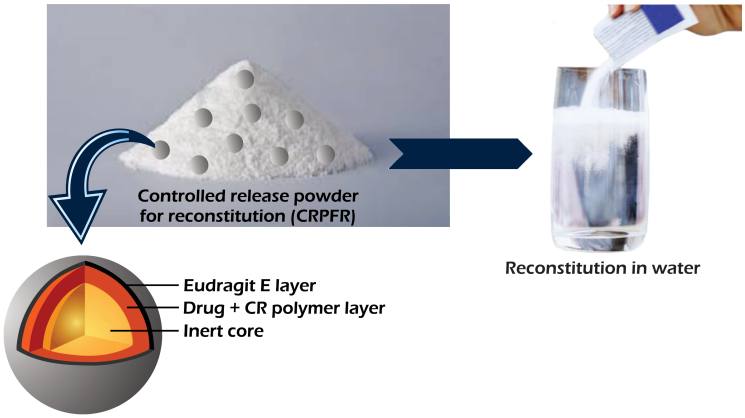
# Formulation Development

## Part A: CRPFR




Chapter 5

## 5.1 Materials and Equipments

### 5.1.1 Materials

Avicel CL-611 was received as gift sample from FMC Biopolymer, USA, Sodium carboxy methyl cellulose, Sodium carbonate, Sodium hydroxide, Magnesium carbonate, Calcium carbonate were purchased from Thermo Fisher Scientific, Mumbai, India. HPMC K15 M, and Xanthan gum were purchased from SD Fine Chemicals, Mumbai, India. Vanilla flavor from Fermenich, Germany, FD&C Yellow no. 6 from Roha Dye Chem Pvt. Ltd., Mumbai, India, and Aspartame from Sigma-Aldrich, India.

### 5.1.2 Equipments

Following is the list of equipments and instruments used in formulation development of CRPFR.

**Table 5.1.1: List of Equipments and Instruments**

| Name of equipment/ Instrument | Model | Make |
|---|---|---|
| Electronic weighing Balance | ELB300 | Shimadzu, Japan |
| UV-visible double beam spectrophotometer | UV-1800 | Shimadzu, Japan |
| USP dissolution apparatus Type II | TDT-06P | Elecrtolab, India |
| pH meter | PICO+ | Lab India, India |
| USP Tapped Density Tester | ETD-1020 | Electrolab, India |
| Stability chamber | Tanco-PLT 258 | S.R Lab Instruments, India |
| Magnetic stirrer | 1MLH | Remi Motors, India |
| Induction sealer | APSL 1510 | Amar packaging, India |
| Viscometer | Brookfield DV-I Prime | Brookfield, USA |

## 5.2 Formulation of Controlled Release Powder for Reconstitution

Formulating a convenient dosage form like controlled release powder for reconstitution (CRPFR), which is easy to swallow, can provide novel way of overcoming the potential barriers associated with the administration of MUPS to children, elderly and patients suffering from dysphagia or unwilling to swallow the solid medication. MUPS formulated into powder for reconstitution will enable patients to easily prepare the

suspension which is physically and chemically stable. Further, the dosage form will retain the attributes of **ease of handling, transportation and storage**.

In the present study, Eudragit® E coated pellets from the optimized batches (MS-40 and MH-33) were pursued further for formulation into suitable dosage form- CRPFR. The CRPFR was prepared by blending the Eudragit® E coated pellets with suitable excipients like suspending agent, alkalizing agents, flavorant and colorant.

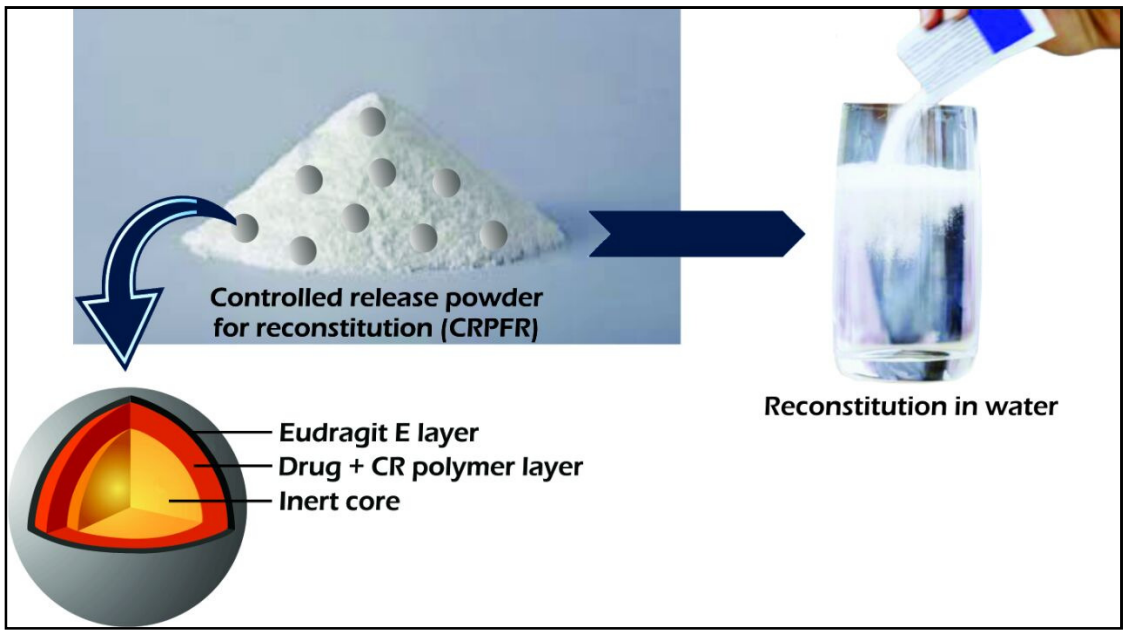



**Figure 5.2.1: Schematic representation of CRPFR containing MUPS**

### 5.2.1 Selection of suspending agent

Suspending agents are used to control or minimize sedimentation and impart suitable viscosity to the final preparation. In the present study, considering the higher bulk density of the MS-Eudragit® E coated pellets (0.810± 0.052 g/mL) and MH- Eudragit® E coated pellets (0.800± 0.054 g/mL) it was anticipated that the pellets would settle down in suspension preparation. The reconstituted suspension was targeted to have sufficient viscosity that would be easily pourable as well as prevent formation of cake. Hence a powder for reconstitution was formulated which upon reconstitution with water would provide a palatable dosage form for the patients either suffering from dysphagia or reluctant to swallow the tablet dosage form.

Avicel CL-611 at a level of 5% w/w of the powder for reconstitution was used the suspending agent in the present study. It is reported that, when Avicel CL-611 is used in combination with protective colloids, the mixed system combines the advantages of both

the components and helps in rapid redispersion of the dispersed particles [1]. Hence trials were taken to select a suitable protective colloid at a suitable concentration so as to get a pourable reconstituted suspension. Accordingly, 60mL water was added into the container holding the PFR and was shaken manually.

To select a protective colloid with its concentration for MS-CRPFR and MH-CRPFR, various trials were taken at fixed concentration of 0.75 and 1.5% (Table 5.2.1 and 5.2.2). The selection was made on the basis of ease of redispersibility and viscosity of the resultant suspension.

**Table 5.2.1: Selection of suspending agent for MS-CRPFR**

| Sr. No. | Ingredients | MS-R1 | MS-R2 | MS-R3 | MS-R4 | MS-R5 | MS-R6 |
|---|---|---|---|---|---|---|---|
| | | mg/unit | mg/unit | mg/unit | mg/unit | mg/unit | mg/unit |
| 1 | MS-Eudragit® E Pellets | 950.00 | 950.00 | 950.00 | 950.00 | 950.00 | 950.00 |
| 2 | Avicel CL 611 | 51.81 | 51.81 | 51.81 | 51.81 | 51.81 | 51.81 |
| 3 | Xanthan gum | 7.77 | 15.54 | 0.00 | 0.00 | 0.00 | 0.00 |
| 4 | Sodium carboxy methyl cellulose | 0.00 | 0.00 | 7.77 | 15.54 | 0.00 | 0.00 |
| 5 | HPMC K15M | 0.00 | 0.00 | 0.00 | 0.00 | 7.77 | 15.54 |
| 6 | Sodium carbonate | 20.73 | 20.73 | 20.73 | 20.73 | 20.73 | 20.73 |
| 7 | Aspartame | 5.18 | 5.18 | 5.18 | 5.18 | 5.18 | 5.18 |
| 8 | Vanilla flavor | 0.52 | 0.52 | 0.52 | 0.52 | 0.52 | 0.52 |
| 9 | FD&C Yellow no. 6 | 0.26 | 0.26 | 0.26 | 0.26 | 0.26 | 0.26 |
| | Total | 1036.27 | 1044.04 | 1036.27 | 1044.04 | 1036.27 | 1044.04 |

**Table 5.2.2: Selection of suspending agent for MH-CRPFR**

| Sr. No. | Ingredients | MH-R1 | MH-R2 | MH-R3 | MH-R4 | MH-R5 | MH-R6 |
|---|---|---|---|---|---|---|---|
| | | mg/unit | mg/unit | mg/unit | mg/unit | mg/unit | mg/unit |
| 1 | MH-Eudragit® E Pellets | 2528.39 | 2528.39 | 2528.39 | 2528.39 | 2528.39 | 2528.39 |
| 2 | Avicel CL 611 | 137.41 | 137.41 | 137.41 | 137.41 | 137.41 | 137.41 |
| 3 | Xanthan gum | 20.61 | 41.22 | 0.0 | 0.0 | 0.0 | 0.0 |
| 4 | Sodium carboxy methyl cellulose | 0.0 | 0.0 | 20.61 | 41.22 | 0.0 | 0.0 |
| 5 | HPMC K15M | 0.0 | 0.0 | 0.0 | 0.0 | 20.61 | 41.22 |
| 6 | Sodium carbonate | 54.97 | 54.97 | 54.97 | 54.97 | 54.97 | 54.97 |
| 7 | Aspartame | 12.97 | 12.97 | 12.97 | 12.97 | 12.97 | 12.97 |
| 8 | Vanilla flavor | 1.30 | 1.30 | 1.30 | 1.30 | 1.30 | 1.30 |
| 9 | FD&C Yellow no. 6 | 0.65 | 0.65 | 0.65 | 0.65 | 0.65 | 0.65 |
| | Total | 2756.30 | 2756.30 | 2756.30 | 2756.30 | 2756.30 | 2756.30 |

### 5.2.2 Selection of alkalizer

The main challenge associated with the formulation development of controlled release powder for reconstitution is diffusion of drug into the suspending vehicle after reconstitution. A simple process for manufacturing above dosage form while overcoming the associated difficulty was developed by creating an alkaline micro environment into the reconstituted suspension by adding an alkalizer in the final dosage form. This alkalizer would prevent the drug leaching from the Eudragit® E (a pH dependent polymer) coated pellets into the reconstituted suspension by creating an alkaline microenvironment after reconstitution.

Batches were taken at fixed concentration of 2% w/w of PFR to select a suitable alkalizer for MS- CRPFR (Table 5.2.3) and MH-CRPFR (Table 5.2.4).

Accordingly, batches MS-R7, MS-R8, MS-R9 and MS-R10 were taken with Sodium hydroxide, Calcium carbonate, Magnesium carbonate and Sodium carbonate respectively.

Similarly, batches MH-R7, MH-R8, MH-R9 and MH-R10 were taken with Sodium hydroxide, Calcium carbonate, Magnesium carbonate and Sodium carbonate respectively.

**Table 5.2.3: Selection of alkalizer for MS-CRPFR**

| Sr. No. | Ingredients | MS-R7 | MS-R8 | MS-R9 | MS-R10 |
|---|---|---|---|---|---|
| | | mg/unit | mg/unit | mg/unit | mg/unit |
| 1 | Eudragit® E Pellets | 950.00 | 950.00 | 950.00 | 950.00 |
| 2 | Avicel CL 611 | 51.81 | 51.81 | 51.81 | 51.81 |
| 3 | HPMC K15M | 7.77 | 7.77 | 7.77 | 7.77 |
| 4 | Sodium hydroxide | 20.73 | 0.00 | 0.00 | 0.00 |
| 5 | Calcium carbonate | 0.00 | 20.73 | 0.00 | 0.00 |
| 6 | Magnesium carbonate | 0.00 | 0.00 | 20.73 | 0.00 |
| 7 | Sodium carbonate | 0.00 | 0.00 | 0.00 | 20.73 |
| 8 | Aspartame | 5.18 | 5.18 | 5.18 | 5.18 |
| 9 | Vanilla flavor | 0.52 | 0.52 | 0.52 | 0.52 |
| 10 | FD&C Yellow no. 6 | 0.26 | 0.26 | 0.26 | 0.26 |
| | Total | 1036.27 | 1036.27 | 1036.27 | 1036.27 |

**Table 5.2.4: Selection of alkalizer for MH-CRPFR**

| Sr. No. | Ingredients | MH-R7 | MH-R8 | MH-R9 | MH-R5 |
|---|---|---|---|---|---|
| | | mg/unit | mg/unit | mg/unit | mg/unit |
| 1 | MH- Eudragit® E Pellets | 2528.39 | 2528.39 | 2528.39 | 2528.39 |
| 2 | Avicel CL 611 | 137.41 | 137.41 | 137.41 | 137.41 |
| 3 | HPMC K15M | 20.61 | 20.61 | 20.61 | 20.61 |
| 4 | Sodium hydroxide | 54.97 | 0.0 | 0.0 | 0.0 |
| 5 | Calcium carbonate | 0.0 | 54.97 | 0.0 | 0.0 |
| 6 | Magnesium carbonate | 0.0 | 0.0 | 54.97 | 0.0 |
| 7 | Sodium carbonate | 0.0 | 0.0 | 0.0 | 54.97 |
| 8 | Aspartame | 12.97 | 12.97 | 12.97 | 12.97 |
| 9 | Vanilla flavor | 1.30 | 1.30 | 1.30 | 1.30 |
| 10 | FD&C Yellow no. 6 | 0.65 | 0.65 | 0.65 | 0.65 |
| | Total | 2756.30 | 2756.30 | 2756.30 | 2756.30 |

**Evaluation**

The pH of the resultant suspension for the selected batch was measured by digital pH meter (Systronics 335, India).

### 5.2.3 Selection of flavor and color

Vanilla flavor and FD&C Yellow no. 6 were used in present formulation at a level of 0.05% and 0.025% w/w of powder for reconstitution as flavouring and coloring agents respectively.

### 5.2.4 Drug leaching study

Although the reconstituted suspension is meant to be used within 30 min of reconstitution the drug leaching was studied for 12h as an extreme condition. The optimized PFR batch was reconstituted with 60mL of distilled water and kept undisturbed for 12 h at ambient room conditions. A sample aliquot of 5mL was withdrawn and analyzed spectrophotometrically at 274 nm and 233nm to determine the amount of MS and MH leached out respectively.

### 5.2.5 Minimization of drug leaching

In order to determine the extent of Eudragit® E coating at which minimal drug leaching occurs, Batches MS-R11 and MS-R12 were taken similar to Batch MS-40 at 5 and 15 % w/w build up of Eudragit® E layer (Table 5.2.5). Batches MH-R10 and MH-R11 were taken similar to Batch MH-33 at 5 and 15 % w/w build up of Eudragit® E layer (Table 5.2.6). Further these pellets were formulated into PFR and the drug leaching study was carried out as mentioned above.

**Table 5.2.5: Batches for minimization of MS leaching**

| Sr. No. | Ingredients | MS-R11 | MS-R12 |
|---|---|---|---|
| | | 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 | 3.72 | 11.14 |
| 8 | Talc-UM | 0.41 | 1.24 |
| 9 | Acetone | q.s. | q.s. |
| 10 | Iso Propyl Alcohol | q.s. | q.s. |
| | **Total** | 86.63 | 94.88 |

**Table 5.2.6: Batches for minimization of MH leaching**

| Sr. No. | Ingredients | MH-R10 | MH-R11 |
|---|---|---|---|
| | | 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 | 3.83 | 11.48 |
| 11 | Talc-UM | 0.43 | 1.28 |
| 12 | Acetone | q.s. | q.s. |
| 13 | Iso Propyl Alcohol | q.s. | q.s. |
| | **Total** | 89.26 | 97.75 |

### 5.2.6 Flow characterization of CRPFR

The final batches for MS-CRPFR (MS-R10) and MH-CRPFR (MH-R5) were characterized for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index.

### 5.2.7 Evaluation of reconstituted suspension

In order to evaluate the suspension capabilities of the reconstituted preparation, the dry powder for reconstitution equivalent to a once daily unit dose of MS (200mg) and MH (500mg) was dispersed under mild agitation in 60 mL water for 30 seconds. The suspensions were left for five minutes to allow hydration of suspending agent and stirred slightly again immediately before testing [2]. The entire contents are meant to be orally administered as a single dose within 30min of reconstitution. Each evaluation test was performed in triplicate (n=3).

**Organoleptic Characteristics**

The appearance of final suspension was checked visually. The odor was also checked manually.

**pH**

The pH of reconstituted suspension was measured by using digital pH meter (Systronics 335, India), standardized using pH 4 and pH 7 standard buffers before use.

**Sedimentation Volume**

Sedimentation volume is a qualitative term used to describe the amount of settling that has occurred in a suspension. It provides a qualitative knowledge about the physical stability of the suspension. Suspension thus prepared was transferred into a 100mL measuring cylinder, kept undisturbed and the final sedimentation volume (*V*) was measured after 30 min. The initial volume ($V_o$) was taken to equal the total volume of the suspension. The ratio $V/V_o$ was instituted as a measure of the sedimentation behaviour of the prepared suspension [3].

**Redispersibility**

The redispersibility of each suspension formulation, i.e. the ability of the sediment to be resuspended upon mild agitation, was assessed following gentle manual shaking of the suspension for 30 seconds. The suspensions were evaluated on the basis of time and the effort required converting the sediment to homogenous suspension. One inversion was considered as 100% easy to redisperse. Every additional inversion decreased the percent ease of redispersibility by 5% [3].

**Viscosity**

The viscosity of the reconstituted suspension of MS-R10 and MH-R5 was determined by using Brookfield Digital Viscometer Model: DV-I Prime, Spindle No.: 64, Speed: 5-50rpm (Brookfield Engineering Laboratories, Inc., USA) under ambient conditions (25± 5ºC).

### 5.2.8 Packaging and stability study

The final formulations (Batch MS-R10 and MH-R5) were packed into high density polyethylene (HDPE) bottle with child resistant cap and were further induction sealed (Amar packaging, Mumbai, India) and subjected to short term stability testing according

to the ICH guidelines for zones III and IV (ICH Q1A (R2), 2003) at 40± $2^0$C/75 ± 5% RH and 25 ± $2^0$C/60 ± 5% RH conditions for three months. The samples were withdrawn periodically (0, 1, 2 and 3 months) and evaluated for different physicochemical parameters like visual inspection, drug content and *in vitro* drug release studies [4].

## 5.3 Results and discussion for MS and MH CRPFR

### 5.3.1 Selection of suspending agent

Batches MS-R1, MH-R1 and MS-R2, MH-R2 were taken with 0.75 and 1.5% Xanthan gum respectively. In all four batches, the resultant suspension was too viscous to pour. Further, batches MS-R3, MH-R3 and MS-R4, MH-R4 were taken with 0.75 and 1.5% sodium carboxy methyl cellulose respectively. In Batches MS-R3 and MH-R3, the resultant suspension was too viscous to pour while in MS-R4 and MH-R4, cake formation occurred after 30 min. Similar results were earlier reported by Morales et. al., [5]. Further, batches MS-R5, MH-R5 and MS-R6, MH-R6 were taken with 0.75 and 1.5% HPMC K15M respectively. In both the Batches (MS-R5 and MH-R5), the resultant suspension was easily pourable and the pellets redispersed easily upon manual shaking, while in case of Batches MS-R6 and MH-R6, the resultant suspension was slightly viscous to pour. Similar results were earlier reported by M. Cuna et. al.,[6]. Hence, for both the drugs, HPMC K15M was selected at a concentration of 0.75% along with 5% w/w of Avicel CL-611 as suspending agent.

### 5.3. 2 Selection of alkalizer

Batches MS-R7, MS-R8, MS-R9, MS-R10 and MH-R7, MH-R8, MH-R9, MH-R10 were prepared with Sodium hydroxide, Calcium carbonate, Magnesium carbonate and Sodium carbonate respectively as alkalizer. In Batches MS-R7 and MH-R7, the PFR appeared to be moist. This might be due to presence of sodium hydroxide, which rapidly absorbs moisture and carbon dioxide from the exposed air due to its extreme deliquescent nature. In case of Batches MS-R8, MH-R8 and MS-R9, MH-R9, the resultant reconstituted suspension appeared to be turbid. This might be due to presence of Calcium carbonate and Magnesium carbonate respectively which are both practically insoluble in water. In Batches MS-R10 and MH-R10 the resultant reconstituted suspension was not turbid. This might be due to free solubility of sodium carbonate in water [7]. Hence sodium

carbonate was selected as alkalizer for both MS and MH CRPFR. The pH of Batch MS-R10 and MH-R10 were found to be in the range of 7.1 to 7.4 and 7.3 to 7.6 respectively.

### 5.3. 3 Drug leaching study

Eudragit® E is a cationic polymer which dissolves below pH 5 [8]. In batches MS-R10 and MH-R5 the pH of reconstituted suspension was found to be in the range of 7.1 to 7.4 and 7.3 to 7.6 respectively. Due to the alkali resistance nature of the Eudragit® E polymer, 3.4± 0.3% and 2.7± 0.6% drug leached out from batches MS-R10 and MH-R5 after 12h respectively.

### 5.3. 4 Minimization of drug leaching study

Batches MS-R11, MS-R12 and MH-R10, MH-R11 were prepared with 5 and 15% w/w build up of Eudragit® E coating, showing drug leaching of 11.5± 0.9, 2.9± 0.5% and 10.2± 1.1, 2.2± 0.5% respectively. It was observed that at lower coating extent, drug leaching was higher. Since no significant difference was observed in drug leaching with 10 and 15% coating levels, (Figure 5.3.1and 5.3.2) 10% weight build up was finalized so as to keep the weight of the pellet minimum and reduce the processing time required for coating. Hence batches MS-R10 and MH-R5 were finalized for CRPFR of MS and MH respectively.

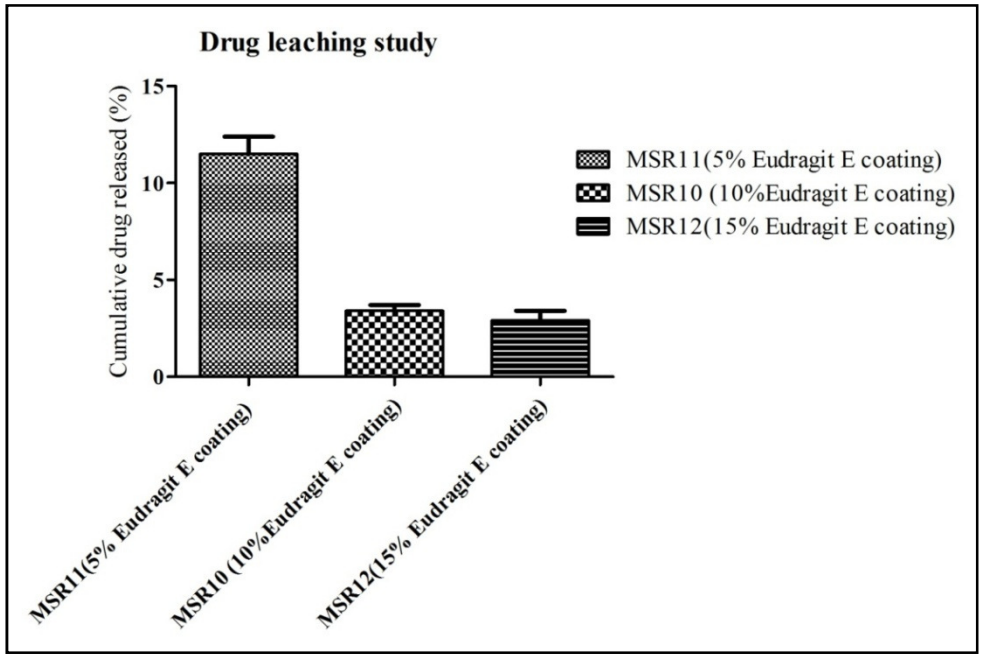



**Figure 5.3.1: Drug leaching study at different coating levels of Eudragit® E layer for MS-CRPFR**

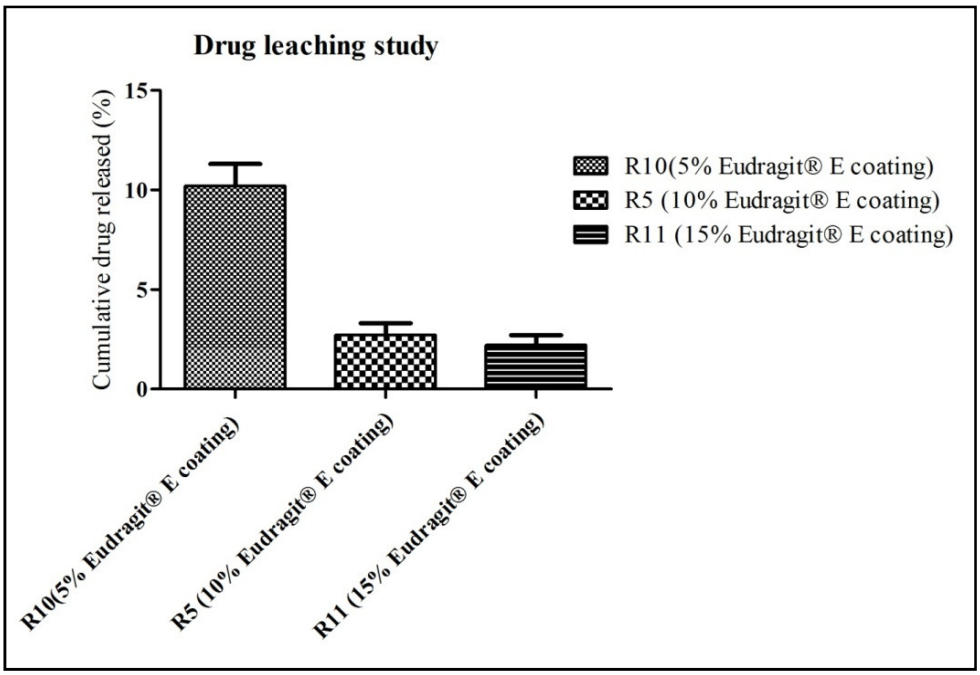



**Figure 5.3.2: Drug leaching study at different coating levels of Eudragit® E layer for MH-CRPFR**

### 5.3.5 Flow characterization of PFR

Angle of repose of final blends of MS and MH (batch MS-R10 and MH-R5) were found to be 32.15±0.42°, 33.26±0.31° which indicated that both blends had good flow and thus there will be smooth passage through hopper. The bulk and tapped density for MS and MH were found to be 0.711± 0.11 g/mL, 0.800± 0.09 g/mL and 0.721± 0.09 g/mL, 0.805± 0.10 g/mL respectively. The results for Hausner's ratio (1.125 ± 0.02 and 1.117 ± 0.03), compressibility index (12.50± 0.35, 11.71± 0.29) for MS and MH respectively also indicated good flow of the PFR.

### 5.3.6 Evaluation of final reconstituted suspension

**Organoleptic Characteristics**

Final suspension after reconstitution was slightly yellow colored with pleasant odor of vanilla for both MS and MH.

**Sedimentation volume**

Optimized batches of CRPFR of MS and MH were suspended for 30 min. As the volume of suspension that appeared occupied by the sediment increases, the value of F, which normally ranges from 0 to 1, increases [9]. For MS-R10 and MH-R5, the sedimentation

volume was found to be 0.90± 0.8 and 0.96±0.12 respectively indicating uniform dispersion of the pellets in the suspension.

**Redispersibility**

Redispersibility is a parameter to evaluate the ease with which the sedimented particles in the suspension can be redispersed upon mild agitation. The ease of redispersion was found to be 93.33% for MS-R10 and 96.66% for MH-R5 indicating easy redispersibility.

**Viscosity**

Increase in viscosity of the suspension, decreases settling of the suspended particles, but a greater increase in viscosity gives rise to problems of pourability, syringibility and redispersibility of suspended particles. In the present study, the MS and MH reconstituted suspensions were easily pourable and had viscosity of 5426 to 5710 cps and 5548 to 5691cps for batches MS-R10 and MH-R5 respectively.

**pH**

pH of final suspension for MS and MH was found to be in the range of 7.1 to 7.4 and 7.3 to 7.6 respectively which was sufficient to maintain the intactness of Eudragit® E coating.

### 5.3.7 Packaging and stability study

The optimized formulations (Batch MS-R10 and MH-R5) showed negligible change under the conditions of storage for parameters like visual inspection, drug content and *in vitro* drug release. The data suggested that the formulation was stable for 3 months for the packaging material selected at $40^0$C/75%RH and $25^0$C/60%RH condition (Table 5.3.1 and 5.3.2).

**Table 5.3.1: Results for stability studies of MS-CRPFR**

| | Initial | 1 Month ($40^0$C/75% RH) | 2 Month ($40^0$C/75% RH) | 3 Month ($40^0$C/75% RH) | 3 Month ($25^0$C/60% RH) |
|---|---|---|---|---|---|
| Description | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets |
| Assay (%) | 102.6± 1.1 | 101.7± 1.3 | 101.1± 1.4 | 101.5± 1.8 | 102.2± 1.7 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 14.8± 2.1 | 12.7± 2.3 | 13.2± 0.8 | 12.5± 1.2 | 13.6± 2.8 |
| 2 | 21.2± 2.3 | 21.9± 1.8 | 20.8± 1.8 | 20.1± 1.1 | 20.9± 0.9 |
| 4 | 32.2± 1.9 | 32.8± 1.9 | 30.6± 1.6 | 29.8± 2.7 | 30.5± 1.8 |
| 6 | 39.4± 2.2 | 40.8± 1.5 | 38.3± 1.5 | 37.9± 1.9 | 38.2± 2.7 |
| 8 | 47.9± 2.0 | 48.7± 1.5 | 46.2± 2.7 | 45.6± 2.7 | 46.7± 1.9 |
| 10 | 55.9± 1.5 | 54.3± 1.1 | 53.6± 0.9 | 52.7± 2.1 | 53.8± 1.5 |
| 12 | 63.7± 2.3 | 61.9± 1.8 | 61.2± 1.8 | 60.5± 1.5 | 61.6± 1.1 |
| 16 | 78.2± 1.3 | 77.6± 1.5 | 76.9± 2.1 | 76.2± 1.4 | 76.7± 2.3 |
| 20 | 95.1± 2.4 | 93.3± 2.6 | 94.7± 1.9 | 96.3± 1.2 | 94.2± 1.9 |
| 24 | 101.1± 1.3 | 98.9± 1.9 | 99.5± 0.9 | 98.8± 1.1 | 99.3± 1.7 |

Note: Avg. value = Mean± SD (n=3)

**Table 5.3.2. Results for stability studies of MH-CRPFR**

| | Initial | 1 Month ($40^0$C/75% RH) | 2 Month ($40^0$C/75% RH) | 3 Month ($40^0$C/75% RH) | 3 Month ($25^0$C/60% RH) |
|---|---|---|---|---|---|
| Description | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets | Off white to light yellow blend with pellets |
| Assay (%) | 101.3± 1.4 | 100.7± 1.2 | 100.1± 1.3 | 99.5± 1.1 | 100.2± 1.5 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 26.6± 2.5 | 25.7± 2.1 | 24.2± 1.8 | 23.5± 1.7 | 24.6± 2.4 |
| 3 | 36.9± 2.6 | 35.8± 1.4 | 34.1± 1.8 | 33.9± 1.7 | 33.4± 1.9 |
| 5 | 47.6± 1.5 | 47.2±1.3 | 46.8± 1.1 | 46.2± 0.8 | 46.5± 1.0 |
| 8 | 54.6± 1.2 | 54.8± 2.4 | 53.3± 1.9 | 52.7± 1.4 | 53.5± 2.7 |
| 12 | 73.1± 1.9 | 73.0± 1.3 | 72.7± 1.2 | 72.4± 1.1 | 72.8± 1.2 |
| 16 | 81.3± 2.4 | 80.8± 2.1 | 80.6± 0.9 | 79.7± 2.1 | 80.1± 1.5 |
| 20 | 92.6± 1.6 | 92.1± 1.2 | 91.2± 1.8 | 90.5± 1.4 | 91.6± 1.9 |
| 24 | 99.8± 1.4 | 99.4± 1.2 | 98.4± 1.1 | 98.2± 0.8 | 98.7± 1.7 |

Note: Avg. value = Mean± SD (n=3)

**References**

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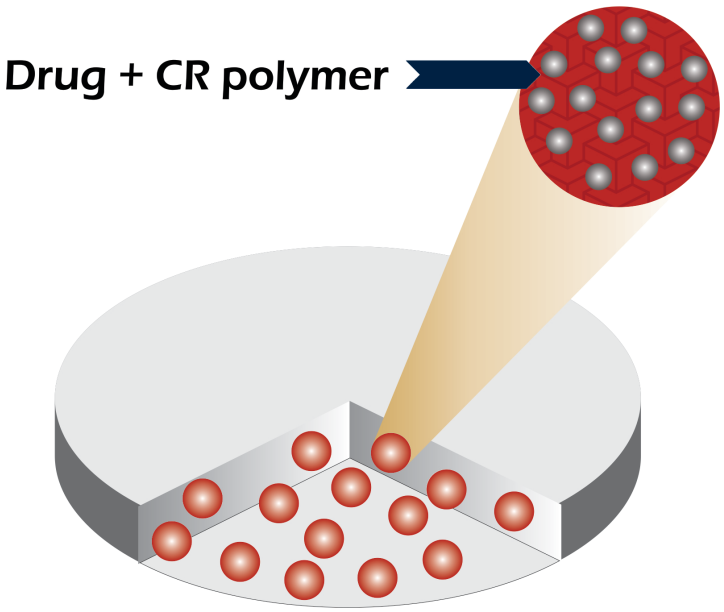
# Formulation Development

## Part B: CRODT




Chapter 5

## 5.4 Materials and Equipments

### 5.4.1 Materials

Hydroxy propyl cellulose was received as gift samples from Ashland Pvt. Ltd., Hyderabad, India, Pearlitol SD 200 from Roquette Pharma, Mumbai, India, Aerosil from Evonik Industries, Singapore. PEG 6000 from Croda, Mumbai, India. Sodium Stearyl Fumarate, Croscarmellose sodium and Polyplasdone XL were procured from Ashland, India, Vanilla flavor from Fermenich, Germany and Aspartame from Sigma-Aldrich, India.

### 5.4.2 Equipments

Following is the list of equipments and instruments used in the CRODT formulation.

**Table 5.4.1: List of Equipments and Instruments**

| **Name of equipment/ Instrument** | **Model** | **Make** |
|---|---|---|
| Electronic weighing Balance | ELB300 | Shimadzu, Japan |
| UV-visible double beam spectrophotometer | UV-1800 | Shimadzu, Japan |
| USP dissolution apparatus Type II | TDT-06P | Elecrtolab, India |
| Centrifuge | CPR-30 | Remi, 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 |
| Compression machine | JM-8 | General Machinery Co., India |
| Disintegration Apparatus | VTD-DV | Veego, India |
| Hardness Tester | Monsanto | Rolex, India |
| Induction sealer | APSL 1510 | Amar packaging, India |
| Vernier caliper | 532 series | Mitutoyo, Japan |
| Microscope | DS-Fi2 | Nikon Digital, Japan |
| Scanning Electron Microscope | JSM-5610LV | Jeol, Japan |

## 5.5 Controlled Release Orally Disintegrating Tablet (CRODT)

After formulation of CR PFR, in order to explore the possibility of alternate dosage form for drugs (MS and MH) used in chronic disorders, it was decided to develop a CRODT formulation. Orally disintegrating tablet is meant to be placed into the oral cavity where it disintegrates and releases the medicament. These are meant to disintegrate rapidly (within 1min) and possess acceptable friability (less than 1%) [1]. Batches were taken to achieve these parameters along with suitable release profile.

Despite successes of ODT formulations, there are currently no formulations available in the market that can release a drug in a sustained manner for more than12h [2]. CRODT formulations would fetch new benefits that were not possible before. In the present study, Eudragit® E coated pellets from the optimized batches (MS-40 and MH-33) were pursued further for formulation into CRODT.

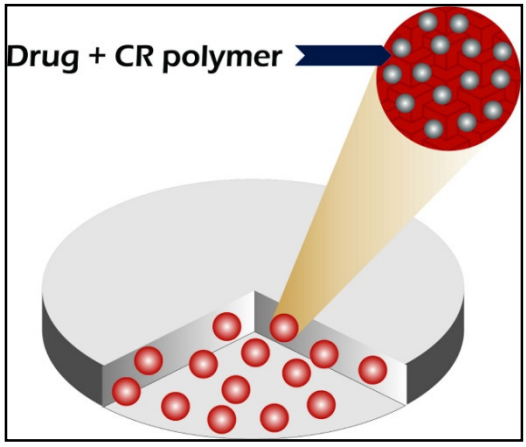



**Figure 5.5.1: Schematic representation of CRODT**

### 5.5.1 Fabrication of CRODT

Direct compression is the most preferred method for tabletting due to its simplicity. In the present study, Eudragit® E coated pellets equivalent to 50mg MS and 50mg MH were mixed with suitable excipients like diluent, superdisintegrants, glidant and lubricant to prepare lubricated blend which was compressed into tablet using 12 mm round shaped punch and single rotary tablet compression machine (General machineries, Ahmedabad, India). The target weight was fixed at 500mg along with fixed levels of Aspartame, Vanilla flavour, Aerosil 200 and Sodium stearyl fumarate. In each batch the diluent, superdisintegrant and Aerosil 200 were passed through sieve #40. Aspartame and Vanilla

flavour were passed through sieve #60 and mixed geometrically with the above blend. Eudragit® E coated pellets were mixed with the above blend for 10 min followed by lubrication with Sodium stearyl fumarate passed through sieve #60. Lubricated blend thus prepared was compressed into tablet.

### 5.5.2 Selection of superdisintegrant

To achieve rapid disintegration, superdisintegrants were employed in the present study. Accordingly, batches MS-T1, MS-T2 and MS-T3 were taken with sodium starch glycolate, croscarmellose sodium and Polyplasdone XL respectively for MS (Table 5.5.1). Similarly batches MH-T1, MH-T2 and MH-T3 were taken with sodium starch glycolate, croscarmellose sodium and Polyplasdone XL respectively for MH (Table 5.5.2).

**Table 5.5.1: Selection of superdisintegrants for MS-CRODT**

| Sr. No. | Ingredients | MS-T1 | MS-T2 | MS-T3 |
|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab |
| 1 | MS-Eudragit® E Pellets | 240.0 | 240.0 | 240.0 |
| 2 | Avicel PH 101 | 230.0 | 230.0 | 230.0 |
| 3 | Sodium starch glycolate | 20.0 | 0.0 | 0.0 |
| 4 | Croscarmellose sodium | 0.0 | 20.0 | 0.0 |
| 5 | Polyplasdone XL | 0.0 | 0.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavor | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 | 500.0 |

**Table 5.5.2: Selection of superdisintegrants for MH-CRODT**

| Sr. No. | Ingredients | MH-T1 | MH-T2 | MH-T3 |
|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab |
| 1 | MH-Eudragit® E Pellets | 252.84 | 252.84 | 252.84 |
| 2 | Avicel PH 101 | 217.16 | 217.16 | 217.16 |
| 3 | Sodium starch glycolate | 20.0 | 0.0 | 0.0 |
| 4 | Croscarmellose sodium | 0.0 | 20.0 | 0.0 |
| 5 | Polyplasdone XL | 0.0 | 0.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavor | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 | 500.0 |

**Evaluation**

The tablets thus prepared were evaluated for Average weight, Hardness, Thickness and Disintegration time.

**Average weight**

Average weight was determined by electronic weighing balance (Shimadzu, Japan) in triplicate. The results were reported as Mean± SD and calculated using following formula:

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

**Hardness**

Hardness was determined using Monsanto hardness tester. Hardness was determined by holding the tablet between the two anvils and applying pressure by the two arms. Hardness was reported in Kp.

**Thickness**

Thickness was determined using digital Vernier caliper (Mitutoyo). The results were reported as Mean± SD (n=3) and represented in mm.

**Friability**

The tablets must possess sufficient mechanical strength so as to withstand the mechanical shocks encountered during production stages and transportation. The friability test was performed by using friability test apparatus (Electrolab, India). In this test, 10 tablets were placed in the friability tester and rotated at the speed of 25 rpm for 4 min. Friability was calculated using following formula:

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

**Disintegration time**

The disintegration time was checked using disintegration test apparatus (Veego, India). The tablets were placed in the basket which was operated at the speed of 28 dips per min and the time required to disintegrate was recorded.

### 5.5.3 Selection of diluent

Diluents or fillers are used to make up the bulk of the tablet. Though considered to be inert, these excipients affect the friability, disintegration and dissolution profile of the tablet. To evaluate the impact of diluents upon these parameters trials were taken with Avicel PH 101(MS-T4), Prosolv SMCC HD 90(MS-T5) and Pearlitol SD 200 (Table 5.5.3). Similar, trials were taken for MH (MH-T4 and MH-T5 with Avicel PH 101 and Prosolv SMCC HD 90 respectively (Table 5.5.4).

**Table 5.5.3: Selection of diluent for MS-CRODT**

| Sr. No. | Ingredients | MS-T4 | MS-T5 |
|---|---|---|---|
| | | mg/tab | mg/tab |
| 1 | MS-Eudragit® E Pellets | 240.0 | 240.0 |
| 2 | Avicel PH 101 | 180.0 | 0.0 |
| 3 | Prosolv SMCC HD90 | 0.0 | 180.0 |
| 4 | Pearlitol SD 200 | 50.0 | 50.0 |
| 5 | Polyplasdone XL | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 |
| 7 | Vanilla flavour | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 |

**Table 5.5.4: Selection of diluent for MH-CRODT**

| Sr. No. | Ingredients | MH-T4 | MH-T5 |
|---|---|---|---|
| | | mg/tab | mg/tab |
| 1 | MH- Eudragit® E Pellets | 252.84 | 252.84 |
| 2 | Avicel PH 101 | 167.16 | 0.0 |
| 3 | Prosolv SMCC HD90 | 0.0 | 167.16 |
| 4 | Pearlitol SD 200 | 50.0 | 50.0 |
| 5 | Polyplasdone XL | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 |
| 7 | Vanilla flavour | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 |

**Evaluation**

Tablets thus prepared were evaluated for hardness, friability and disintegration time.

### 5.5.4 Optimization of super disintegrant level

In order to achieve rapid disintegration, trials were taken with different levels and combination of super disintegrant(s) and different ratio of diluent. Accordingly, Batches MS-T6, MS-T7 and MS-T8 were taken with increased concentration of Polyplasdone XL, combination of Polyplasdone XL and croscarmellose sodium and increased level of Pearlitol SD 200 respectively (Table 5.5.5). Similar trials were taken for MH (MH-T6, MH-T7 and MH-T8) (Table 5.5.6).

**Table 5.5.5: Optimization of super disintegrant level to achieve fast disintegration for MS-CRODT**

| Sr. No. | Ingredients | MS-T6 | MS-T7 | MS-T8 |
|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab |
| 1 | Eudragit® E Pellets | 240.0 | 240.0 | 240.0 |
| 2 | Prosolv SMCC HD90 | 180.0 | 175.0 | 145.0 |
| 3 | Pearlitol SD 200 | 45.0 | 45.0 | 75.0 |
| 4 | Croscarmellose sodium | 0.0 | 10.0 | 10.0 |
| 5 | Polyplasdone XL | 25.0 | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavor | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 | 500.0 |

**Table 5.5.6: Optimization of super disintegrant level to achieve fast disintegration for MH-CRODT**

| Sr. No. | Ingredients | MH-T6 | MH-T7 | MH-T8 |
|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab |
| 1 | MH- Eudragit® E Pellets | 252.84 | 252.84 | 252.84 |
| 2 | Prosolv SMCC HD90 | 167.16 | 162.16 | 132.16 |
| 3 | Pearlitol SD 200 | 45.0 | 45.0 | 75.0 |
| 4 | Croscarmellose sodium | 0.0 | 10.0 | 10.0 |
| 5 | Polyplasdone XL | 25.0 | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavor | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 |
| | Total | 500.0 | 500.0 | 500.0 |

**Evaluation**

Tablets thus prepared were evaluated for hardness, friability, disintegration time and Drug release study.

### 5.5.5 Optimization of cushioning agent to prevent rupture of MS and MH pellets

Rupture of functionally coated pellet is the most common problem associated with the compression of pellets which has been also been acknowledged in the literature. Various approaches have been reported in the literature to prevent rupture of functionally coated pellet during compression [3, 4]. Of these the simplest is use of a cushioning agent, which prevents the rupture of functionally coated pellet.

Hydroxy Propyl Cellulose (Batch MS-T9 and MH-T9) and Poly Ethylene Glycol (Batch MS-T10 and MH-T10) were evaluated for their cushioning effect (Table 5.5.7 and 5.5.8). Further, after selection of the cushioning agent in MS-CRODT, its level was also optimized (Batch MS-T11 and MS-T12). After selection of the cushioning agent in MH-CRODT, its level was optimized along with percentage of pellets in the tablet formulation (Batch MH-T11, MH-T12 and MH-T13). Tablets thus prepared were evaluated for hardness, friability, disintegration time and percent drug release.

**Table 5.5.7: Optimization of cushioning agent for prevention of rupture of MS pellets**

| Sr. No. | Ingredients | MS-T9 | MS-T10 | MS-T11 | MS-T12 |
|---|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab | mg/tab |
| 1 | Eudragit® E Pellets | 240.0 | 240.0 | 240.0 | 240.0 |
| 2 | Prosolv SMCC HD90 | 135.0 | 125.0 | 115.0 | 105.0 |
| 3 | Pearlitol SD 200 | 75.0 | 75.0 | 75.0 | 75.0 |
| 4 | Croscarmellose sodium | 10.0 | 10.0 | 10.0 | 10.0 |
| 5 | Polyplasdone XL | 20.0 | 20.0 | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavour | 0.25 | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 | 2.5 |
| 10 | Hydroxy Propyl Cellulose EXF | 10 | 0.0 | 0.0 | 0.0 |
| 11 | Poly Ethylene Glycol 6000 | 0.0 | 20.0 | 30.0 | 40.0 |
| | Total | 500.0 | 500.0 | 500.0 | 500.0 |

**Table 5.5.8: Optimization of cushioning agent for prevention of rupture of MH pellets**

| Sr. No. | Ingredients | MH-T9 | MH-T10 | MH-T11 | MH-T12 | MH-T13 |
|---|---|---|---|---|---|---|
| | | mg/tab | mg/tab | mg/tab | mg/tab | mg/tab |
| 1 | MH- Eudragit® E Pellets | 252.84 | 252.84 | 252.84 | 252.84 | 252.84 |
| 2 | Prosolv SMCC HD90 | 122.16 | 112.16 | 142.16 | 132.16 | 122.16 |
| 3 | Pearlitol SD 200 | 75.0 | 75.0 | 95.0 | 95.0 | 95.0 |
| 4 | Croscarmellose sodium | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 |
| 5 | Polyplasdone XL | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 |
| 6 | Aspartame | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 |
| 7 | Vanilla flavour | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| 8 | Aerosil 200 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| 9 | Sodium stearyl fumarate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| 10 | Hydroxy Propyl Cellulose EXF | 10.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 11 | Poly Ethylene Glycol 6000 | 0.0 | 20.0 | 20.0 | 30.0 | 40.0 |
| | Total | 500.0 | 500.0 | 550.0 | 550.0 | 550.0 |

**Evaluation**

Tablets thus prepared were evaluated for hardness, friability, disintegration time and drug release study.

**Characterization of Blend**

The final lubricated blend-ready for compression- was characterized for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index.

### 5.5.6 Packaging and stability study

The final formulation (**Batch MS-T11 and MH-T12)** was packed into high density polyethylene (HDPE) bottle with child resistant cap and were further induction sealed (Amar packaging, Mumbai, India) and subjected to short term stability testing according to the ICH guidelines for zones III and IV (ICH Q1A (R2), 2003) at 40± $2^0$C/75 ± 5% RH and 25 ± $2^0$C/60 ± 5% RH conditions for three months. The samples were withdrawn

periodically (0, 1, 2 and 3 months) and evaluated for different physicochemical parameters like visual inspection, drug content and *in vitro* drug release studies [5].

## 5.6 Results and Discussion for MS and MH CRODT

### 5.6.1 Selection of super disintegrants

Disintegrants are routinely included in the tablet formulations to aid in the break up of the tablet when it is put into a fluid environment. These promote moisture penetration and dispersion of the tablet matrix. Superdisintegrants are new substances that are more effective at lower concentrations with greater disintegrating efficiency. On contact with water the superdisintegrants rapidly swell, hydrate or change volume of the tablet to achieve faster disintegration of the tablet [6].

Batches MS-T1, MS-T2, MS-T3 for MS and batches MH-T1, MH-T2 and MH-T3 for MH were taken with sodium starch glycolate, croscarmellose sodium and Polyplasdone XL respectively. The disintegration time observed were 6-7, 5-6, 4.5-5.5 min (Table 5.6.1) and 6.5-7, 5.5-6.5 and 4.5-5 min respectively (Table 5.6.2). In process quality control tests (IPQC) were performed for all batches.

The mechanism of disintegration with sodium starch glycolate is rapid uptake of water followed by quick and enormous swelling. Croscarmellose sodium possesses both, wicking as well as swelling abilities. Crospovidone is a water-insoluble tablet disintegrant which rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels [7]. It was observed that the tablets prepared with Polyplasdone XL gave the shortest disintegration time and hence selected for further batches for both the drugs.

Friability was found to be 1.8, 1.9, 1.7% (Table 5.6.1) and 2.0, 1.8 and 1.8% for batches MS-T1, MS-T2, MS-T3 and MH-T1, MH-T2, MH-T3 (Table 5.6.2). The acceptable value for friability is NMT 1%[1]. Thus all failed in friability test. Avicel was used as a diluent in these formulations; but it did not exhibit sufficient compressibility which is reflected from the hardness value (3-5kp) leading to high friability for both MS and MH.

**Table 5.6.1: IPQC tests for MS-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MS-T1 | 510.6± 12.2 | 3.51± 0.12 | 3-5 | 1.8 | 6-7 |
| MS-T2 | 505.9± 10.4 | 3.47± 0.15 | 3-5 | 1.9 | 5-6 |
| MS-T3 | 505.6± 7.3 | 3.54± 0.13 | 3-5 | 1.7 | 4.5-5.5 |

**Table 5.6.2: IPQC tests for MH-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MH-T1 | 503.6± 10.1 | 3.61± 0.11 | 3-4 | 2.0 | 6.5-7 |
| MH-T2 | 496.9± 8.4 | 3.54± 0.12 | 3-4 | 1.8 | 5.5-6.5 |
| MH-T3 | 501.2± 9.3 | 3.49± 0.15 | 3-4 | 1.8 | 4.5-5 |

### 5.6.2 Selection of diluent

Pearlitol SD 200 is routinely used for manufacturing ODT. Pearlitol SD 200 has advantages in terms of sweet taste and negative heat of solution which makes the ODT more palatable [8, 9]. Further trials were taken with it along with other diluents.

Batches MS-T4, MH-T4 and MS-T5, MH-T5 were prepared with fix quantity of Pearlitol SD 200, with and without Avicel PH 101 and Prosolv SMCC HD90 respectively (Table 5.5.3. and 5.5.4). Both the batches of MS and MH exhibited similar DT (3-3.5 min) and (3.5-4 min) respectively. However, the batch with Prosolv SMCC HD 90 exhibited better compactibility for MS-T5 (Hardness= 5-7 kp, friability= 0.8%) as well as MH-T5 (Hardness= 5-6 kp, friability= 0.9%) as compared to corresponding batches with Avicel PH 101 for MS-T4 (Hardness= 4-6 kp, friability= 1.7%) and MH-T4 (Hardness= 4-6 kp, friability= 1.5%) (Table 5.6.3 and 5.6.4).

Prosolv SMCC HD 90 is prepared by co-processing microcrystalline cellulose and colloidal silicon dioxide and is reported to have better compressibility than microcrystalline cellulose alone and in combination with colloidal silicon dioxide [10]. Hence, a combination of Prosolv SMCC HD90 and Pearlitol SD 200 was selected for further trials of both the drugs.

**Table 5.6.3: IPQC tests for MS-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MS-T4 | 496.1± 9.5 | 3.45± 0.18 | 4-6 | 1.7 | 3-3.5 |
| MS-T5 | 508.7± 11.2 | 3.33± 0.11 | 5-7 | 0.8 | 3-3.5 |

**Table 5.6.4: IPQC tests for MH-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MH-T4 | 497.1± 10.5 | 3.40± 0.12 | 4-6 | 1.5 | 3.5-4 |
| MH-T5 | 503.7± 7.2 | 3.44± 0.09 | 5-6 | 0.9 | 3.5-4 |

### 5.6.3 Optimization of super disintegrant level to achieve fast disintegration

Batches MS-T6 and MH-T6 were prepared with increased concentration of disintegrant (Polyplasdone XL) which yielded DT of 2-2.5 min and 2.5-3.5 min respectively (Table 5.6.5 and Table 5.6.6). In order to further reduce the DT, a combination of Polyplasdone XL and croscarmellose sodium was tried in batches MS-T7 and MH-T7 which gave DT of 1.5-2.5 min and 2-2.5 min respectively. Hence a combination of super disintegrants was used for further trials to combine their individual properties of pronounced hydration, high wicking and swelling abilities.

In order to further reduce the DT, Batch MS-T8 and MH T8 were prepared by increasing the concentration of Pearlitol SD 200 (75mg). When Pearlitol (a water soluble diluent) comes in contact with water, it gets dissolved and creates water filled channels. Thus, faster disintegration is achieved through this capillary action which was also observed in case of batch MS-T8 and MH T8, where DT was found to be lesser than batch MS T7 and MH T7 respectively (Table 5.6.7 and Table 5.6.8) .

It was found that the dissolution profile of MS-T8 and MH-T8 were slightly higher than that of the respective Eudragit® E coated pellets used to fabricate the same batch (Table 5.6.7 and Table 5.6.8). This suggested that the functional pellets were ruptured due to compression pressure exerted during the production of CRODT. Such change in release profile upon compression of MUPS is also reported previously [11].

**Table 5.6.5: IPQC tests for MS-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MS-T6 | 491.1± 12.1 | 3.39± 0.12 | 5-7 | 0.8 | 1-2.0 |
| MS-T7 | 511.3± 9.9 | 3.31± 0.13 | 5-7 | 0.8 | 1.5-2.0 |
| MS-T8 | 490.6± 6.4 | 3.41± 0.15 | 5-7 | 0.9 | 0.5-1 |

**Table 5.6.6: IPQC tests for MH-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MH-T6 | 498.1± 10.2 | 3.46± 0.10 | 5-7 | 0.8 | 2.5-3.5 |
| MH-T7 | 509.3± 8.5 | 3.38± 0.10 | 5-7 | 0.8 | 2-2.5 |
| MH-T8 | 496.9± 10.4 | 3.35± 0.13 | 5-7 | 0.9 | 1-2 |

**Table 5.6.7: Drug release study for optimization of super disintegrant level-MS-CRODT**

| | **Eudragit® E Pellets (Batch MS-40)** | **Batch MS-T8** |
|---|---|---|
| Assay (%) | 98.9± 1.9 | 102.3± 0.6 |
| Time (h) | Cumulative drug release (%) | |
| 1 | 17.6± 1.9 | 23.9± 2.1 |
| 2 | 22.4± 2.1 | 32.5± 4.2 |
| 4 | 31.9± 3.2 | 41.4± 3.4 |
| 6 | 40.6± 1.2 | 52.4± 2.3 |
| 8 | 48.9± 1.5 | 63.5± 1.5 |
| 10 | 56.4± 2.1 | 71.2± 1.1 |
| 12 | 64.3± 1.9 | 79.3± 1.6 |
| 16 | 79.5± 1.8 | 92.1± 1.8 |
| 20 | 95.9± 1.7 | 99.9± 1.0 |
| 24 | 102.3± 1.0 | 101.4± 1.0 |

**Table 5.6.8: Drug release study for optimization of super disintegrant level-MH-CRODT**

| | **Eudragit® E Pellets (Batch MH-33)** | **Batch MH-T8** |
|---|---|---|
| Assay (%) | 99.1± 1.4 | 101.6± 1.2 |
| Time (h) | Cumulative drug release (%) | |
| 1 | 27.7± 2.9 | 35.6± 3.8 |
| 3 | 39.5± 2.1 | 47.4± 3.3 |
| 5 | 48.1± 1.1 | 55.7± 3.0 |
| 8 | 56.2± 1.3 | 64.4± 2.5 |
| 12 | 73.4± 1.6 | 78.7± 1.8 |
| 16 | 82.5± 2.0 | 84.2± 1.7 |
| 20 | 93.4± 1.4 | 96.3± 1.6 |
| 24 | 101.5± 1.0 | 100.1± 1.9 |

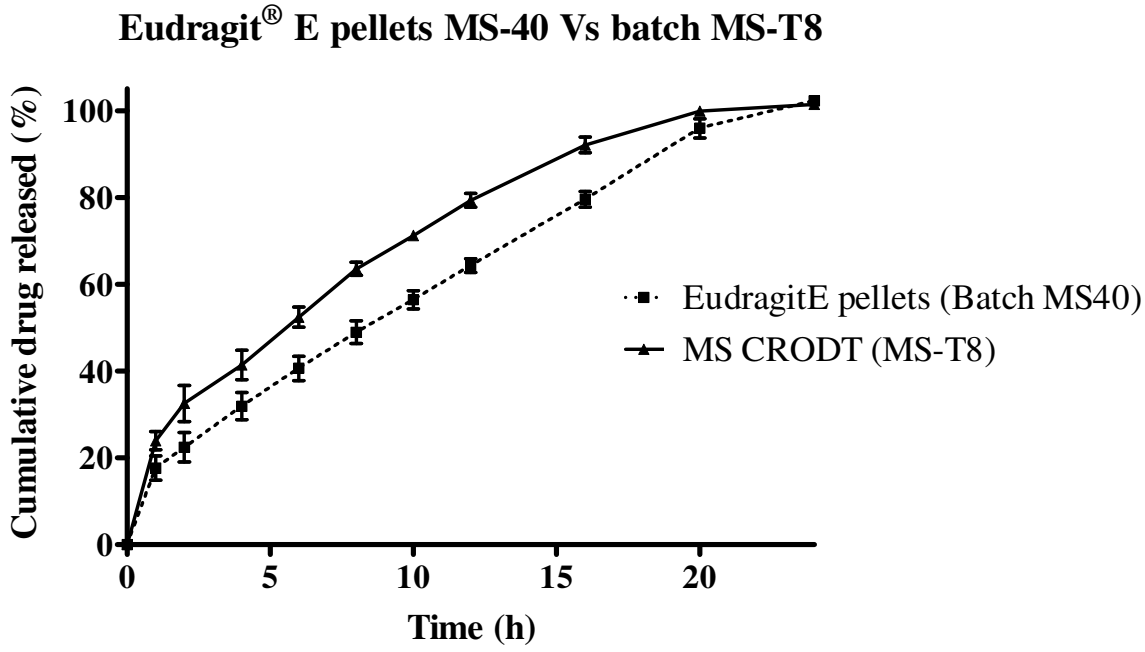



**Figure 5.6.1: Dissolution profile for MS-Eudragit® E pellets and MS-CRODT**

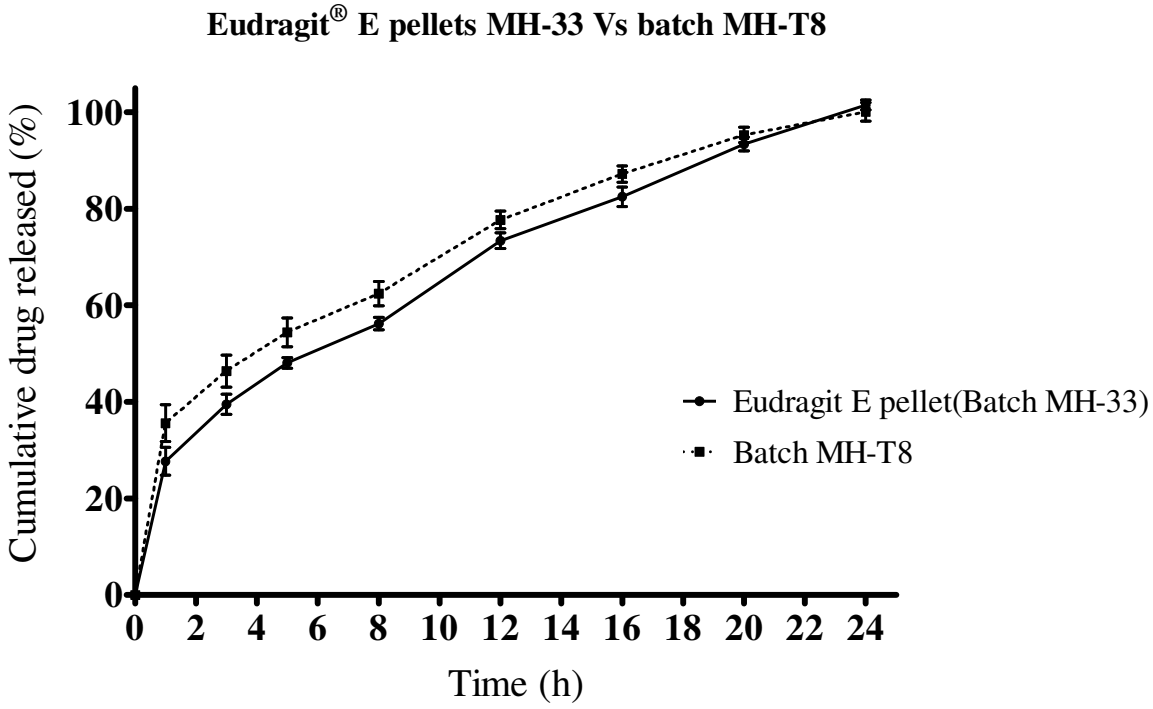



**Figure 5.6.2: Dissolution profile for MH-Eudragit® E pellets and MH-CRODT**

### 5.6.4 Optimization of cushioning agent and prevention of rupture of pellets

To overcome the problem of rupture of MUPS during compression, it was decided to incorporate a cushioning agent -plastically deforming excipient-into the formulation.

Accordingly, batches MS-T9 and MH-T9 were taken with Hydroxy Propyl Cellulose EXF. Dissolution of tablets was found to be similar to their respective Eudragit® E coated pellets. Thus, use of a cushioning agent proved to be beneficial to avoid the rupture of pellets. However, the DT was prolonged to 2.5-4 min for MS-T9 and 3-3.5 min for MH-T9 (Table 5.6.9 and Table 5.6.10) (Figure 5.6.3 and Figure 5.6.5). This was attributed to the gelling tendency of Hydroxy Propyl Cellulose EXF [7].

It is reported that a combination of microcrystalline cellulose, polyethylene glycol and crospovidone have a low yield pressure value, which is suitable excipient mixture for compression of coated particles. The tablet matrix thus produced has a lower yield pressure than the pellet, such that the compression pressure is absorbed by the matrix, and that the matrix is preferentially deformed thereby avoiding the rupture of pellet [12]. Hence batches MS-T10 and MH-T10 were prepared by using water soluble Poly Ethylene Glycol 6000 as a cushioning agent. Dissolution for MS-T10 was found similar to MS-Eudragit® E coated pellets and the DT was observed to be 1-1.5 min. However in

case of batch MH-T10, DT was observed to be 1.5-2 min and dissolution was found to be faster than that of MH-Eudragit® E coated pellets. This reduction in DT was attributed to the greater water solubility of Poly Ethylene Glycol 6000 as compared to Hydroxy Propyl Cellulose EXF. For MH-CRODT, in order to further reduce the DT and prevent rupture of pellets, batch MH-T11was taken with increased tablet weight, thereby decreasing the percentage of pellet in the tablet (45.97%) as compared to batch MH-T10 (50.57%). It was observed that the DT was reduced to 1-1.5 min and dissolution profiles of batch MH-T11was similar to that of MH-Eudragit® E coated pellets, suggesting that the rupturing of pellets was reduced by the combination of cushioning agent and reduced pellet concentration in the tablet.

Various inert excipients have to be used to assist the compaction process and to prevent the rupture and damage of the coated pellets. The ideal filler materials used for the tabletting of pellets should prevent the direct contact of the pellets (ex. polymer coatings) and act as cushion during compression. Theoretically, 29% of excipient are needed to fill the void space between densely packed spheres. A layer has to be formed between the pellets to prevent adhesion or fusion of the coated pellets[13].

In order to further reduce the DT and optimize the level of Poly Ethylene Glycol 6000, for both the drugs, batches MS-T11, MS-T12 and MH-T12, MH-T13 were taken with increased quantity of Poly Ethylene Glycol 6000 (30 and 40mg respectively). For MS, the improvement in DT was found in case of Batch MS-T11 (0.5 - 1 min) which remained unchanged in Batch MS-T12. It was also observed that the dissolution profiles of Batches MS-T10, MS-T11 and MS-T12 were similar to each other (Table 5.6.11) (Figure 5.6.4). Hence Batch **MS-T11** was considered to be the optimized batch for MS-CRODT. While for MH-CRODT, the DT was found to be 0.6-1 min and dissolution profile was similar to that of Eudragit® E coated pellets in both the batches MH-T11 and MH-T12 (Table 5.6.12) (Figure 5.6.6). Hence batch **MH-T12** was considered to be the optimized batch for MH- CRODT and batch MH-T13 was not evaluated further. Similar results for prolongation of DT by Hydroxy Propyl Cellulose and improvement by use of Poly Ethylene Glycol 6000 have also been reported [14]. Bechard and Leroux (1992) [15], Tirkkonen and Paronen (1993) [16] and Torrado and Augsburger (1994) [12] have also reported the combination of polyethylene glycol and microcrystalline cellulose to produce rapidly disintegrating tablets containing pellets.

**Table 5.6.9: IPQC tests for MS-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MS-T9 | 497.8± 12.1 | 3.42± 0.19 | 6-8 | 0.7 | 2.5-4 |
| MS-T10 | 508.6± 10.3 | 3.44± 0.17 | 6-8 | 0.8 | 1-1.5 |
| MS-T11 | 511.1± 12.8 | 3.41± 0.13 | 6-8 | 0.8 | 0.5-1 |
| MS-T12 | 509.2± 11.1 | 3.42± 0.16 | 6-8 | 0.8 | 0.5-1 |

**Table 5.6.10: IPQC tests for MH-CRODT**

| Batch | Average weight (mg) | Thickness (mm) | Hardness (Kp) | Friability (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| MH-T9 | 494.8± 11.2 | 3.45± 0.12 | 7-9 | 0.6 | 3-3.5 |
| MH-T10 | 511.6± 9.3 | 3.51± 0.17 | 6-8 | 0.7 | 1.5-2 |
| MH-T11 | 554.5± 8.8 | 3.58± 0. 13 | 7-8 | 0.6 | 1-1.5 |
| MH-T12 | 559.3± 7.1 | 3.56± 0.16 | 7-8 | 0.6 | 0.6-1 |

**Table 5.6.11: Results for optimization of cushioning agent and prevention of rupture of MS-pellets**

| | Eudragit®E Pellets (Batch MS-40) | Batch MS-T9 | Batch MS-T10 | Batch MS-T11 | Batch MS-T12 |
|---|---|---|---|---|---|
| Assay (%) | 98.9± 1.9 | 101.3± 1.1 | 101.7± 1.5 | 102.6± 1.1 | 100.9± 1.6 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 17.6± 1.9 | 22.5± 2.1 | 18.2± 2.1 | 16.5± 1.3 | 15.9± 1.6 |
| 2 | 22.4± 2.1 | 31.3± 4.2 | 29.1± 4.2 | 26.9± 3.2 | 25.7± 2.7 |
| 4 | 31.9± 3.2 | 39.4± 3.4 | 36.4± 3.4 | 35.6± 2.5 | 33.8± 2.6 |
| 6 | 40.6± 1.2 | 50.1± 2.2 | 47.4± 2.3 | 46.2± 2.7 | 46.5± 1.7 |
| 8 | 48.9± 1.5 | 61.5± 1.5 | 58.7± 1.4 | 55.7± 2.0 | 54.7± 2.1 |
| 10 | 56.4± 2.1 | 69.5± 2.5 | 66.0± 2.4 | 63.4± 1.9 | 62.4± 3.2 |
| 12 | 64.3± 1.9 | 77.1± 3.1 | 75.8± 2.1 | 73.1± 1.7 | 72.5± 2.5 |
| 16 | 79.5± 1.8 | 88.8± 1.9 | 87.4± 2.9 | 84.2± 2.7 | 83.9± 2.7 |
| 20 | 95.9± 1.7 | 96.8± 3.1 | 96.8± 2.3 | 96.5± 2.6 | 96.0± 2.5 |
| 24 | 102.3± 1.0 | 100.2± 1.1 | 100.2± 2.0 | 100.0± 1.7 | 100.0± 3.1 |

**Table 5.6.12: Results for optimization of cushioning agent and prevention of rupture of MH-pellets**

| | **Eudragit® E Pellets (Batch MH-33)** | **Batch MH-T9** | **Batch MH-T10** | **Batch MH-T11** | **Batch MH-T12** |
|---|---|---|---|---|---|
| Assay (%) | 99.1± 1.4 | 102.2± 1.0 | 100.6± 1.1 | 101.6± 1.2 | 101.1± 1.4 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 27.7± 2.9 | 26.5± 3.1 | 34.1± 2.2 | 32.5± 1.2 | 29.2± 1.2 |
| 3 | 39.5± 2.1 | 39.9± 2.5 | 46.1± 3.2 | 44.9± 2.2 | 41.7± 2.1 |
| 5 | 48.1± 1.1 | 49.8± 3.0 | 54.5± 2.4 | 53.4± 2.1 | 51.8± 2.3 |
| 8 | 56.2± 1.3 | 57.1± 2.4 | 63.8± 1.7 | 62.2± 1.7 | 59.8± 1.1 |
| 12 | 73.4± 1.6 | 74.6± 2.1 | 77.1± 1.2 | 75.7± 2.1 | 74.7± 2.5 |
| 16 | 82.5± 2.0 | 84.1± 1.7 | 84.8± 1.6 | 83.4± 1.5 | 83.2± 2.2 |
| 20 | 93.4± 1.4 | 96.1± 3.1 | 95.8± 2.1 | 94.1± 1.1 | 93.5± 2.7 |
| 24 | 101.5± 1.0 | 98.9± 2.2 | 101.0± 1.7 | 100.2± 1.7 | 101.4± 2.0 |

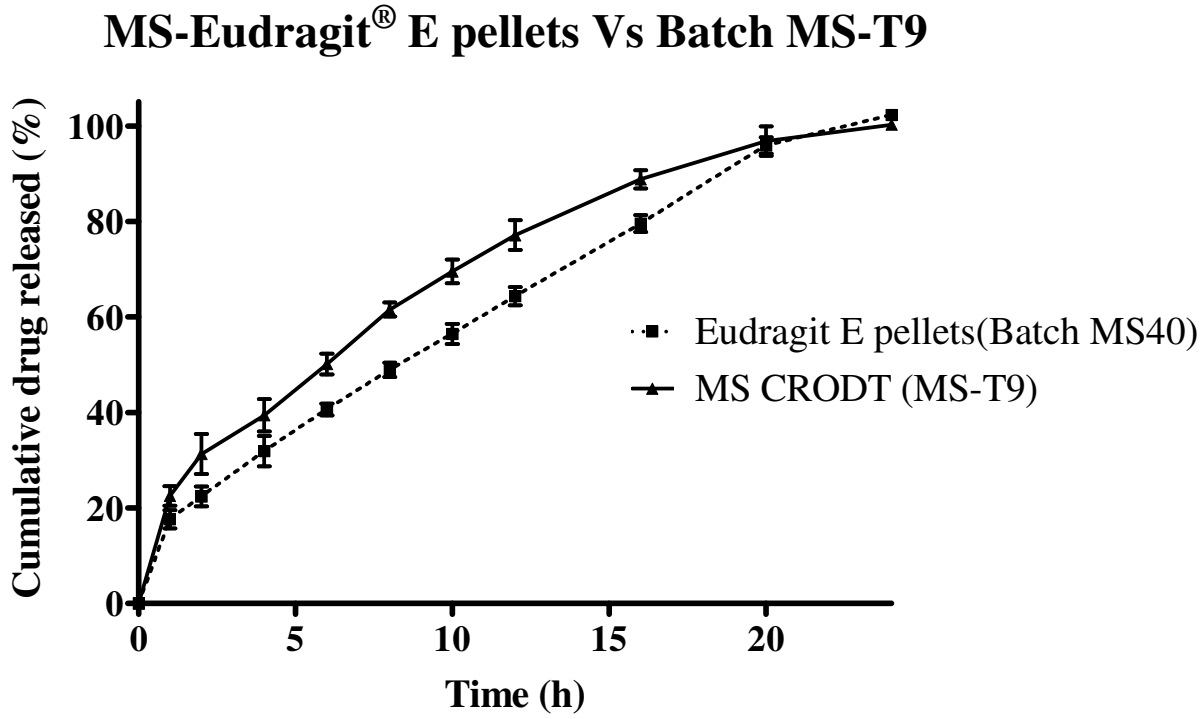



**Figure 5.6.3: Comparative dissolution profile for MS-Eudragit® E pellets and Batch MS-T9**

**MS-Eudragit® E pellets Vs Batch MST10, MST11 and MST12**

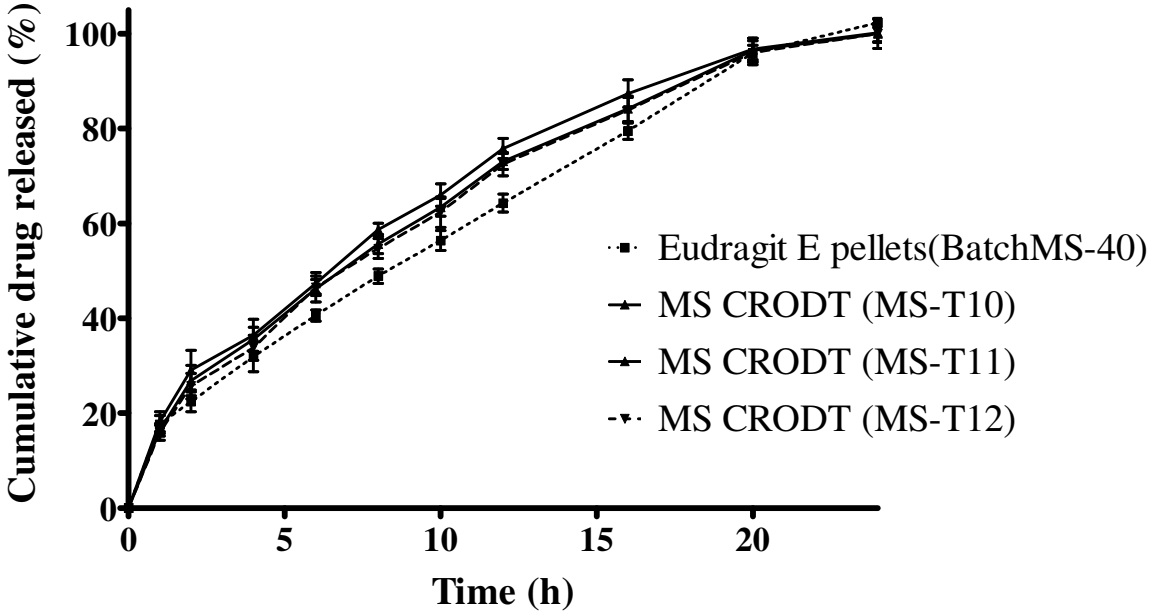



**Figure 5.6.4: Comparative dissolution profile for MS-Eudragit® E pellets, Batch MS-T10, MS -T11 and MS-T12**

**MH-Eudragit E pellet Vs MH-T9**

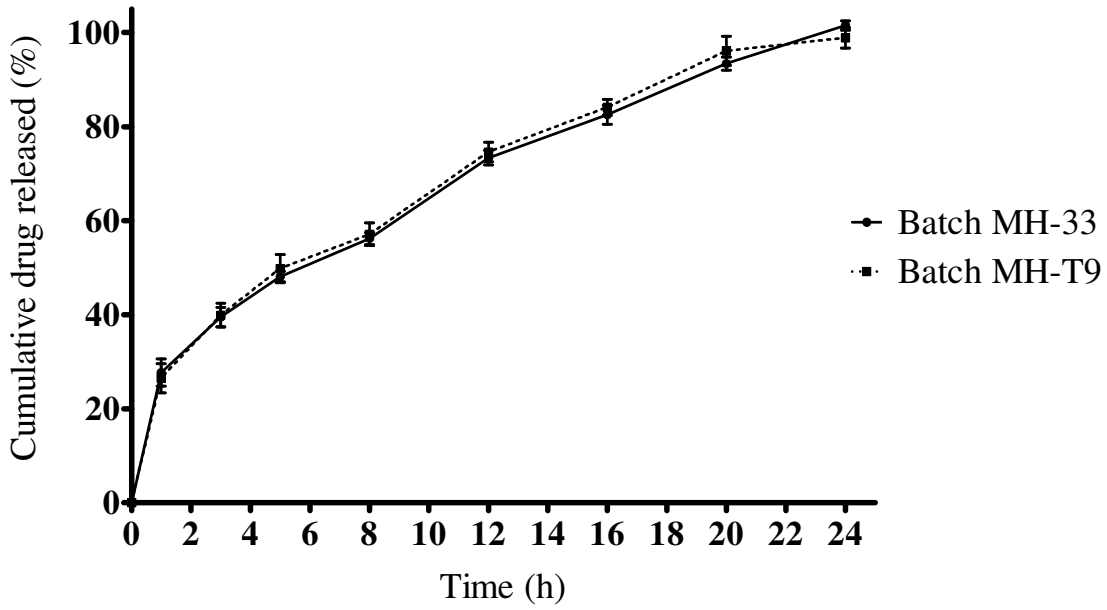



**Figure 5.6.5: Comparative dissolution profile for MH-Eudragit® E pellets and Batch MH-T9**

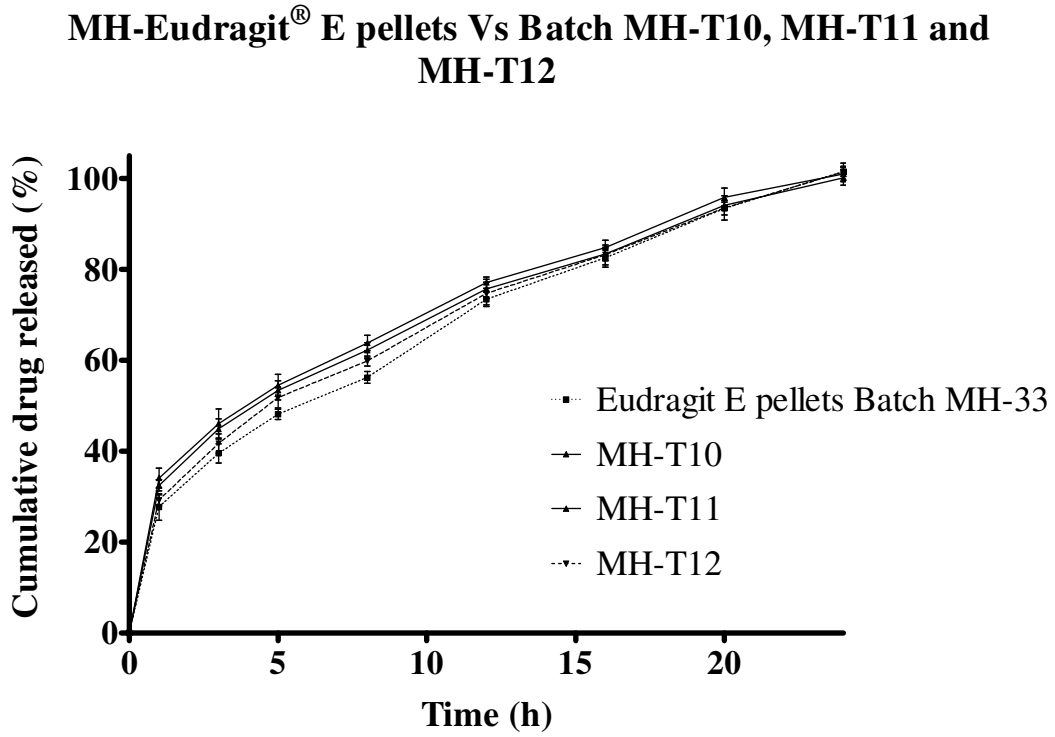



**Figure 5.6.6: Comparative dissolution profile for MH-Eudragit® E pellets, Batch MH-T10, MH-T11 and MH-T12**

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

### 5.6.5 Characterization of blend

Angle of repose for final lubricated blend of MS-T11 and MH-T12 was found to be 32.15± 0.42° and 33.21±0.37° which indicated that blend had good flow and thus there will be smooth passage through hopper. The bulk and tapped density were found to be 0.625± 0.031 g/mL, 0.714± 0.022 g/mL and 0.652± 0.039 g/mL, 0.746± 0.032 g/mL respectively. The results for Hausner's ratio (1.143 ± 0.031 and 1.114 ± 0.028) and compressibility index (14.29± 0.43 and 14.44± 0.37) also indicated good flow of the blend for MS and MH respectively.

**Microscopy**

Transverse section of tablets from Batches MS-T11 and MH-T12 were checked for intactness of pellets using SEM images. Figures 5.6.7 and 5.6.8 show uniformly distributed intact pellets for MS CRODT and MH CRODT respectively.

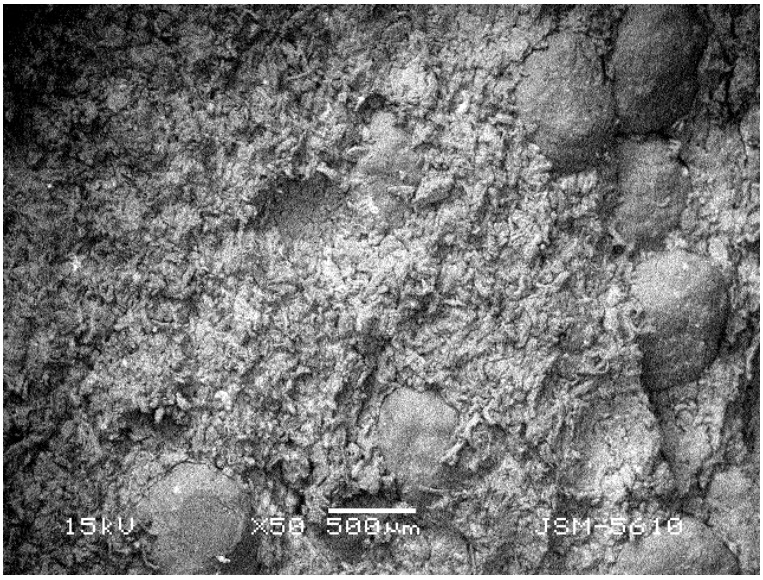



**Figure 5.6.7: SEM of transverse section of MS-CRODT (Batch MS- T11)**

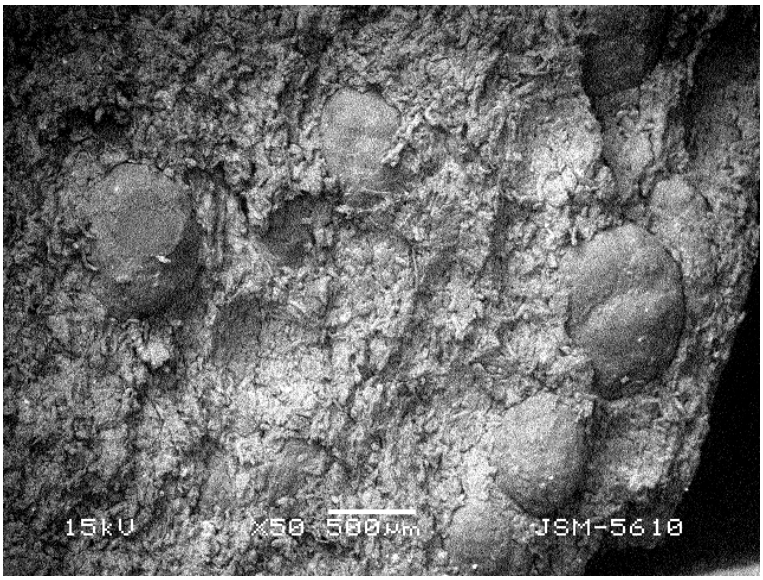



**Figure 5.6.8: SEM of transverse section of MH-CRODT (Batch-MH- T12)**

### 5.6.6 Packaging and stability study

The optimized formulation (Batch MS-T11 and Batch MH-T12) showed negligible change under the conditions of storage for parameters like visual inspection, drug content and *in vitro* drug release (Table 5.6.13 and Table 5.6.14).The data suggested that the

formulation was stable for 3 months for the packaging material selected at $40^0$C/75%RH and $25^0$C/60%RH conditions.

**Table 5.6.13. Results for stability studies of Batch MS-T11**

| | Initial | 1 Month (40°C/75% RH) | 2 Month (40°C/75% RH) | 3 Month (40°C/75% RH) | 3 Month (25°C/60% RH) |
|---|---|---|---|---|---|
| Description | White to off white tablet | White to off white tablet | White to off white tablet | White to off white tablet | White to off white tablet |
| Assay (%) | 102.6± 1.1 | 101.9± 1.3 | 101.1± 1.4 | 101.5± 1.8 | 101.2± 1.7 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 16.5± 1.3 | 16.1± 1.2 | 15.4± 2.6 | 14.9± 2.3 | 16.9± 2.8 |
| 2 | 26.9± 3.2 | 25.3± 1.1 | 25.1± 1.9 | 24.7± 1.8 | 24.8± 2.7 |
| 4 | 35.6± 2.5 | 36.2± 2.7 | 34.9± 1.3 | 34.2± 1.9 | 36.1± 1.5 |
| 6 | 46.2± 2.7 | 45.2± 1.9 | 44.2± 1.5 | 44.2± 2.7 | 45.2± 2.7 |
| 8 | 55.7± 2.0 | 53.1± 1.8 | 54.5± 1.5 | 53.2± 2.1 | 55.1± 0.9 |
| 10 | 63.4± 1.9 | 62.9± 2.1 | 62.7± 1.1 | 61.6± 1.5 | 65.5± 1.8 |
| 12 | 73.1± 1.7 | 72.1± 1.9 | 72.2± 0.9 | 71.3± 1.4 | 74.6± 1.1 |
| 16 | 84.2± 2.7 | 84.9± 1.5 | 83.9± 1.8 | 82.9± 1.2 | 86.1± 0.9 |
| 20 | 96.5± 2.6 | 97.7± 0.8 | 96.8± 1.5 | 97.1± 1.1 | 98.9± 1.6 |
| 24 | 100.0± 1.7 | 98.5± 1.8 | 99.2± 2.5 | 98.7± 2.1 | 99.6± 1.7 |

Note: Avg. value = Mean± SD (n=3)

**Table 5.6.14. Results for stability studies of Batch MH-T12**

| | Initial | 1 Month (40°C/75% RH) | 2 Month (40°C/75% RH) | 3 Month (40°C/75% RH) | 3 Month (25°C/60% RH) |
|---|---|---|---|---|---|
| Description | White to off white tablet | White to off white tablet | White to off white tablet | White to off white tablet | White to off white tablet |
| Assay (%) | 101.1± 1.4 | 100.9± 1.3 | 100.3± 1.5 | 100.1± 1.2 | 101.6± 1.2 |
| Time (h) | Cumulative drug release (%) | | | | |
| 1 | 29.2± 1.2 | 28.8± 2.2 | 27.1± 2.5 | 27.9± 2.4 | 28.1± 2.0 |
| 3 | 41.7± 2.1 | 40.5± 2.0 | 40.1± 1.4 | 38.7± 1.7 | 40.8± 1.2 |
| 5 | 51.8± 2.3 | 51.2± 1.5 | 48.9± 1.2 | 48.0± 1.8 | 49.1± 1.6 |
| 8 | 59.8± 1.1 | 58.4± 1.5 | 57.2± 1.4 | 56.9± 1.7 | 57.2± 1.6 |
| 12 | 74.7± 2.5 | 73.5± 1.7 | 73.0± 1.9 | 72.2± 2.3 | 73.7± 2.5 |
| 16 | 83.2± 2.2 | 82.9± 1.4 | 82.7± 1.5 | 81.1± 2.5 | 81.9± 1.3 |
| 20 | 93.5± 2.7 | 92.6± 1.3 | 92.2± 2.3 | 91.3± 1.9 | 92.7 ± 2.1 |
| 24 | 101.4± 2.0 | 100.9± 1.8 | 100.1± 1.2 | 98.9± 1.6 | 99.3± 1.2 |

Note: Avg. value = Mean ± SD (n=3)

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