch** MH-**25**
Percentage yield (%)	96.1± 2.7	95.3± 2.2
Assay (%)	94.8± 2.4	98.4± 2.1
Time (h)	Cumulative drug release (%)	
0.5	21.3± 2.3	14.7± 2.4
1.0	29.5± 2.1	24.2± 2.6
1.5	41.4± 1.6	34.3± 1.5
2.0	62.5± 1.8	49.4± 2.3
3.0	84.6± 2.0	55.6± 2.1
4.0	91.9± 1.8	66.9± 1.8
5.0	93.2± 2.1	69.5± 1.5
6.0	98.1± 2.3	72.0± 2.2
8.0	101.4± 2.6	78.9± 1.8
10.0	--	81.5± 1.6
12.0	--	93.8±1.7
16.0	--	100.3±1.2

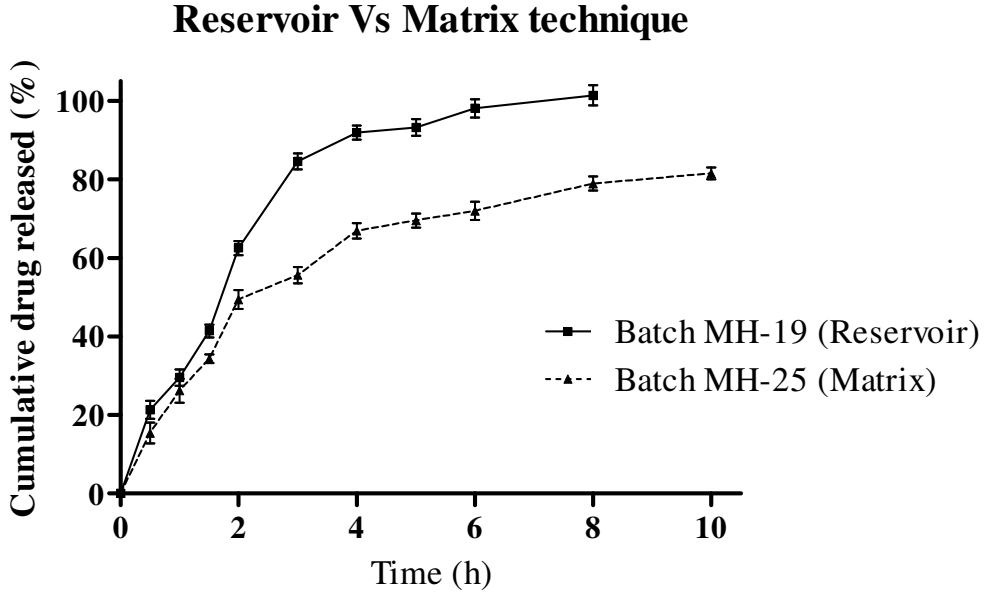

Figure 4.5.9: Reservoir and matrix techniques for MH loading

Optical microscopy

For MS, the particle size of batch MS-25 was found to be 650-700 µm (Figure 4.5.10) and that of batch MS-31 was found to be 400-500µm (Figure 4.5.11), while for MH, the particle size of batches MH-19 and MH-25 were found to be 750-800 µm (Figure 4.5.12) and 400-550 µm (Figure 4.5.13) respectively. Thus, size of pellets prepared by matrix technique was smaller as compared to reservoir technique for both the drugs. Considering the simple one step approach along with better control over drug release and lesser pellet size, matrix technique was selected for both the drug (MS and MH) loading step.

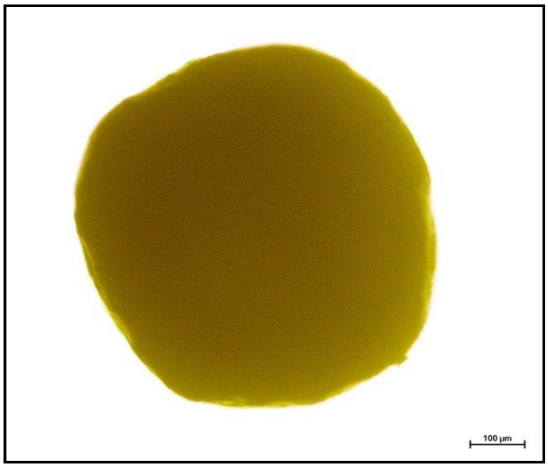

Figure 4.5.10: MS-CR coated pellet prepared by reservoir technique

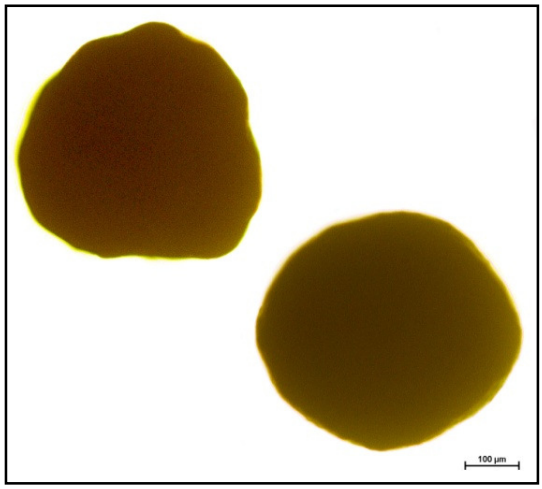

Figure 4.5.11: MS-CR coated pellet prepared by matrix technique

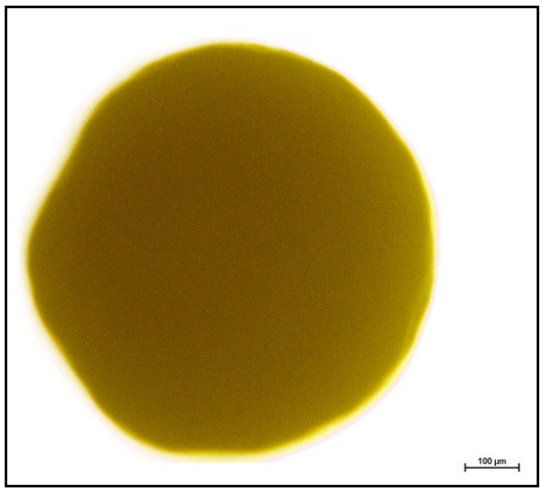

Figure 4.5.12: MH-CR coated pellet prepared by reservoir technique

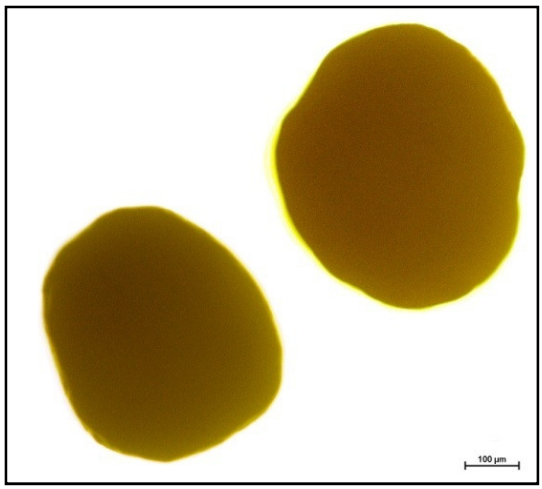

Figure 4.5.13: MH-CR coated pellet prepared by matrix technique

4.5.11 Optimization for solid content of coating solution in matrix system

For MS Matrix System

Batches MS-32, MS-31 and MS-33 were taken with 5, 7.5 and 10% solid content for drug (MS) + CR polymer (EC+ HPC) coating solution respectively. In case of batch MS-A, the yield achieved was 95.4± 2.6% while that in case of batch MS-31 it was 96.8± 2.9%. However in case of batch MS-33, agglomeration was observed (Yield= 31.3± 3.8%) which might be due to the increased viscosity of the coating solution. Use of comparatively dilute solution (5% against 7.5%) would require more time to spray equivalent amount of solid content. As similar percentage yield were achieved with 5 and 7.5% solid content, it was decided to select 7.5% w/w solid content for drug+ CR polymer coating solution so as to reduce the process time.

Table: 4.5.23: Optimization for solid content of coating solution for MS matrix system

Batch	Batch MS-32	Batch MS-31	Batch MS-33
Percentage yield (%)	95.4± 2.6	96.8± 2.9	31.3± 3.8
Observation	No Agglomeration	No Agglomeration	Agglomeration

For MH matrix system

Batches MH-25 and MH-26 were taken with 6 and 8% solid content for drug+ CR polymer coating solution respectively. In case of batch MH-25, no agglomeration was observed. This suggested that the processing conditions and the solid content of the drug+ CR coating solution selected were appropriate (yield achieved= 95.3± 2.2%). However in case of batch MH-26, agglomeration was observed (yield= 37.4± 4.1%). Hence a solid content of 6% w/w was selected for drug+ CR polymer coating solution considering an agglomeration free process.

Table 4.5.24: Optimization for solid content of coating solution for MH matrix system

Batch	Batch MH-25	Batch MH-26
Percentage yield (%)	95.3± 2.9	37.4± 4.1
Observation	No Agglomeration	Agglomeration

4.5.13 Extent of CR coating and drug: polymer ratio in matrix system

MS matrix system

In case of batch MS-31 (drug: polymer= 1:1.4 and EC: HPC =60:40); 100.2± 1.2% drug was released in 16h. So to prolong the drug release for 24h, batches MS-34 and MS-35 were taken by taking the EC: HPC ratio of 80:20 and 100:0 respectively. It was observed that as the concentration of EC was increased, complete release of drug was not achieved.

To overcome this problem it was decided to increase the amount of drug in the drug : polymer ratio and also increase the coating extent. So Batches MS-36 and MS-37 were taken with 60 and 70% w/w coating and 1:1 ratio of drug: polymer. Suitable dissolution profile was achieved from Batch MS-36 which met the desired target profile while slightly slower profile was achieved from Batch MS-37. This slower profile might be

due to the higher coating extent which increased the diffusion length for the drug molecule into the dissolution media.

Hence it was decided to optimize the formulation parameters of batch MS-36 viz. coating extent and drug: polymer ratio by design of experiment.

Table 4.5.25: Results for optimization of extent of CR coating and drug: polymer ratio -MS matrix system

	Batch MS-31	**Batch MS-34**	**Batch MS-35**	**Batch MS-36**	**Batch MS-37**
Percentage yield (%)	95.9± 2.8	97.8± 3.1	95.2± 2.4	96.8± 2.3	97.1±2.2
Assay (%)	99.9± 1.2	99.2± 3.6	97.9± 1.1	98.7± 1.6	101.1± 1.0
Time (h)	Cumulative drug release (%)				
1	9.8± 1.7	5.6± 1.8	2.9± 1.1	15.3± 3.2	11.2± 2.1
2	29.1± 2.3	10.3± 2.1	7.3± 3.1	21.2± 2.1	17.3± 1.2
4	61.1± 3.1	14.9± 3.8	10.3± 2.5	25.1± 3.3	21.8± 3.5
6	66.3± 2.4	30.6± 3.2	17.6± 3.6	37.7± 2.6	32.9± 2.5
8	75.4± 1.9	36.4± 2.6	26.8± 2.1	54.2± 2.3	39.3± 2.6
10	79.6± 2.3	46.0± 2.9	36.4± 1.9	60.3± 2.1	51.8± 2.9
12	89.4± 1.6	56.2± 3.2	45.7± 3.2	67.8± 1.6	62.5± 1.8
16	100.2± 1.2	62.8± 2.9	53.2± 2.7	75.2± 3.4	71.3± 3.2
20	--	70.2± 2.5	60.9± 3.6	88.2± 1.5	77.5± 2.1
24	--	75.0± 3.0	70.8± 3.8	99.7± 2.5	89.9± 2.3

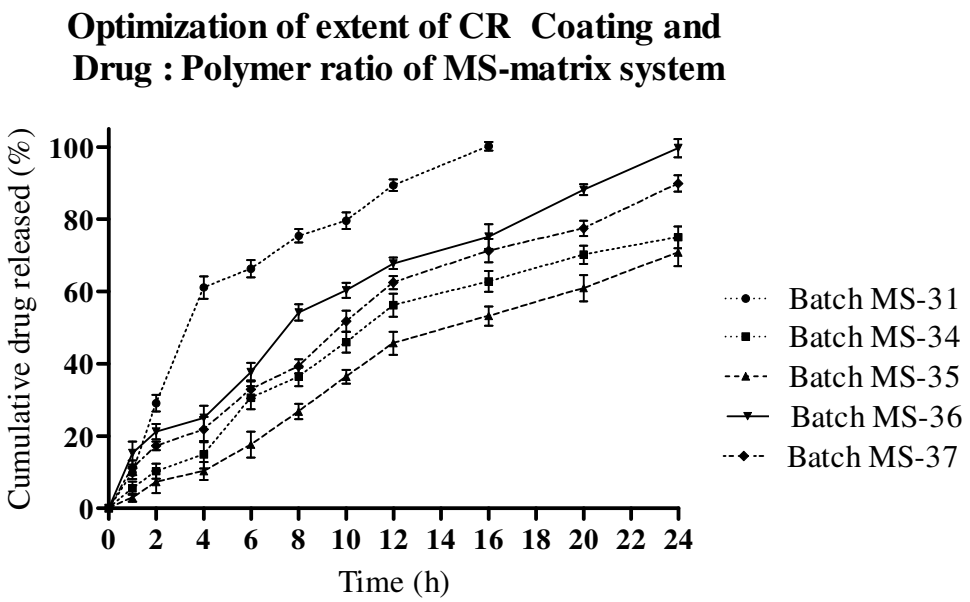

Figure 4.5.14: Optimization for Extent of CR Coating and Drug: Polymer Ratio - MS matrix system

MH matrix system

In batch MH-25 prepared with Eudragit® RS and Eudragit® RL (coating extent 57.50% w/w, drug: polymer ratio= 1:0.87) 100.3± 1.2% drug was released in 16h indicating lower coating extent. Hence in order to prolong the drug release, batch MH-27 with increased extent of coating (65% w/w) was taken. It was observed that as the extent of coating was increased, the drug release was very slow and sustained for 24h. However, complete release of MH was not achieved (71.2± 2.4% drug released at 24h). Hence batch MH-28 was taken with inclusion of increased quantity of Eudragit® RL (more permeable polymer) along with Tri Ethyl Citrate (TEC as plasticizer). The ratio of Eudragit® RS: Eudragit® RL was kept at 9:1.

Eudragit® RS and Eudragit® RL contain 5% and 10% of quaternary ammonium groups respectively which increase the permeability of the polymers[14]. Thus inclusion of Eudragit® RL imparts permeability to the drug+ CR polymer coating film. Addition of plasticizer TEC imparts more flexibility to the film. Hence the drug release profile was slightly faster than batch MH-27. However, complete release of drug was not achieved (78.1± 2.3% drug released at 24h).

Further to improve the drug release profile and achieve complete release of MH after 24h, the concentration of drug in the drug+ CR polymer matrix (drug: polymer ratio) was made to 1:0.8, and Eudragit® RS: Eudragit® RL ratio was made to 8.5:1.5 in batch MH-29. The drug release profile was observed to be faster than batch MH-28, along with improvement of drug recovery (89.8± 2.4% drug released at 24h).

Further to improve the drug release profile, the drug: polymer ratio was changed to 1:0.7 in batch MH-30. Satisfactory drug release profile matching the USP specification of 20-40% in 1h , 45-65% in 5h, 70-90% in 12h and NLT 85% in 20h; along with complete drug release (99.6± 2.2% drug released at 24h) was achieved. Hence it was decided to optimize the formulation parameters of batch MH-30 viz. coating extent and drug: polymer ratio by design of experiment.

Table 4.5.26: Results for optimization of extent of CR coating and drug: polymer ratio- MH matrix system

	Batch MH-25	**Batch MH-27**	**Batch MH-28**	**Batch MH-29**	**Batch MH-30**
Percentage yield (%)	95.3	98.9	97.6	97.8	97.1
Assay (%)	98.4± 2.1	98.2± 2.6	99.2± 1.3	98.4± 2.6	99.7± 1.6
Time (h)	Cumulative drug release (%)				
1	26.2± 3.1	18.9± 2.1	23.2± 2.1	27.1± 2.5	32.1± 2.2
3	55.6± 2.1	26.8± 1.6	29.4± 2.1	34.7± 1.1	41.2± 1.8
5	69.5± 1.8	34.8± 2.8	38.3± 1.5	49.2± 2.1	50.1± 2.5
8	78.9± 1.8	46.6± 2.2	49.7± 2.6	66.8± 2.2	58.8± 2.6
12	93.8± 1.7	51.1± 2.1	57.2± 2.4	81.2± 2.5	73.2± 2.8
16	100.3± 1.2	58.7± 1.6	66.9± 1.5	84.7± 2.4	81.9± 2.2
20	--	64.6± 2.2	71.5± 2.1	87.2± 1.3	92.3± 1.5
24	--	71.2± 2.4	78.1± 2.3	89.8± 2.4	99.6± 2.2

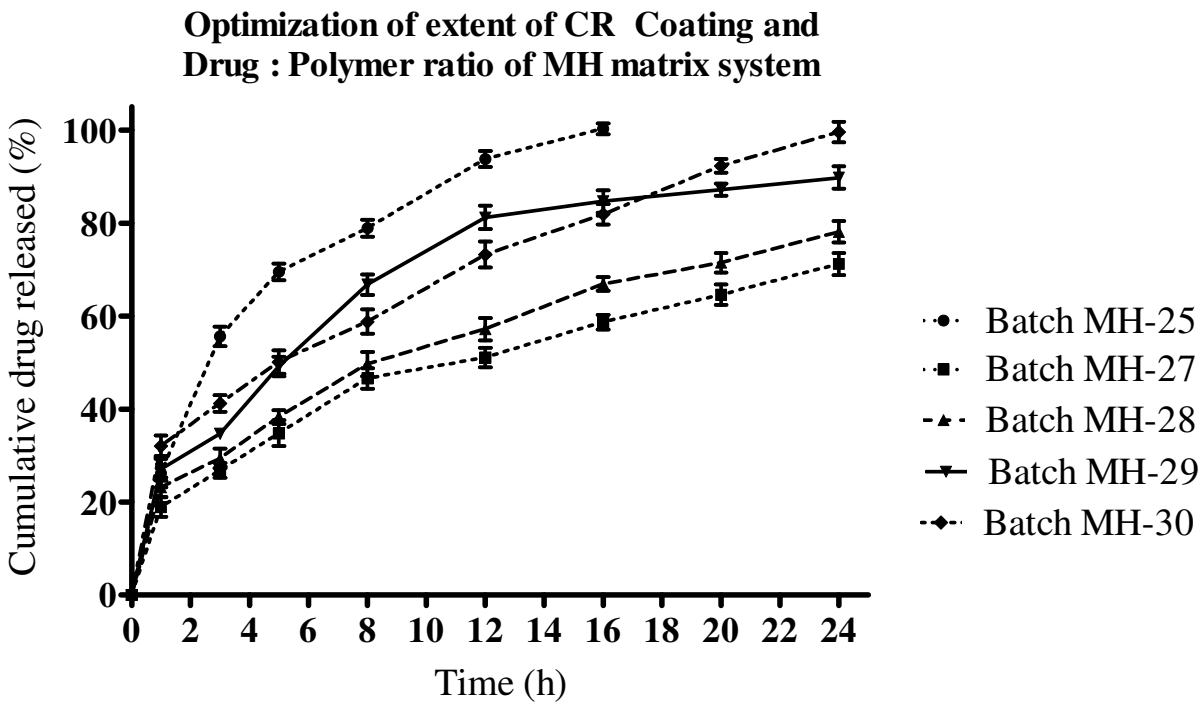

Figure 4.5.15: Optimization of extent of CR coating and drug: polymer ratio -MH matrix system

4.5.14 Curing time

As the rate controlling polymer dispersion is sprayed on the substrate, the droplets form a thin film over it. As the solvent evaporates the polymer particles approach each other and become closely packed. Upon further solvent evaporation, the (softened) particles deform due to capillary pressure effects (air–solvent surface tension) and coalesce to form a continuous film [16]. However, in practice, it is often difficult to assure complete film formation during coating. In an incomplete coalesced film, polymer particle fusion can continue during storage or upon stability testing. An increase in temperature and /or upon passage of time, the mobility of the polymer particle increases thereby facilitating the fusion (coalescence) of neighboring polymer particles rendering the polymeric membranes less permeable for the drug and decreasing drug release rate [17]. Hence a thermal post-treatment (curing) is required to enhance the degree of polymer particle coalescence. The most critical parameters for curing are time, temperature and relative humidity. Several studies have been reported in the literature addressing the impact of the curing step on the drug release profile upon storage stability [18, 19]. Hence, curing study was carried out to by taking several trials at different curing times to achieve best outcome for both the drugs.

Curing study for MS-CR pellets

The MS-CR pellets from batch MS-36A, MS-36B and MS-36C were cured for 10, 20 and 30 min respectively. Batch MS-36A showed faster drug release profile as compared to batches MS-36B and MS-36C which showed similar drug release profiles (Table 4.5.27) (Figure 4.5.16) Hence it was decided to finalize 20 min as the curing time.

Table: 4.5.27: Results for curing study of MS MUPS

Time (h)	Batch MS-36 A	Batch MS-36 B	Batch MS-36 C
	Cumulative drug released (%)		
1	16.4± 1.9	15.3± 1.5	13.7± 2.1
2	24.8± 2.5	21.2± 2.1	20.1± 2.7
4	36.7± 3.5	28.6± 3.1	26.5± 3.7
6	47.4± 2.7	37.7± 2.6	33.5± 3.2
8	56.7± 2.4	55.4± 2.6	52.1± 3.2
10	65.8± 2.5	60.3± 2.1	57.9± 2.7
12	74.9± 2.0	67.8± 1.6	63.6± 2.2
16	81.8± 3.5	75.2± 3.4	72.9± 2.1
20	94.8± 2.9	88.5± 3.4	87.1± 1.9
24	101.1±2.9	99.7± 2.5	98.2± 2.5

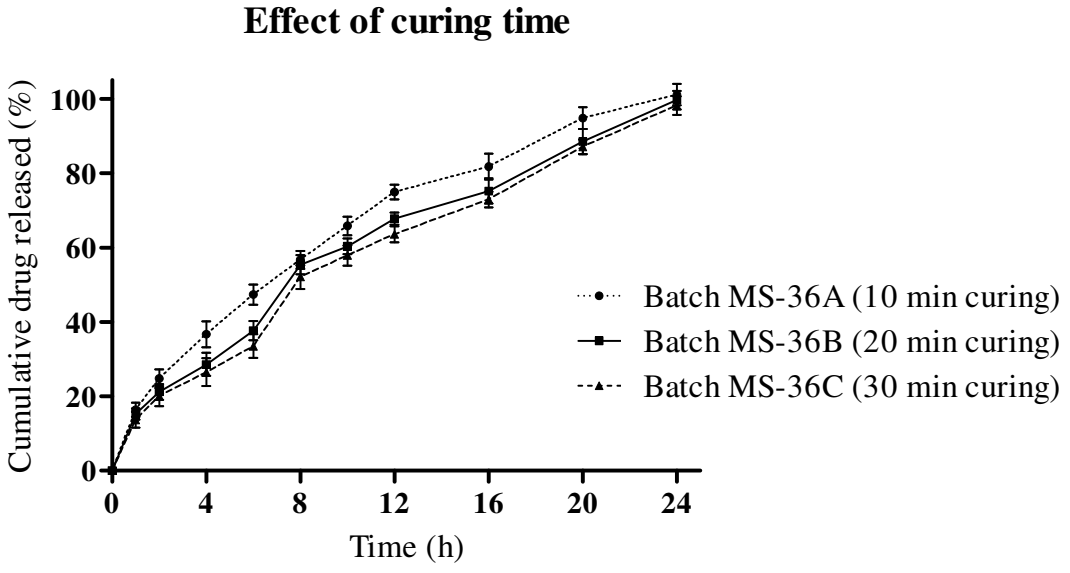

Figure 4.5.16: Cumulative drug released Vs time for batches MS-36A, MS-36B and MS-36C at different curing time

Curing study for MH-CR pellets

The MS-CR pellets from batch MH-30A, MH-30B and MH-30C were cured for 10, 20 and 30 min respectively. Batch MH-30A showed faster drug release profile as compared to batches MH-30B and MH-30C which showed similar release profiles (Table: 4.5.28) (Figure 4.5.17). Hence it was decided to finalize 20 min as the curing time.

Table: 4.5.28: Results for curing study of MH MUPS

Time (h)	**Batch MH-30A**	**Batch MH-30B**	**Batch MH-30C**
1	38.5± 2.4	32.1± 2.2	28.6± 3.2
3	46.0± 2.7	41.2± 1.8	39.4± 2.4
5	53.5± 2.4	50.1± 2.5	48.5± 2.1
8	64.9± 2.3	58.8± 2.6	57.6± 1.7
12	77.7± 1.7	73.2± 2.8	72.4± 1.5
16	84.2± 2.6	81.9± 2.2	79.2± 1.7
20	93.3± 1.9	92.3± 1.5	91.3± 2.5
24	100.6± 1.1	99.6± 2.2	96.9± 3.2

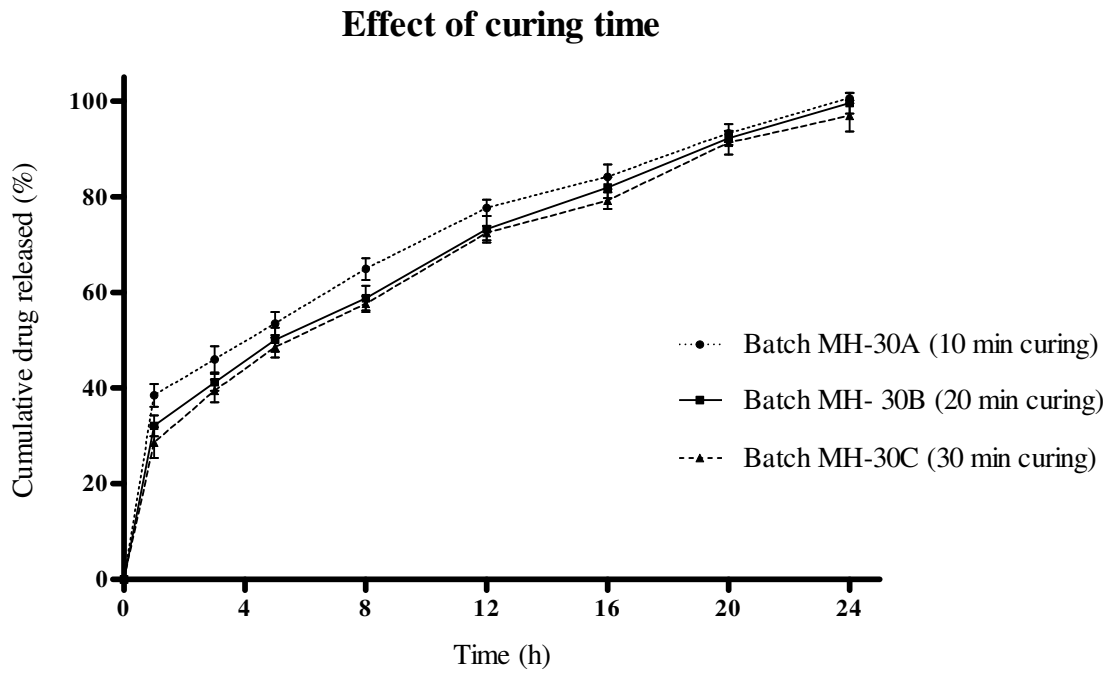

Figure 4.5.17: Cumulative drug released Vs time for batch MH-30A, MH-30B and MH-30C at different curing time

4.5.15 Design of Experiment

According to the Face Centered Central Composite Design (CCF) statistical design, center runs are necessary to augment the statistical design as they increase the number of levels of each causal factor and provide extra degrees of freedom needed to test for pure error [20]. In the present study, for both the drugs, CCF comprised of four ‘‘vertices”, four ‘‘star points” and five centre points (Figure 4.5.18, 4.5.19). whereby the centre point was repeated five times to prove reproducibility and accuracy of the statistical model [21]. The five center runs were conducted with the extent of coating (X_0) 60 % w/w and 65 % w/w with ratio of drug : polymer (X_1) 1: 0.9 and 1: 0.7 for MS and MH respectively.

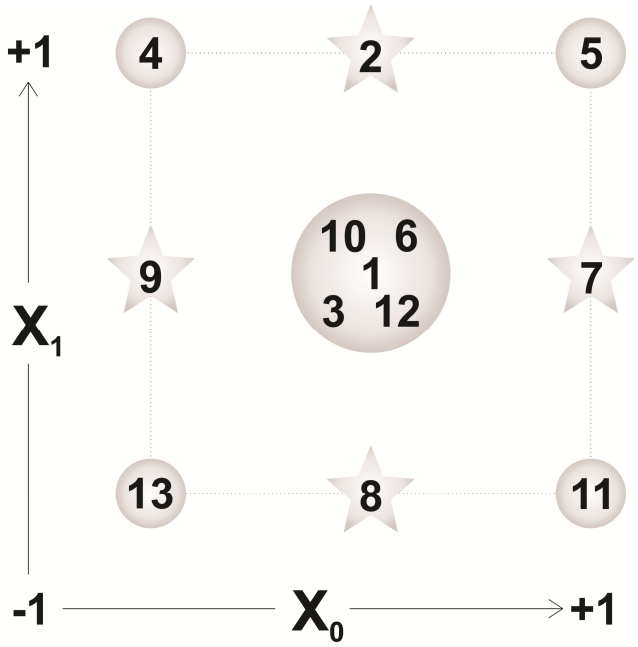

Figure 4.5.18: Pictorial depiction of MS MUPS face centered central composite design

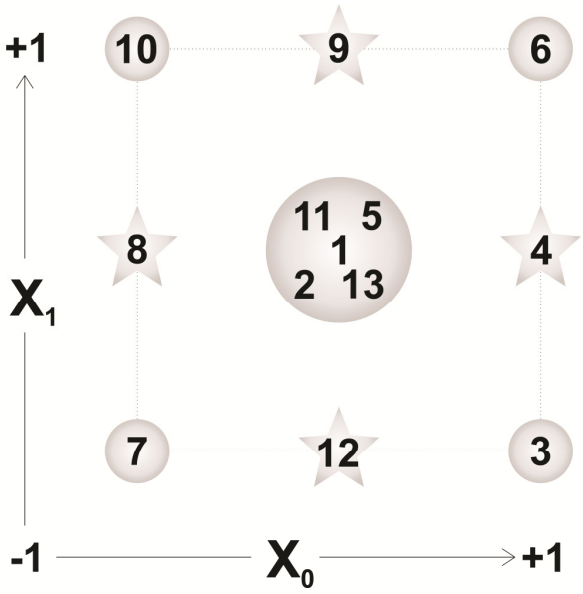

Figure 4.5.19: Pictorial depiction of MH MUPS face centered central composite design

Table 4.5.29: Design matrix for MS MUPS-CCF along with observed response values for matrix system

Runs	Independent variables (coded levels)		Response variables			
	Extent of Coating (X_0)	Drug : Polymer Ratio (X_1)	Release at 1h (Y_1; %)	Release at 4h (Y_2; %)	Release at 8h (Y_3; %)	Release at 20h (Y_4; %)
1	0	0	16.3 ± 4.1	31.2 ± 3.7	50.2 ± 2.4	87.1 ± 1.1
2	0	+1	15.3 ± 3.2	25.1 ± 3.3	54.2 ± 2.3	88.2 ± 1.5
3	0	0	16.7 ± 3.7	29.8 ± 2.5	48.1 ± 2.1	86.7 ± 1.9
4	-1	+1	14.3 ± 4.4	23.1 ± 3.0	57.1 ± 2.3	95.4 ± 2.0
5	+1	+1	7.5 ± 3.1	21.2 ± 3.6	42.9 ± 3.1	81.9 ± 1.8
6	0	0	16.7 ± 4.5	33.5 ± 3.6	51.5 ± 2.1	88.2 ± 1.8
7	+1	0	14.2 ± 3.5	27.6 ± 3.4	49.3 ± 2.4	96.1 ± 2.0
8	0	-1	17.2 ± 4.8	31.6 ± 2.9	55.9 ± 2.6	84.5 ± 1.6
9	-1	0	18.2 ± 5.4	31.1 ± 4.7	49.8 ± 3.2	95.2 ± 1.8
10	0	0	17.8 ± 4.1	32.1 ± 4.1	50.2 ± 3.2	90.2 ± 1.4
11	+1	-1	21.2 ± 3.2	34.9 ± 3.1	58.7 ± 3.0	100.1 ± 1.5
12	0	0	19.1 ± 3.4	31.3 ± 4.2	49.1 ± 3.9	92.3 ± 1.7
13	-1	-1	8.2 ± 3.9	20.8 ± 3.4	43.1 ± 3.2	81.2 ± 2.0

Table 4.5.30: Design matrix for MH MUPS-CCF along with observed response values for matrix system

Runs	Independent variables (coded levels)		Response variables			
	Extent of Coating (X_0)	Drug : Polymer Ratio (X_1)	Release at 1h (Y_1; %)	Release at 5h (Y_2; %)	Release at 12h (Y_3; %)	Release at 20h (Y_4; %)
1	0	0	31.2± 1.6	57.1± 1.3	73.2± 1.1	91.2± 1.5
2	0	0	35.2± 1.4	56.4± 1.8	74.1± 1.2	89.2± 1.8
3	+1	-1	28.3± 1.7	47.3±1.5	72.4±1.1	91.3±1.4
4	1	0	32.1± 2.9	50.1± 2.4	73.2± 1.8	92.3± 2.0
5	0	0	27.4± 2.4	51.2± 2.9	81.2± 3.1	89.1± 2.1
6	1	1	29.5± 3.4	47.1± 1.4	84.5± 2.9	87.3± 3.5
7	-1	-1	32.4± 3.0	62.4± 2.1	86.5± 2.4	92.1± 2.9
8	-1	0	36.2± 2.2	64.5± 2.4	85.3± 2.7	94.5± 2.6
9	0	1	27.1± 1.5	49.2± 3.1	81.2± 2.5	87.2± 1.9
10	-1	+1	36.1± 2.2	61.2± 2.6	84.3± 3.4	88.9± 2.3
11	0	0	34.6± 2.3	57.7± 3.3	74.5± 2.1	89.8± 2.9
12	0	-1	23.2± 1.3	51.2± 1.9	77.3± 2.6	90.2± 2.0
13	0	0	31.2± 1.2	56.1± 2.0	72.1± 1.1	91.2± 1.8

The drug release at 1, 4, 8 and 20 h showed a wide variation from 7.5 ± 3.1 to 21.2 ± 3.2 %, 20.8 ± 3.4 to 34.9 ± 3.1 %, 42.9 ± 3.1to 58.7 ± 3.0 % and 81.2 ± 2.0 to 100.1 ± 1.5% respectively (Table 4.5.29) for MS and at 1, 5, 12 and 20 h from 23.2± 1.3 to 36.2± 2.2%, 47.1± 1.4 to 64.5± 2.4 %, 72.1± 1.1 to 86.5± 2.4 % and 87.2± 1.9 to 94.5± 2.6 % respectively (Table 4.5.30) for MH. Polynomial models including interaction and quadratic term were generated for all the four response variables using multiple linear regression for both MS and MH. When the results were subjected to data analysis by multiple linear regression followed by ANOVA employing Design Expert® software (Version 7.0.0, Suite, Minneapolis, USA), the model fitting was found to be highly significant for all the response variables ($p < 0.0001$). All release point responses were found to have good model fitting with insignificant Lack of Fit indicating aptness of the model for future prognostic purposes for all responses. All the four responses Y_1, Y_2, Y_3 and Y_4 were individually investigated using response surface models as described in

equations Eq. 4.4.1, 4.4.2, 4.4.3, 4.4.4 for MS and equations 4.4.5, 4.4.6, 4.4.7, 4.4.8 for MH respectively.

The model describing the release from MS MUPS at 1 h was:

$$Y_1=17.64+0.37X_0-1.58X_1-4.95X_0X_1- 2.24X_0^2- 2.19X_1^2 \quad \text{(Eq. 4.4.1)}$$

The quadratic model and interaction were found to be significant for response Y_1. The Model F-value of 8.20 implies that the model is significant. Value of regression coefficient (R^2 = 0.8541) indicated a good correlation between the response Y_1 (release at 1h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0077. Extent of coating had positive while drug: polymer ratio had negative effect on the release of drug. Thus, it reflects that as the extent of coating increases, the drug release at 1h increases, while it decreases on increasing drug: polymer ratio.

In the present study, the core is coated with a matrix system comprising of drug+ CR polymer. As the extent of coating increases, the drug release at 1h increases.

At a constant ratio of drug : polymer, as the extent of coating increases, the number of pores created by dissolution of highly hydrophilic drug (MS) increases, leading to increase in drug release.

The model describing the release from MS MUPS at 4 h was:

$$Y_2=31.73+1.45X_0-2.98X_1-4.00X_0X_1-2.77X_0^2 - 3.77X_1^2 \quad \text{(Eq. 4.4.2)}$$

The quadratic model and interaction were found to be significant for response Y_2. The Model F-value of 8.10 implies that the model is significant. Value of regression coefficient (R^2 = 0.8526) indicated a good correlation between the response Y_2 (release at 4h) and the selected factors.Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0079. Extent of coating had positive while drug: polymer ratio had negative effect on the release of drug. Thus, an increase in extent of coating increased the drug release at 4h, while an increase in drug: polymer ratio decreased the drug release at 4h.

The model describing the release from MS MUPS at 8 h was:

$$Y_3=50.42+0.15\ X_0-\ 0.58X_1-\ 7.45X_0X_1-2.36\ X_0^2+3.14X_1^2 \qquad \text{(Eq. 4.4.3)}$$

The quadratic model and interaction were found to be significant for response Y_3. The Model F-value of 17.72 implies the model is significant.Value of regression coefficient ($R^2 = 0.9268$) indicated a good correlation between the response (release at 8 h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.008. Extent of coating had positive while drug: polymer ratio had negative effect on the release of drug. Thus, an increase in extent of coating increased the drug release at 8h, while an increase in drug: polymer ratio decreased the drug release at 8h.

The model describing the release from MS MUPS at 20 h was:

$$Y_4=89.38+1.05X_0-0.050X_1-8.10\ X_0X_1+5.08X_0^2-4.22\ X_1^2 \qquad \text{(Eq. 4.4.4)}$$

The quadratic model and interaction were found to be significant for Y_4 response. The Model F-value of 11.93 implies the model is significant.Value of regression coefficient ($R^2 = 0.8949$) indicated a good correlation between the response (release at 8 h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.026. Extent of coating had positive while drug: polymer ratio had negative effect on the release of drug. Thus, an increase in extent of coating increased the drug release at 20h, while an increase in drug: polymer ratio decreased the drug release at 20h.

The model describing the release from MH MUPS at 1 h was:

$$Y_1=31.51-2.07X_0+1.47X_1+0.62X_0X_1+4.88X_0^2-\ 5.32X_1^2 \qquad \text{(Eq. 4.4.5)}$$

The quadratic model and interaction were found to be significant for response Y_1. The Model F-value of 5.16 implies that the model is significant. Value of regression coefficient ($R^2 = 0.7865$) indicated a good correlation between the response Y_1 (release at 1h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0266. Drug: polymer ratio had positive while extent of coating had negative effect on the release of drug. Thus, it reflects that as the drug: polymer ratio increases, the drug release at 1h increases, while it decreases on increasing extent of coating.

The model describing the release from MH MUPS at 5 h was:

$$Y_2=55.33-7.27X_0-0.57X_1+0.25X_0X_1+2.90X_0^2 - 4.20X_1^2 \quad \text{(Eq. 4.4.6)}$$

The quadratic model and interaction were found to be significant for response Y_2. The Model F-value of 16.09 implies that the model is significant. Value of regression coefficient (R^2 = 0.9200) indicated a good correlation between the response Y_2 (release at 4h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0010. Both extent of coating and drug: polymer ratio had negative effect on the release of drug. Thus, an increase in extent of coating and drug: polymer ratio decreased the drug release at 4h.

The model describing the release from MH MUPS at 8 h was:

$$Y_3=75.23-4.33\ X_0+2.30X_1+3.58X_0X_1+3.48\ X_0^2+3.48X_1^2 \quad \text{(Eq. 4.4.7)}$$

The quadratic model and interaction were found to be significant for response Y_3. The Model F-value of 6.85 implies the model is significant. Value of regression coefficient (R^2 = 0.8303) indicated a good correlation between the response (release at 8 h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0126. Drug : polymer ratio had positive while extent of coating had negative effect on the release of drug. Thus, an increase in drug: polymer ratio increased the drug release at 8h, while an increase in extent of coating decreased the drug release at 8h.

The model describing the release from MH MUPS at 20 h was:

$$Y_4=90.39-0.77X_0-1.70X_1-0.20\ X_0X_1+2.29X_0^2-2.41\ X_1^2 \quad \text{(Eq. 4.4.8)}$$

The quadratic model and interaction were found to be significant for Y_4 response. The Model F-value of 7.73 implies the model is significant. Value of regression coefficient (R^2 = 0.8467) indicated a good correlation between the response (release at 8 h) and the selected factors. Statistical analysis using ANOVA revealed a significant model fit with a *P* value of 0.0091. Both extent of coating and drug: polymer ratio had negative effect on the release of drug. Thus, an increase in extent of coating and drug: polymer ratio decreased the drug release at 20h.

Contour Plots and Response Surface Analysis

For every response, contour plots were generated between two variables, extent of coating (X_0) and drug : polymer ratio (X_1). In all the cases, the contour plot formed parabolic shape (Figure 4.5.20 and 4.5.21).

For MS MUPS

Response Y_1 was selected to check burst release of drug , if any, at 1h. Responses Y_2 and Y_3 were selected to check the drug release at 4 and 8h respectively so as to ensure that the drug was continuosly being released from the system. Response Y_4 was selected to ensure release of more than 85% of drug after 20 h.

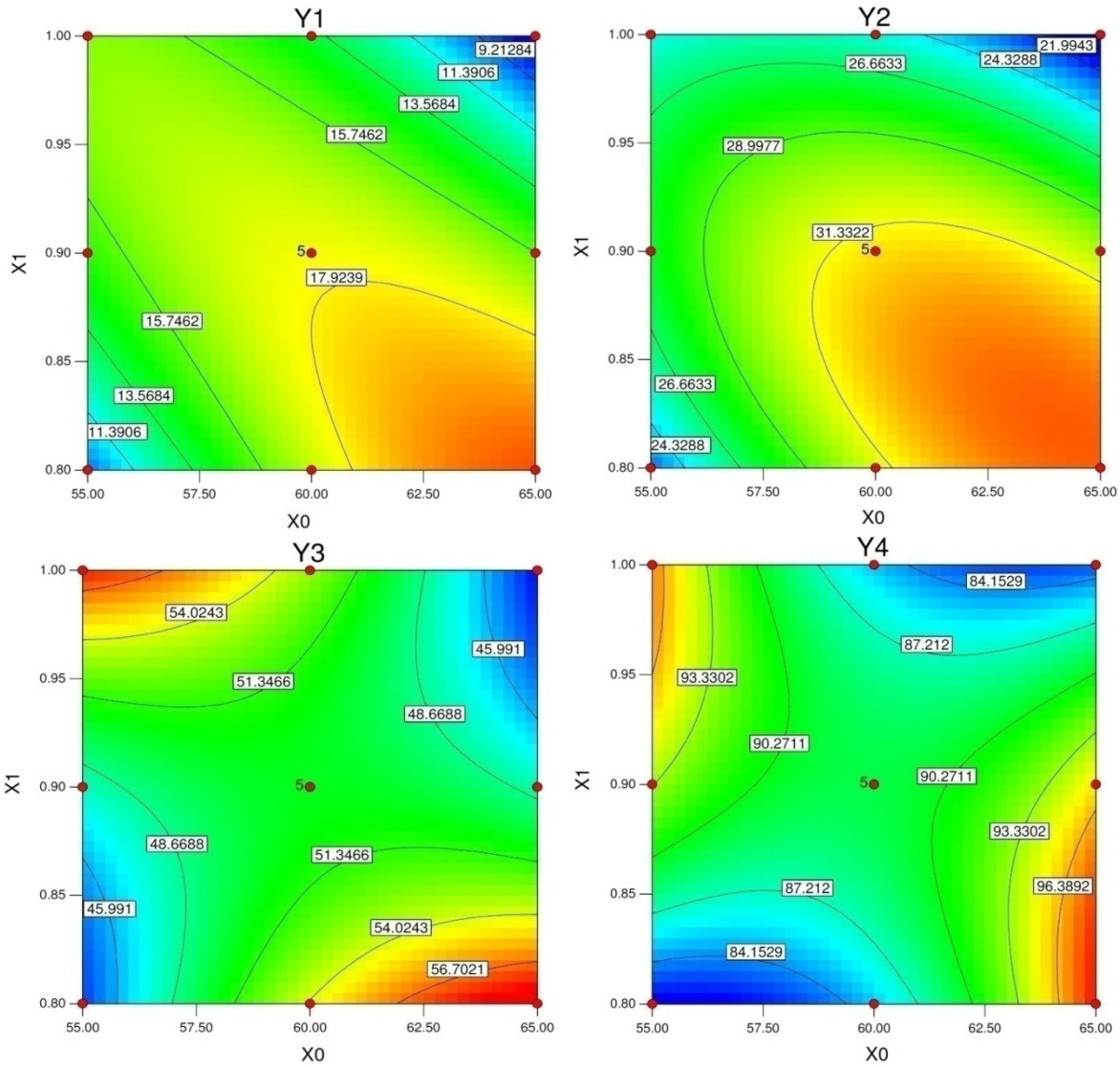

Figure 4.5.20: Contour plots showing effect of X_0 and X_1 on responses Y1, Y2, Y3 and Y4 for MS MUPS

Response Y_1: Drug release at 1h was found to be less than 25% in all the experiments. Maximum release of 21.2 ± 3.2% was observed for value of X_0= 65 and X_1= 1:0.8 (Run 11). This suggests that at higher coating extent and lower concentration of hydrophobic (ethyl cellulose) polymer, maximum drug release was achieved for response Y1. Drug release from matrix pellets is controlled by its diffusion through the polymeric matrix and/or the pores formed by the leached drug and hydrophilic polymer (HPC). At higher drug loading, more pores are formed through which the drug can diffuse into the dissolution medium. Moreover, at high drug to polymer ratio, the drug will diffuse rapidly from the matrix due to high concentration gradient [22].

Response Y_2 and Y_3: The observed values ranged from 20.8 ± 3.4 to 34.9 ± 3.1 % and 42.9 ± 3.1 to 58.7 ± 3.0 % respectively. This continuous release from the system suggests that the drug is uniformly dispersed into the polymer matrix.

Response Y_4: In case of Run no. 5 with values of X_0= 65 and X_1= 1.1 and Run no. 13 with values of X_0= 55 and X_1= 1: 0.8, the drug release at 20h was less than 85%. This suggests that at higher concentration of hydrophobic content (ethyl cellulose), the drug release rate is drastically decreased which may be due to increased diffusion length for the drug molecule from the hydrophobic matrix.

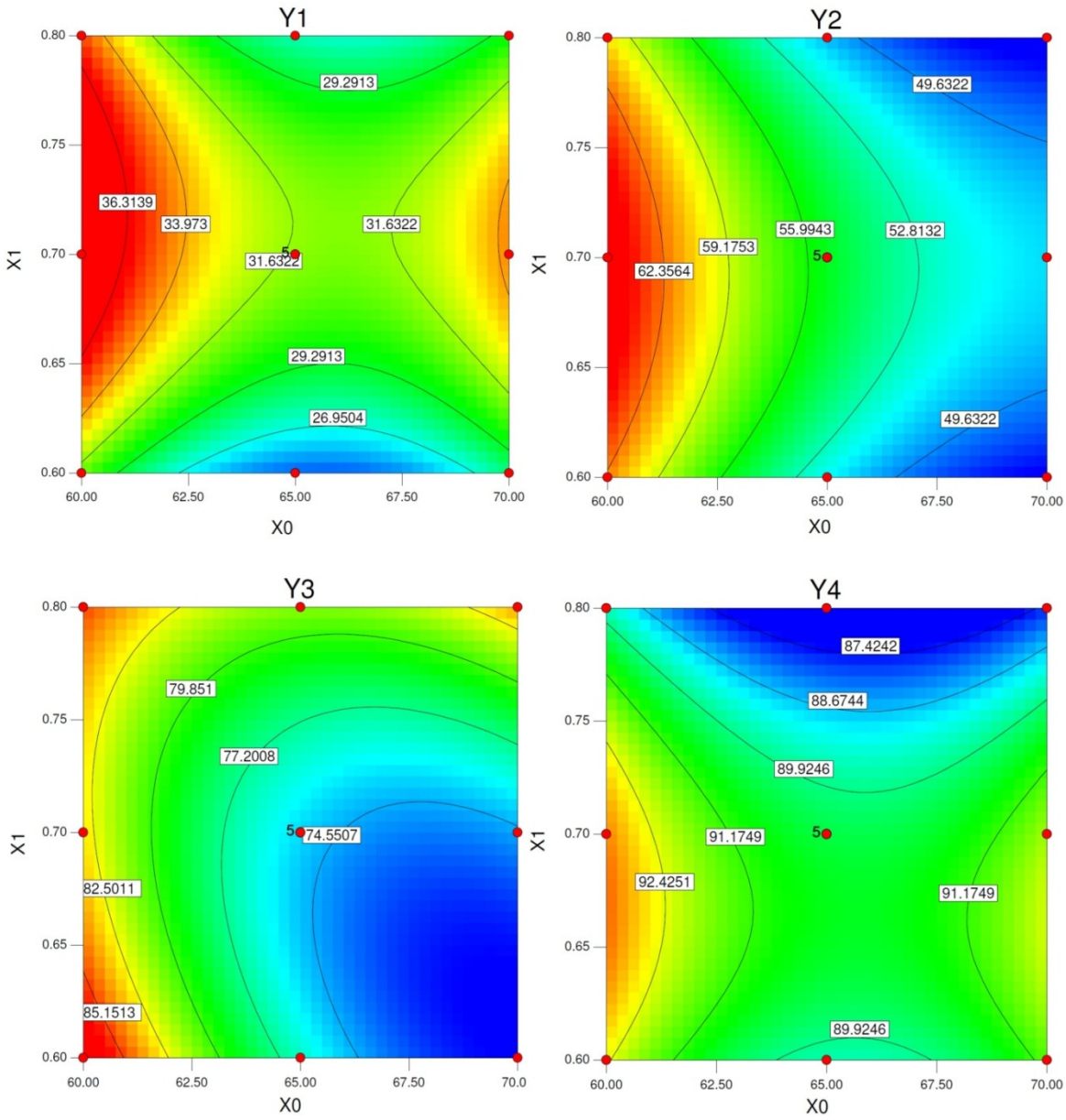

Figure 4.5.21: Contour plots showing effect of X_0 and X_1 on responses Y1, Y2, Y3 and Y4 for MH MUPS

For MH MUPS

Response Y_1 was selected to check burst release of drug , if any, at 1h. Responses Y_2 and Y_3 were selected to check the drug release at 5 and 12h respectively so as to ensure that the drug was continuosly being released from the system. Response Y_4 was selected to ensure complete release of drug after 20 h.

Response Y_1: Drug release at 1h was found to be in between 20 - 40% in all the experiments, i.e. no burst release was observed, as desired in this formulation as per reported specifications of release by USFDA . Maximum release of 36.2± 2.2% was

observed for value of X_0= 60 and X_1= 1:0.7 (Run 8). This suggests that at lower coating extent and medium concentration of polymer combination, maximum drug release was achieved for response Y1. Drug release from matrix pellets is controlled by its diffusion through the polymeric matrix and/or the pores formed by the leached drug. At higher drug loading, more pores are formed through which the drug can diffuse into the dissolution medium.

Response Y_2 and Y_3: The observed values ranged from 47.1± 1.4 to 64.5± 2.4 %, 72.1± 1.1 to 86.5± 2.4 % respectively. This suggests that the drug was uniformly dispersed throughout the polymer matrix and as it was released continuously.

Response Y_4: In all the cases, drug release was found not less than 85% as desired by reported product specifications. Therefore, complete drug release was observed.

Response surface plots for each drug showed the relationship between these variables even more clearly when plotted between X_0 and X1 for all four responses (Figure 4.4.22 and 4.4.23). The plots for each drug were found to be linear between X_0 and X_1 for all four responses.

For MS, at lower coating extent and lower concentration of hydrophobic polymer, release for selected time points was found to be maximum as depicted from response surface plots, while at higher concentration of EC, drug release was minimal.

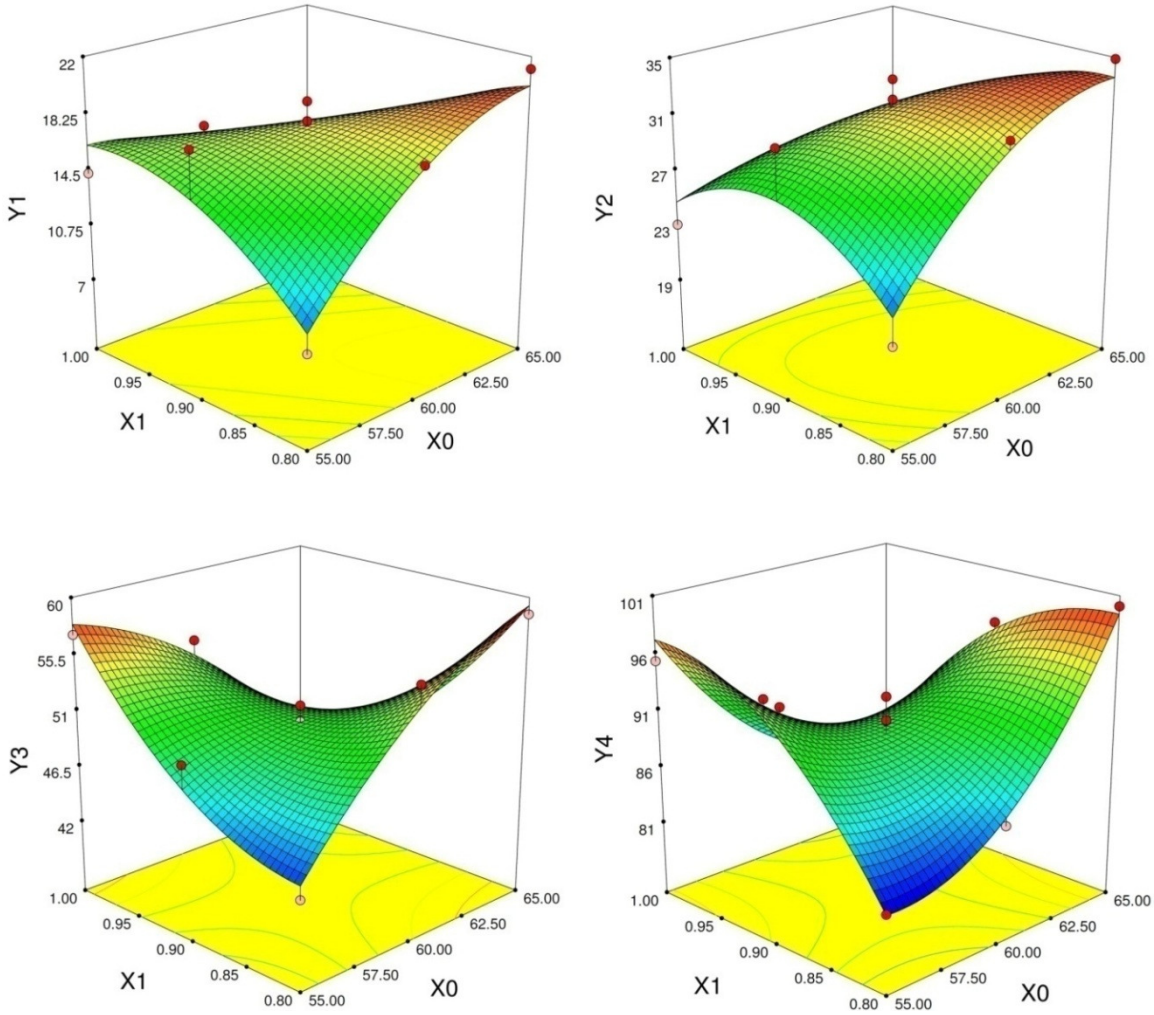

Figure 4.5.22: Response surface plots showing effect of X_0 and X_1 on responses Y1, Y2, Y3 and Y4 for MS MUPS

For MH, at lower coating extent and medium concentration of hydrophobic polymer, release for selected time points was found to be maximum as depicted from response surface plots, while at higher concentration of Eudragit® polymer and lower level of coating, the drug release was minimal. Finally, based on the responses of runs from CCF design, at 65% extent of coating and 1:0.8 Drug : Polymer ratio (Run no.11) desired release was found for MS while that for MH it was achieved with 70% extent of coating and 1:0.6 Drug: Polymer ratio (Run no.3).

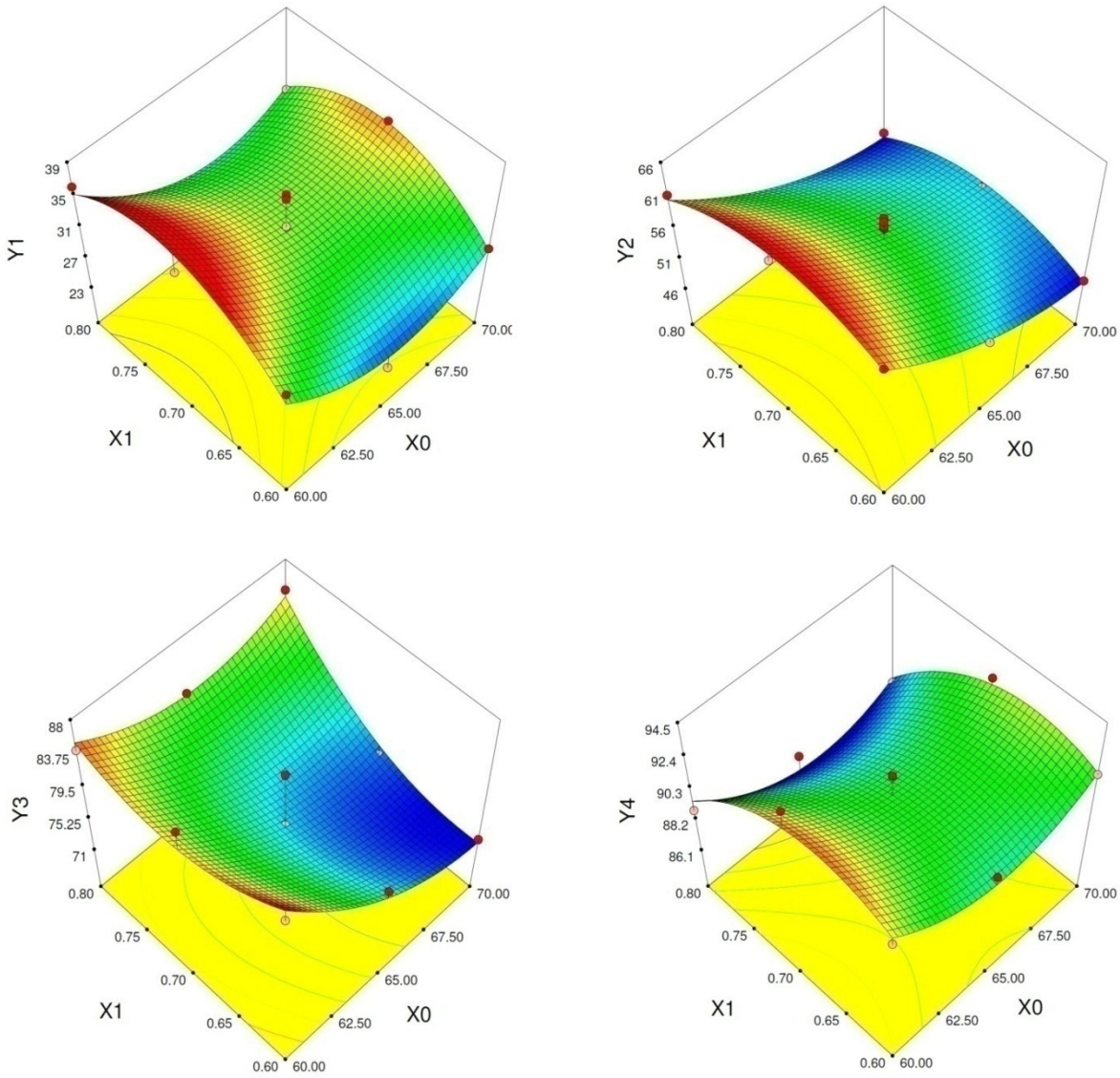

Figure 4.5.23: Response surface plots showing effect of X_0 and X_1 on responses Y1, Y2, Y3 and Y4 for MH MUPS

4.5.16 Risk mitigation and control strategy

The risk mitigation and control strategy demonstrates product knowledge of the current process and assures that quality is built into the product and not just tested- the objective of QbD. As seen in the initial risk assessment, the formulation attribute like API particle size had least chances of affecting dissolution (CQA) since the highly soluble drugs (MS and MH) were dissolved and sprayed over core pellets in solution form. Hence, it was not further investigated and marked as low risk (green color) in risk control strategy. Formulation attributes which had medium risk (marked in yellow in initial risk assessment) were addressed by design (development trials). For other formulation

attributes which had high risk (marked in red in initial risk assessment), the Proven Acceptance Range (PAR) was identified.

Thus, in case of both the drugs, control over core pellet quantity (50 mg/unit) and core pellet size (Celphere CP-203, 150-300µ), ensured that the coating process would be smooth, drug release will occur in a controlled manner and a balance would be maintained between the bulk of the product and final size of the pellets. The matrix drug layering technique was selected for its simplicity and better control over drug release. Face Centered Central Composite Design was used to investigate the multidimensional interaction of extent of coating (X_0) and Drug: Polymer Ratio (MS: EC+ HPC; MH: Eudragit®RS+ Eudragit®RL) (X_1) on dissolution. A design space for X_0 (MS: 55-65%, MH: 60-70%) and X_1 (MS: 1:08- 1:1; MH: 1:0.6 - 1:0.8) was established for these input variables which were ranked as high risk in the initial risk assessment and hence marked green in the final risk assessment for MS and MH (Table 4.5.31).

Table 4.5.31: Final Formulation Risk Assessment for MS and MH MUPS

Drug Product CQA	Formulation attribute					
	API particle size	Core pellet size	Core pellet quantity	Drug layering technique	Extent of CR coating	Drug: Polymer
Dissolution	Low	Addressed by Design	Addressed by Design	Addressed by Design	Critical-PAR identified	Critical-PAR identified

4.5.17 Eudragit® E coating

Despite palpable advantages of the controlled release powder for reconstitution (CRPFR), till date there are very few such preparations available in the market. This is due to challenges associated with the formulation development like 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 drug+ CR coating layer 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 [23]. 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.

4.5.17.1 Selection of process parameters

Selection of process parameters for MS Eudragit® E coating

In case of batch MS-38 which was taken with spray rate of 0.20- 0.60 g/min, no agglomeration was observed and satisfactory yield (93.4± 2.3%) was achieved. So to check the impact of spray rate on the percentage yield, batch MS-39 was taken with increased spray rate (0.50- 0.90 g/min). As the spray rate was increased, the formation of liquid bridge across the substrate and coating droplets occurred, which led to agglomeration and reduced yield to 36.1± 4.1%. Hence the spray rate of 0.20-0.60 g/min and other process parameters used in batch MS-38 (Table 4.3.42) were finalized for further trials considering an agglomerate free process having higher percentage yield.

Table: 4.5.32: Selection of process parameters for MS Eudragit® E coating trials

	Batch MS-38	**Batch MS-39**
Percentage yield (%)	93.4± 2.3	36.1± 4.1
Observation	No Agglomeration	Agglomeration

Selection of process parameters for MH Eudragit® E coating

Similarly, batches MH-31 and MH-32 were taken with spray rate of 0.20- 0.60 and 0.50-0.90g/min respectively. In case of batch MH-31 no agglomeration was observed and 91.3± 3.0% yield was achieved (Table 4.5.33). So to check the impact of spray rate on the percentage yield, batch MH-32 was taken with increased spray rate. But due to formation of agglomerates, the yield was reduced to 38.4± 3.5%. Hence the spray rate of 0.20-0.60 g/min and other process parameters used in batch MH-31 (Table 4.3.44) were finalized for further trials considering an agglomerate free process having higher percentage yield.

Table: 4.5.33: Percentage yield for selection of process parameters for MH Eudragit® E coating trials

	Batch MH-31	**Batch MH-32**
Percentage yield (%)	91.3± 3.0	38.4± 3.5
Observation	No Agglomeration	Agglomeration

4.5.17.2 Solid content

Selection of solid content for MS Eudragit® E coating dispersion

Batches MS-40 and MS-41 were taken with 6 and 8% w/w solid content of Eudragit® E coating solution respectively. In case of batch MS-40, no agglomeration was observed. The percentage yield and assay value were 96.6± 2.7% and 98.9± 1.9% respectively. This suggested that the processing conditions and the solid content selected for Eudragit® E coating solution were appropriate. In order to check whether these conditions can be improved further, Batch MS-41 with 8% w/w solid content of Eudragit® E coating solution was prepared, but agglomeration was observed. The percentage yield and assay value were 42.1± 3.4% and 39.8± 2.7% respectively. Hence a solid content of 6 % w/w was selected for Eudragit® E coating and Batch MS-40 was selected as the optimized batch and characterized further.

Table 4.5.34: Selection of solid content for MS-Eudragit® E coating

	Batch MS-40	**Batch MS-41**
Percentage yield (%)	96.6± 2.7	42.1± 3.4
Assay (%)	98.9± 1.9	39.8± 2.7
Observation	No Agglomeration	Agglomeration

Selection of solid content for MH Eudragit® E coating dispersion

Batches MH-33 and MH-34 were taken with 6 and 8% % w/w solid content of Eudragit® E coating solution respectively. In case of batch MH-33, no agglomeration was observed. The percentage yield and assay value were 93.8± 2.8% and 99.1± 1.4% respectively. This suggested that the processing conditions and the solid content selected for Eudragit® E coating solution in batch MH-33 were appropriate. Batch MH-34 with 8% w/w solid content of Eudragit® E coating solution was carried out, showed agglomeration leading to lower percentage yield and assay value (43.2± 3.7% and 42.8± 1.9% respectively). Hence a solid content of 6% w/w was selected for Eudragit® E coating and Batch MH-33 was selected as the optimized batch and characterized further.

Table 4.5.35: Selection of solid content for MH-Eudragit® E coating

	Batch MH-33	Batch MH-34
Percentage yield (%)	93.8± 2.8	43.2± 3.7
Assay (%)	99.1± 1.4	42.8± 1.9
Observation	No Agglomeration	Agglomeration

Evaluation of Eudragit® E coated pellets

The Eudragit® E coated pellets for MS and MH were evaluated for Particle Size Distribution, morphology, micromeritic properties and drug release study.

Particle Size Distribution

The particle size distribution for Eudragit® E coated pellets of batch MS-40 and batch MH-33 were determined by sieve analysis method. It was observed that 0.9± 0.4%, 2.3± 1.2%, 93.1± 2.1, 1.3± 0.8% and 2.4± 1.3% fraction of pellets of MS (Figure 4.5.24) and 1.3± 0.7%, 24.8± 1.6%, 71.5± 1.9, 1.4± 0.3% and 1.1± 0.9% fraction of pellets of MH (Figure 4.5.25) were retained on sieve numbers 30, 35, 40 and 60 respectively corresponding to 93.1± 2.1% pellets having size range of 425-500µ, suggesting D_{90} value of 500µ of MS and 600µ for MH. Above findings suggest uniform and narrow size distribution of pellets, ensuring accurate and reproducible coating.

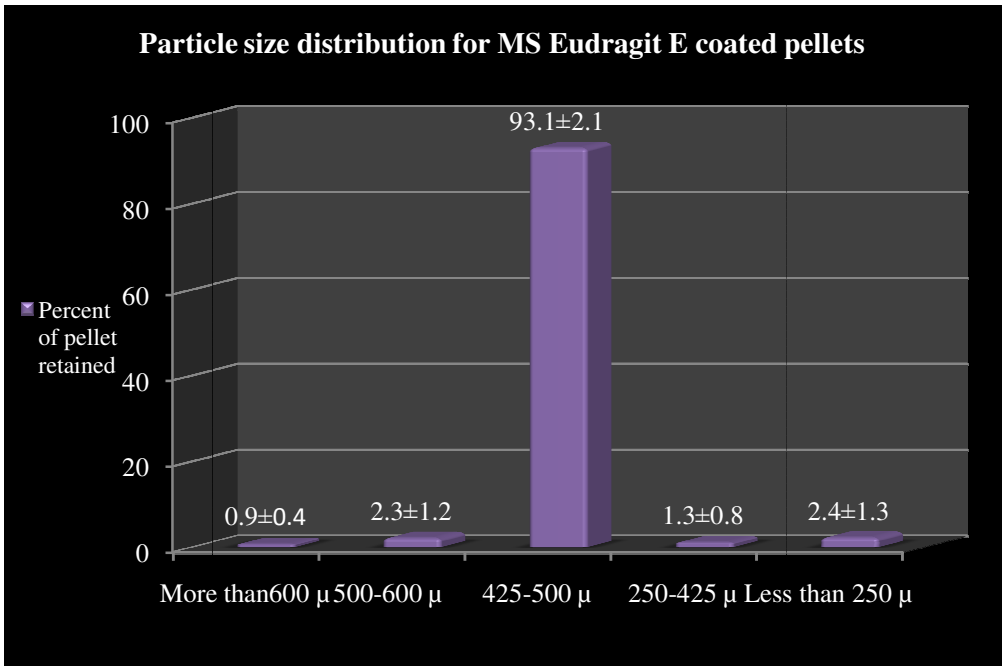

Figure 4.5.24: Particle size distribution for MS Eudragit® E coated pellets

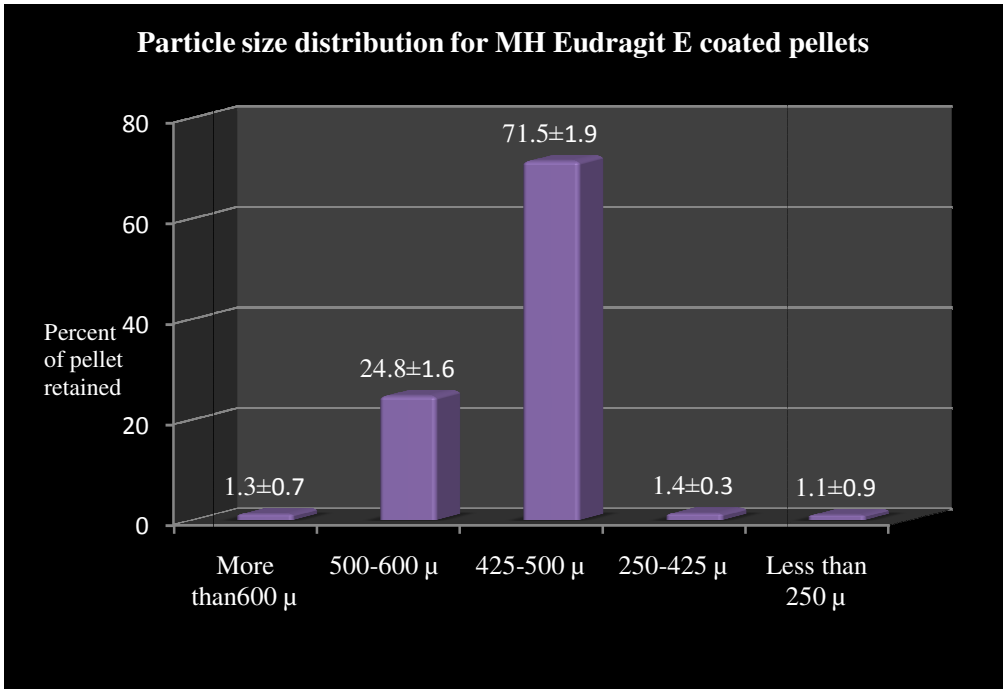

Figure 4.5.25: Particle size distribution for MH Eudragit® E coated pellets

Morphology

Surface morphology of Eudragit® E coated pellet for Batch MS-40 and Batch MH-33 are shown in Figure 4.5.26 and Figure 4.5.27 respectively. The pellets appeared to be spherical in shape with smooth surface. Figure 4.5.28 and Figure 4.5.29 shows transverse section of Eudragit® E coated pellet of MS and MH respectively. The core and two coating layers (drug+ CR polymer and Eudragit® E layer) can be easily distinguished. The thickness of drug+ CR polymer layer was determined to be 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.

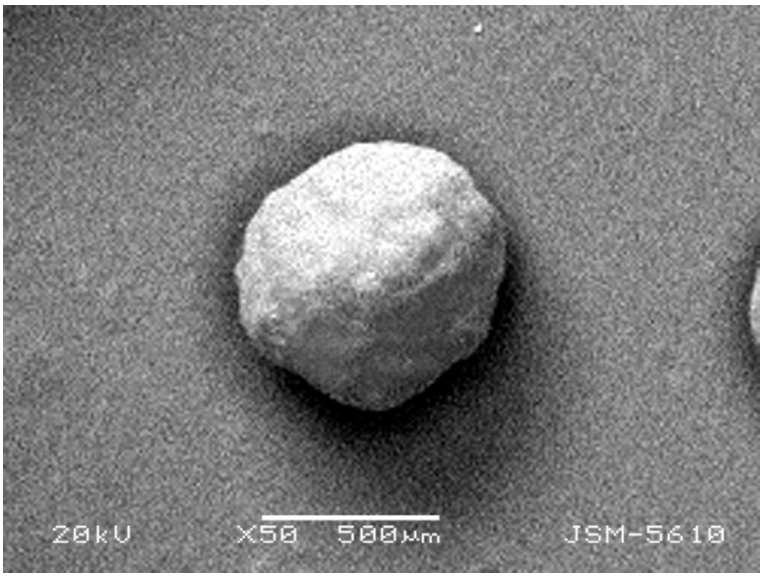

Figure 4.5.26: Scanning electron microphotograph of MS Eudragit® E coated pellet

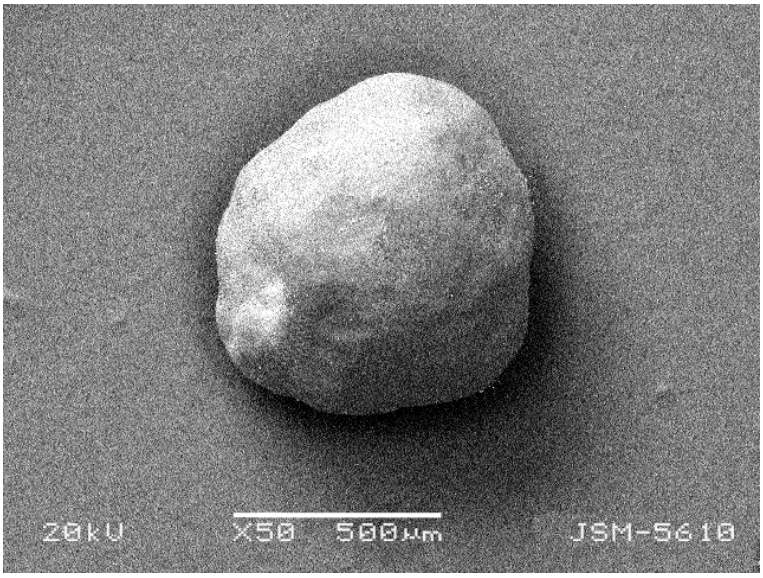

Figure 4.5.27: Scanning electron microphotograph of MH Eudragit® E coated pellet

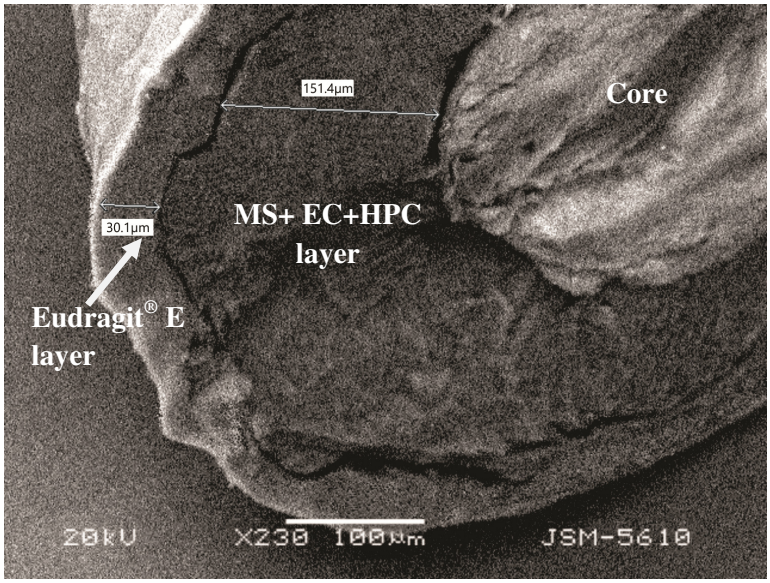

Figure 4.5.28: Scanning electron microphotograph of transverse section Eudragit® E coated pellet of MS

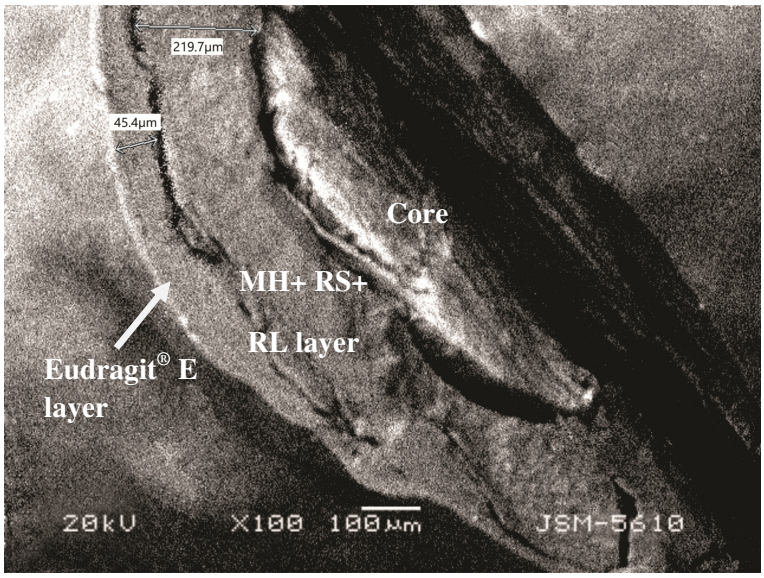

Figure 4.5.29: Scanning electron microphotograph of transverse section Eudragit® E coated pellet of MH

Differential Scanning Calorimetry (DSC)

Sharp endothermic peaks at 135.38°C and 231.93°C corresponding to the melting points of pure drugs were prominent in optimized batches MS-40 and MH-33 respectively. This clearly suggests that the drugs were present in unchanged form (Figure 4.5.30 and Figure 4.5.31) in final MUPS formulation.

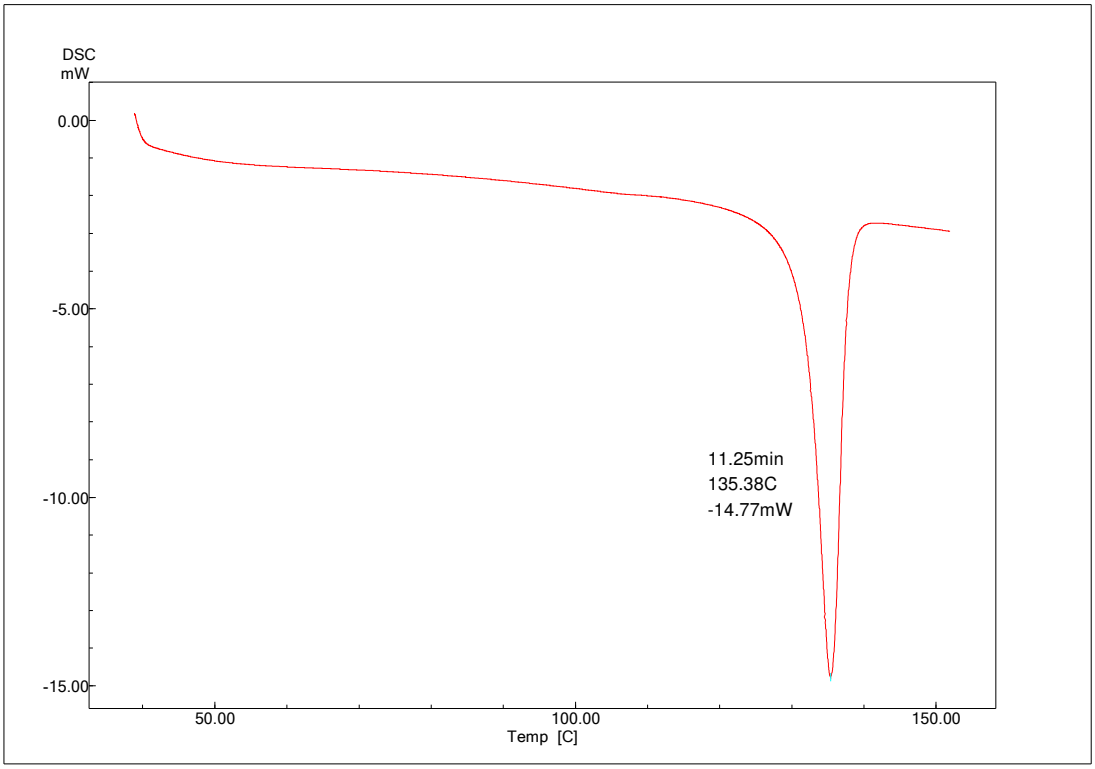

Figure 4.5.30: DSC thermogram of MS Eudragit® E coated pellets of MS

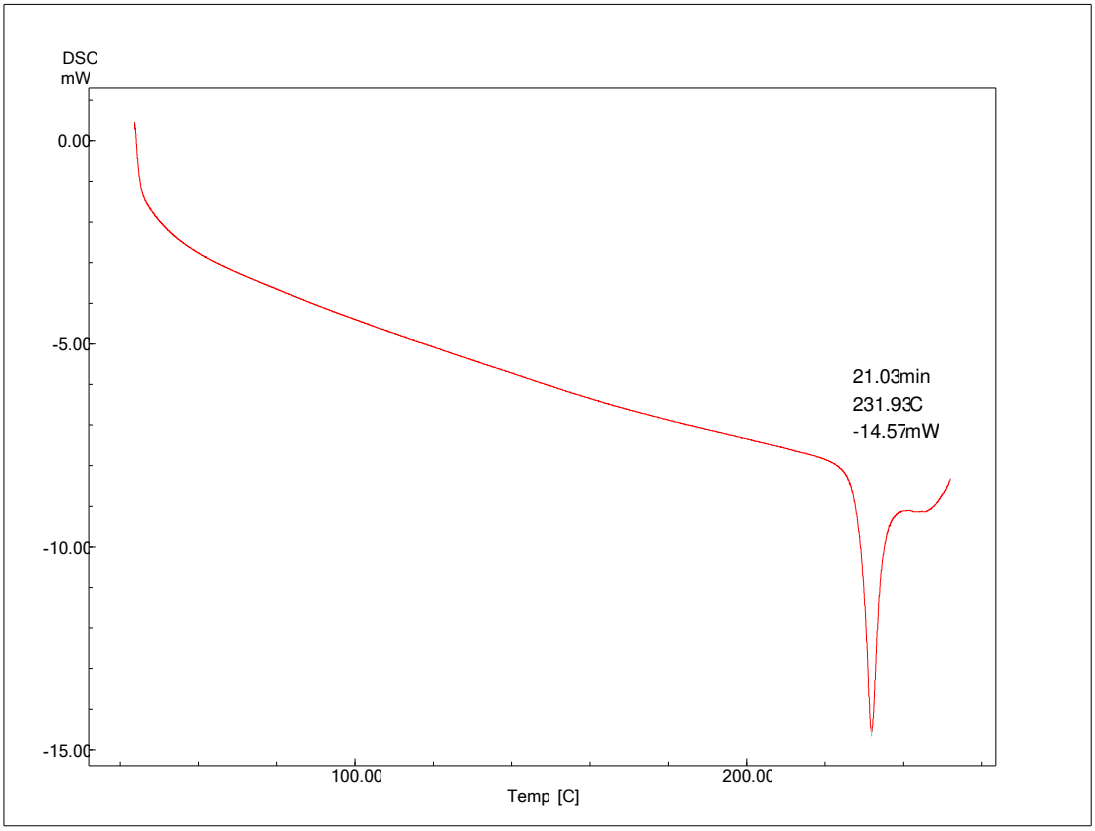

Figure 4.5.31: DSC thermogram of MH Eudragit® E coated pellets of MH

Micromeritic properties

Angle of repose for Eudragit® E coated pellets of the MS and MH optimized batch was 28.15±0.27° and 29.65±0.30° respectively which indicated that pellets had excellent flow. The bulk and tapped density were found to be 0.810± 0.052 g/mL and 0.895± 0.031 g/mL for MS and 0.791± 0.054 g/mL and 0.872± 0.026g/mL for MH respectively. The results for Hausner's ratio (1.103± 0.03), compressibility index (10.26± 0.4) for MS and Hausner's ratio (1.125± 0.05), compressibility index (12.50± 0.2) for MH indicated good flow of the pellets. The friability was found to be 0.03± 0.02% and 0.05± 0.02% for MS and MH respectively indicating that the pellets possessed sufficient mechanical strength to withstand the rigors and shocks encountered during production and transportation.

Drug release study

The drug release at 1, 4, 8 and 20h was 17.6± 3.8, 31.9± 3.1, 48.9± 2.6 and 95.9± 1.1 % for MS (Figure 4.5.32) and at 1, 5, 12 and 20h was 27.7± 2.9, 48.1± 1.1, 73.4± 1.6 and 93.4± 1.4% for MH (Figure 4.5.33) respectively. This release profile (Table 4.5.36) 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 (Table 4.5.37). 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. Drug dissolution curves for all three models for both the drugs were plotted against time (Fig. 4.5.34, Fig. 4.5.35, Fig. 4.5.36 for MS and Fig. 4.5.37, Fig. 4.5.38, Fig. 4.5.39 for MH respectively).The regression coefficient value for both the drugs (Table 4.5.38) was found to be highest (r^2 = 0.991 for MS and r^2 = 0.982 for MH) for zero order model. Hence, it was concluded that 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.

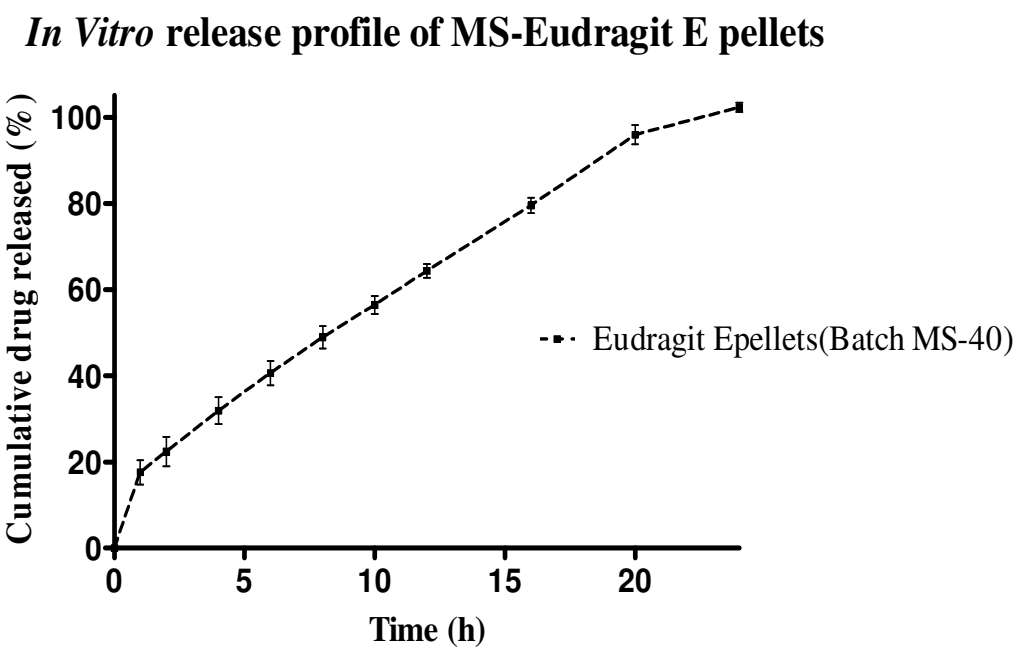

Figure 4.5.32: Cumulative drug released (%) Vs time from MS-Eudragit® E coated pellets

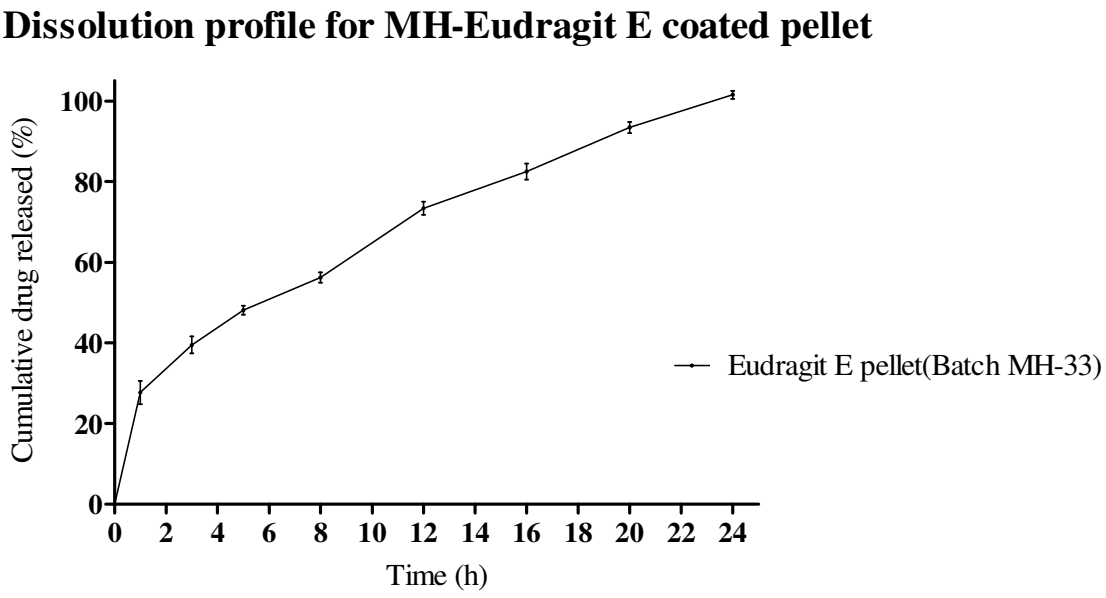

Figure 4.5.33: Cumulative drug released (%) Vs time from MH-Eudragit®E coated pellets

Table 4.5.36: Drug release profile for optimized MS-Eudragit® E coated pellets (Batch MS-40)

Time (h)	Cumulative drug released (%)
1	17.6± 2.8
2	22.4± 3.4
4	31.9± 3.1
6	40.6± 2.8
8	48.9± 2.6
10	56.4± 2.1
12	64.3± 1.6
16	79.5± 1.8
20	95.9± 2.1
24	102.3± 1.1

Table 4.5.37: Drug release profile for optimized MS-Eudragit® E coated pellets (Batch MH-33)

Time (h)	Cumulative drug released (%)
1	27.7± 2.9
3	39.5± 2.1
5	48.1± 1.1
8	56.2± 1.3
12	73.4± 1.6
16	82.5± 2.0
20	93.4± 1.4
24	101.5± 1.0

Table 4.5.38: Linear correlation coefficient values of various models for *in vitro* release study of MUPS

In vitro release study	Linear Correlation Coefficient (r^2) Values		
	Zero order model	First order model	Higuchi model
MS	0.991	0.874	0.982
MH	0.9820	0.9732	0.9295

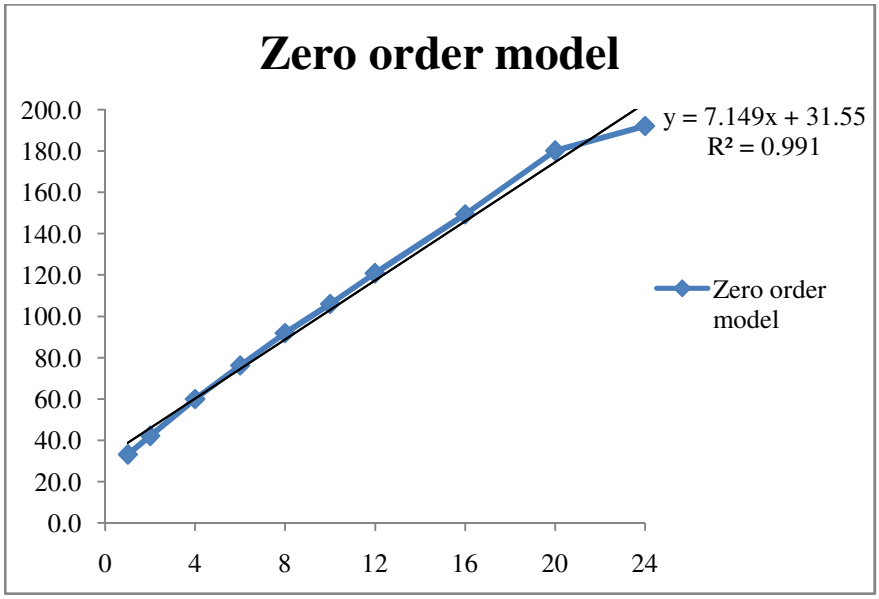

Figure 4.5.34: MS dissolution curve for zero order model

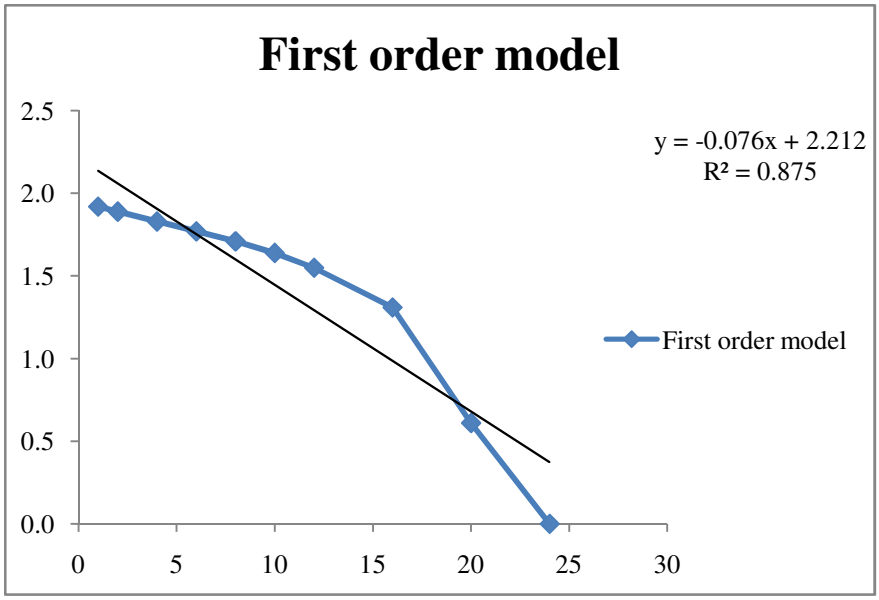

Figure 4.5.35: MS dissolution curve for first order model

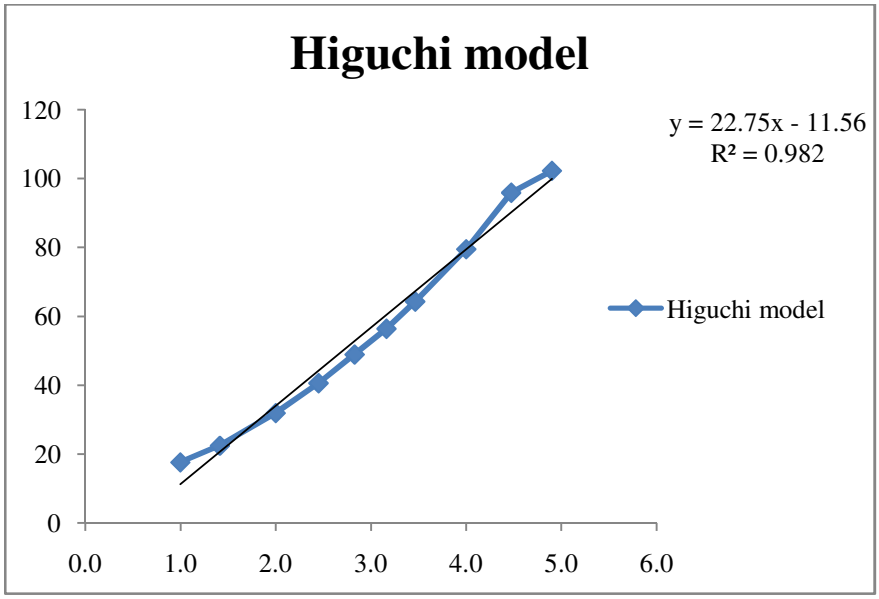

Figure 4.5.36: MS dissolution curve for Higuchi model

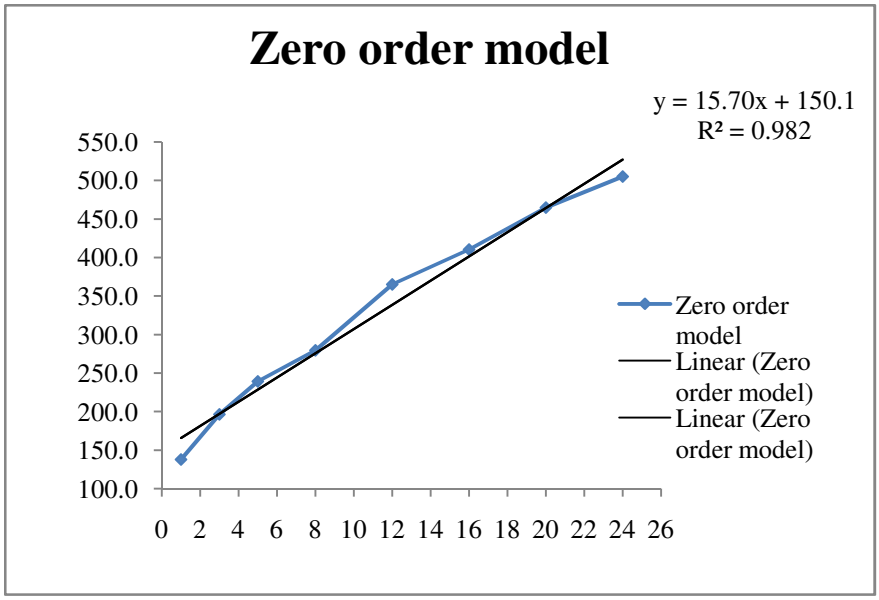

Figure 4.5.37: MH dissolution curve for zero order model

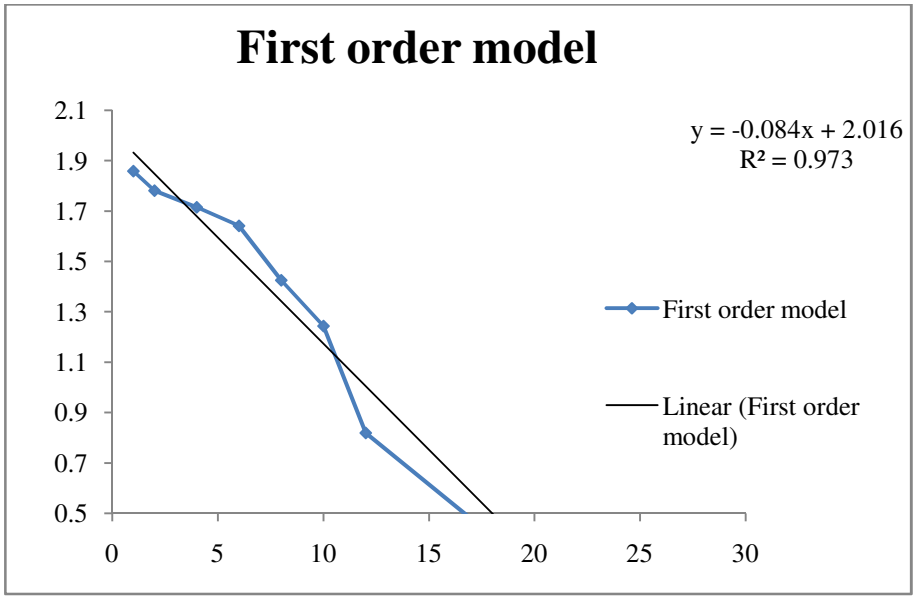

Figure 4.5.38: MH dissolution curve for first order model

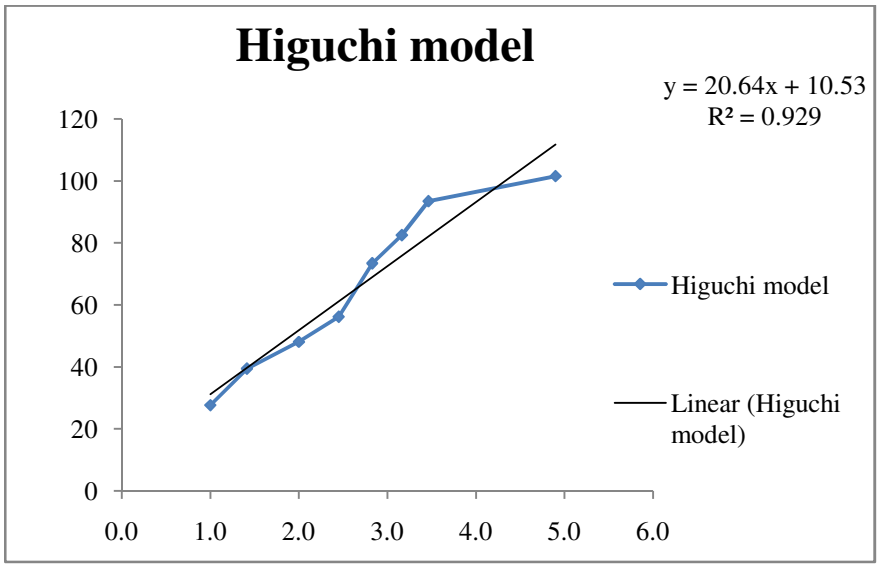

Figure 4.5.39: MH dissolution curve for Higuchi model

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