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Advances in Bioresearch

## ORIGINAL ARTICLE

# Development of Modified Release Dosage form of Midodrine Hydrochloride using Quality by Design Approach

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**ABSTRACT**
*Midodrine Hydrochloride is mainly used for treatment of Orthostatic hypotension. The purpose of the development of modified release dosage form is to minimizing the frequency of dosing while maintaining therapeutic concentration. The objective of the present research work is to formulate and evaluate once daily extended release capsules of Midodrine Hydrochloride by applying QbD approaches using various tooling for optimization of drug products. MCC sphere were drug layered, Polymer coated and again drug layered using fluid bed processor to achieve desired drug release over extended period of time. Central composite design (CCD) was used to optimize Midodrine Hydrochloride pellets selecting independent variables (Pore former level, Plasticizer level and % weight gain) and responses (% drug release at 2, 4, 8 and 12 hrs). Stability study carried out for final formulation and there is no any major changes observed for% drug release over 12 hours.*
***Keywords:*** *Midodrine Hydrochloride (MIDH), Quality by Design, Pellets, Risk Assessment.*

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## INTRODUCTION

Drug administration by oral route is the widely used and popular among all the other routes for different kind dosage form due to ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Sustained release dosage form, prolonged release dosage form, modified release dosage form, extended release dosage form or depot dosage form, these all terminology mainly used for extend of drug release by using different polymer concentration to provide medication continuously over extended period of time. Modified release drug delivery is advantageous than conventional dosage forms because it enhance pharmacokinetic and pharmacodynamics properties of the drugs by reducing dose frequency of drug and maintain therapeutic of drug over extended period of time by reducing local and systemic side effects of the drugs and assuring improve of patient compliance [1, 2].

Orthostatic hypotension describe as lowering in blood pressure of at least 20 mmHg for systolic or 10 mmHg of diastolic blood pressure within 3 minutes of standing up. In other word Orthostatic hypotension can describe the drop in blood pressure when a person in standing position [3, 4].

MIDH is a prodrug which is mainly activated by enzymatic hydrolysis within the body to forms an active metabolite (desglymidodrine). Desglymidodrine is a α1-receptor agonist and use its actions via activation of α -adrenergic receptors of the arteriolar and venous vasculature, producing an expansion in vascular tone and promotion of blood pressure. Cardiac β-adrenergic receptors does not stimulated by Desglymidodrine and it is diffuses poorly over the blood–brain barrier (BBB), therefore does not shows any effects on the central nervous system (CNS) [5, 6].

Quality by design (QbD) is crucial part for developing quality product for pharmaceutical industry. As per ICH Q8 guidelines, QbD is defined as it is systematic approach mainly used in beginning of development of the products with predefined objectives, understanding and controlling process and quality risk

management. Quality Target Product Profile (QTPP), Critical Process Parameters (CPPs), Critical Material Attributes (CMAs) and critical quality attributed (CQA) need to identify for development and designing of pharmaceutical products by employing Quality by design approach. Quality of the products and robust formulation could be produced using Quality by design approach [7, 8].

## MATERIAL AND METHODS

### Materials

MIDH used as a model drug and gifted sample from Emcure Pharmaceuticals Ltd. Microcrystalline cellulose spheres (MCC sphere #25-35) were used as inner core. Hypromellose was used as binder during drug layering process and as pore former during extended release coating process. Ethyl cellulose (10 cps)(ETHOCEL STANDARD 10 PREMIUM, Colorcon, Inc) used as ER coating polymer. Triethylcitrate (Merck Limited) was used as plasticizer during extended release coating process. Talc was used as anti-adherent material during process.Methylene Chloride, Isopropyl Alcohol and purified water were selected as vehicle during process.

### Quality Target Product Profile for MIDH ER Capsules.

Quality Target Product Profile (QTPP) was defined for proposed drug product are given in below table.

**Table 1: Quality Target Product Profile for MIDH ER Capsules.**

| QTPP Elements | | Target | Justification |
|---|---|---|---|
| Dosage form | | Capsules | Capsule is commonly accepted dosage form. |
| Dosage design | | Extended release Capsules | Faster onset of action followed by longer duration |
| Dosage strength | | 15 mg | It is the unit dose of MIDHwhich needs to be incorporated for once a daily administration |
| Route of administration | | Oral | Oral route is most convenient and accepted route for dosage form administration. |
| Stability | | At least 12 months at room temperature | To maintain therapeutic potential of the drug during storage period |
| Drug product quality attributes | Physical attributes | Pharmaceutical equivalent requirement | Must meet the Pharmaceutical equivalent or other applicable quality standards. |
| | Assay | | |
| | Content uniformity | | |
| | Dissolution | | |
| Container Closure System | | Suitable for storage and stability formulation. | Need to achieve target shelf-life and to ensure capsule integrity during shipping. |

Following table summarizes the critical quality attributes (CQAs) of proposed drug product of MIDH ER Capsules.

**Table 2: Critical Quality Attributes (CQAs) of MIDH ER Capsules**

| Quality attributes of the DP (Drug Product) | | Target | | Is this CQA? | Justification |
|---|---|---|---|---|---|
| Physical Attributes | Appearance | Colour of capsule acceptable to the patient. | | No | Colour and appearance of the products does not directly linked to safety and efficacy. Hence, they are not critical. |
| | Odor | No unpleasant odor | | No | Generally, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. |
| | Size | Size of capsule acceptable to the patient. | | No | For patient convenient as well as easy of swallowing, capsule size were selected "Size 2" |
| Assay | | 90%-110% w/w of label claim | | Yes | Variability of process may affect assay of the drug products and variability of the assay directly affect safety and efficacy. Therefore, assay will be evaluate throughout development of product. |
| Dissolution | | Media : 0.1N HCl followed by pH 6.8 buffer<br>Apparatus : USP- II (Paddle)<br>Volume :900 mL<br>Speed : 50 rpm | | Yes | The drug release profile is important for preparation of Modified release of Dosage form of MIDH. Both the formulation as well as process related parameters may affect dissolution of MIDH from capsule dosage form. This CQA will be investigated throughout formulation and process development. |
| | | **Time (hours)** | **% Drug Release** | | |

| Quality attributes of the DP (Drug Product) | Target | | Is this CQA? | Justification |
|---|---|---|---|---|
| | 2 | Not more than 35% | | |
| | 4 | Between 40% to 50% | | |
| | 8 | Between 60% to 75% | | |
| | 12 | Not less than 85% | | |

**Manufacturing process diagram:**

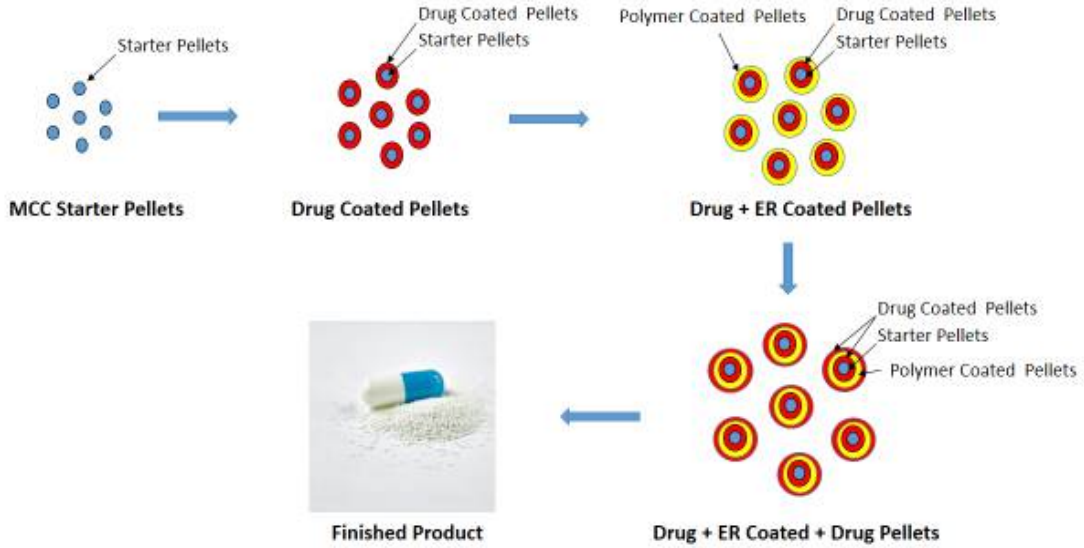


**Figure 1. Manufacturing diagram of MIDH extended release dosage form**

**Manufacturing of Drug-Layered Pellets (First layer)**

MCC spheres (25-35#) was taken and drug layering was performed on it by applying drug solution of MIDH. The drug solution was prepared by Hypromellose (Methocel E5 Premium LV) was dissolved into purified water under continuous stirring to get clear solution. MIDH was added to the Hypromellose solution with continuous stirring and stir till clear solution obtained. Dispersion was passed through # 80sieve.Fluid bed processor (Wruster coating process) was used for drug layering of MIDH. First layer of drug pellets have 10.130 mg of MIDH in 165 mg of drug pellets.

**Table 3: Composition of MIDH drug layered pellets**

| Ingredients | MD1 (mg) | MD2 (mg) | MD3 (mg) | MD4 (mg) |
|---|---|---|---|---|
| MCC Sphere (25-30 #) | 152.540 | 151.527 | 150.514 | 150.311 |
| Midodrine Hydrochloride USP | 10.130 | 10.130 | 10.130 | 10.130 |
| Hypromellose USP (Methocel E5 Premium LV) | 0.304 | 0.304 | 0.304 | 0.507 |
| Talc | 2.026 | 3.039 | 4.052 | 4.052 |
| Purified Water | Q.S. | Q.S. | Q.S. | Q.S. |
| **Total** | **165.00** | **165.00** | **165.00** | **165.00** |

**Manufacturing of Extended Release Coated pellets**

Drug layered pellets were coated with ethyl cellulose as extended release polymer, hypromellose as pore former and triethyl citrate as plasticizer. Extended release coating was settled inbetween15-30% of the drug layer pellets, polymer to pore former ratio was taken as 95:5 &90:10. Triethyl citrate concentration selected was 10% of total polymer. Extended release dispersion (5%w/w) was prepared by adding ethyl cellulose into isopropyl alcohol under continuous stirring. Hypromellose was dissolved into it under continuous stirring. Stirring was continued to get homogenous dispersion. Methylene Chloride was added

into above dispersion under continuous stirring to get clear homogeneous dispersion. Triethyl citrate was added into above dispersion under continuous stirring. Finally dispersion was sifted through #100 sieve (ASTM).

**Table 4: Composition of MIDH extended release coated pellets**

| Ingredients | MER 5 (mg) | MER 6 (mg) | MER 7 (mg) | MER 8 (mg) |
|---|---|---|---|---|
| Drug pellets | 165.000 | 165.000 | 165.000 | 165.000 |
| Ethyl cellulose 10 cps (Ethocel STD 10 PREM) | 42.322 | 35.269 | 28.215 | 26.730 |
| Hypromellose (Methocel E5 Premium LV) | 2.227 | 1.856 | 1.485 | 2.970 |
| Triethyl citrate | 4.950 | 4.125 | 3.300 | 3.300 |
| Dichloromethane | q.s. | q.s. | q.s. | q.s. |
| Isopropyl alcohol | q.s. | q.s. | q.s. | q.s. |
| **Total** | **198.00** | **198.00** | **198.00** | **198.00** |
| Concentration of extended release dispersion | 5% | 5% | 5% | 5% |
| Total % of extended release coating | 30% | 25% | 20% | 20% |
| % Ratio of ethyl cellulose and Hypromellose | 95:5 % | 95:5 % | 95:5 % | 90:10 % |

**Table 5: Processing parameters used for drug layering and extended coating of MIDH.**

| Parameters | Drug Layering | Extended Release Coating |
|---|---|---|
| Machine | GPCG 1.1 | GPCG 1.1 |
| Air distribution plate | C | C |
| Spray nozzle diameter (mm) | 1.0 | 1.0 |
| Inlet air temperature ($^{o}$C) | 40 – 60 | 40 – 60 |
| Product temperature ($^{o}$C) | 30 – 40 | 17 – 40 |
| Inlet air flow (cfm) | 40 – 60 | 40 – 80 |
| Atomization air pressure (Bar) | 0.9 – 1.0 | 0.9 – 1.0 |
| Spray rate (g/min) | 1 – 7 | 1 – 10 |
| Drying temperature ($^{o}$C) | 60 | 55 |
| Drying time (min) | 30 | 30 |

**Optimization of the Extended Release Coating**

To perform polymer layer optimization, central composite design (CCD) was adopted for Pore former level, Plasticizer level and % weight gain is consider as independent parameters. The dependent parameters selected was drug release at 1, 4, 8 and at 12 hours.

**Table 6:Summary of central composite design (CCD)**

| Independent Variable | Level | |
|---|---|---|
| | -1 | +1 |
| Pore former level (HPMC content in EC:HPMC) | 0.0 | 20.0 |
| Plasticizer Level (Triethyl citrate) | 8.0 | 12.0 |
| % Weight Gain | 18 | 22 |
| **Response to be studied** | | **Limit** |
| Drug Release at 1hrs | | Not more than 15% |
| Drug Release at 4 hrs | | Between 25 to 40% |
| Drug Release at 8 hrs | | Between 60 to75 % |
| Drug Release at 12 hrs | | Note less than 85% |

**Manufacturing of Drug-Layered Pellets (Second layer)**

Polymer coated pellets were taken and drug layering was performed on it by applying drug solution of MIDH. The drug solution was prepared by Hypromellose (Methocel E5 Premium LV) was dissolved into purified water under continuous stirring to get clear solution. MIDH was added to the Hypromellose solution with continuous stirring and stir till clear solution obtained. Dispersion was passed through # 80 sieve. Fluid bed processor (Wruster coating process) was used for drug layering of MIDH. First layer of drug pellets have 4.870 mg of MIDH in 205 mg of drug pellets.

**Table 7: Composition of MIDH drug layered pellets (Second layer)**

| Ingredients | MDL9 (mg) |
|---|---|
| Polymer Coated Pellets | 198.00 |
| Midodrine Hydrochloride USP | 4.870 |
| Hypromellose USP (Methocel E5 Premium LV) | 0.195 |
| Talc | 1.948 |
| Purified Water | q.s. |
| **Total** | **205.000** |

**Evaluation of Pellets [9-15]**

Both the pellets (Drug layered and extended release coated pellets) were evaluated for particle size distribution by using a nest of the standard sieve (ASTM). % process efficiency was also evaluated for the pellets using equation (1). Assay of drug pellets and extended release coated pellet and in-vitro dissolution study (0.1 N Hydrochloroc acid followed by pH 6.8 phosphate buffer / 900ml / USP Apparatus – II / 50 RPM) of extended release pellets was evaluated at specified time interval and measure the concentration of drug release in time profile.

$$\% \text{ Process efficiency} = \frac{(\text{Practical Weight of Coated Pellets} - \text{Initial wt of Starter Pellets})}{\text{Amount of total Solid sprayed from Solution}} * 100 \quad \text{.....e.q.(1)}$$

**RESULTS**

**Introductory Trials of Drug Layered Pellets**

Drug layering was performed using fluid bed processor (Wurster coating process). Amount of drug layer on inner layer play major role for extended release pellets. Therefore, % process efficiency and assay of the drug was evaluated in preliminary trials. Results are given in**table 8.**

**Table 8: Results of drug layered pellets**

| Parameters | | Batch Number | | | |
|---|---|---|---|---|---|
| | | MD1 | MD2 | MD3 | MD4 |
| % Process Efficiency | | 93.28 | 95.47 | 96.42 | 97.56 |
| Assay (%) | | 95.1 | 99.9 | 99.0 | 99.3 |
| Particle Size Distribution (by sieve analysis) | >20# | Nil | Nil | Nil | Nil |
| | 20 – 25# | 4.0 | 8.5 | 9.4 | 6.5 |
| | 25 – 30# | 85.5 | 82.4 | 80.6 | 85.9 |
| | 30 – 35# | 10.4 | 8.5 | 9.5 | 7.5 |
| | <35# | 0.1 | 0.0 | 0.2 | Nil |

**Introductory trials of Extended Release Coating**

Introductory trials of extended release coated pellets were evaluated for % process efficiency, assay, particle size distribution and drug release of MIDH Extended Release Tablets. The results of extended release pellets shown in **table 9 and table 10.**

**Table 9: Results of extended release pellets**

| Parameters | | Batch Number | | | |
|---|---|---|---|---|---|
| | | MER 5 | MER 6 | MER 7 | MER 8 |
| Process Efficiency | | 98.1 | 97.8 | 98.5 | 99.1 |
| Assay | | 98.6 | 99.2 | 98.2 | 99.4 |
| Particle Size Distribution (by sieve analysis) | >18# | 0.1 | 0.5 | Nil | 0.2 |
| | 18 – 20# | 4.0 | 8.5 | 5.4 | 6.5 |
| | 20 – 25# | 90.2 | 89.5 | 94.2 | 93.5 |
| | 25 – 30# | 5.1 | 1.0 | 0.1 | 0.0 |
| | <30# | 0.1 | 0.0 | 0.2 | Nil |

**Table 10:% Drug release of extended release pellets**

| Time (Hrs) | Limit | MER 5 | MER 6 | MER 7 | MER 8 |
|---|---|---|---|---|---|
| 1 | Note more than15% | 1.1 ± 3.9 | 2.9 ± 3.5 | 1.5 ± 6.8 | 3.5 ± 3.6 |
| 2 | | 5.4 ± 3.2 | 9.9 ± 3.8 | 12.7 ± 3.1 | 11.5 ± 5.6 |
| 4 | Between 20 to 40% | 18.3 ± 2.4 | 23.2 ± 2.3 | 26.1 ± 1.9 | 25.7 ± 4.0 |
| 6 | | 37.5 ± 2.3 | 40.3± 1.9 | 46.7± 1.6 | 43.8± 2.9 |
| 8 | Between 60 to 75% | 48.7 ± 1.7 | 57.8 ± 1.6 | 68.9 ± 1.5 | 65.8 ± 2.7 |
| 10 | | 62.8 ± 1.5 | 66.4 ± 1.1 | 85.7 ± 1.0 | 83.4 ± 1.9 |
| 12 | Note less than 85% | 74.9 ± 0.9 | 84.9 ± 0.8 | 97.4 ± 0.7 | 99.1 ± 1.0 |

 

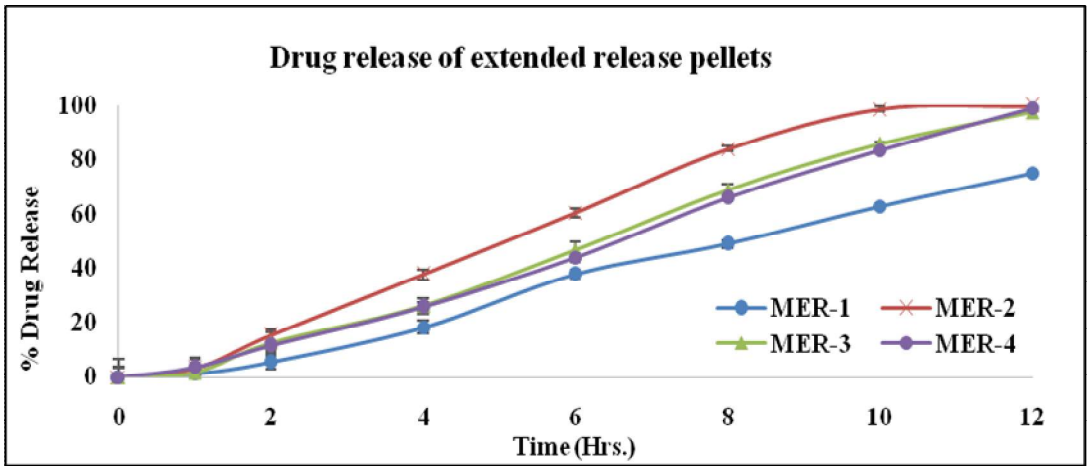


**Figure 2. Comparative dissolution profile of extended release coated pellets.**

**Table 11: Optimization results of extended release coating with CCD design**

| Std Run | MHOP-1 | MHOP-2 | MHOP-3 | MHOP-4 | MHOP-5 | MHOP-6 | MHOP-7 | MHOP-8 | MHOP-9 | MHOP-10 | MHOP-11 | MHOP-12 | MHOP-13 | MHOP-14 | MHOP-15 | MHOP-16 | MHOP-17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Independent variables | | | | | | | | | | | | | | | | | |
| Pore former level | 0 | 10 | 20 | 10 | 0 | 0 | 10 | 10 | 20 | 0 | 20 | 20 | 10 | 10 | 20 | 10 | 0 |
| Plasticizer Level | 8 | 10 | 12 | 8 | 8 | 12 | 10 | 10 | 8 | 10 | 12 | 8 | 10 | 10 | 10 | 12 | 12 |
| % Weight Gain | 18 | 20 | 18 | 20 | 22 | 18 | 20 | 20 | 18 | 20 | 22 | 22 | 18 | 22 | 20 | 20 | 22 |
| Dependent variables | | | | | | | | | | | | | | | | | |
| Time | % Drug Release | | | | | | | | | | | | | | | | |
| 2 | 2.1 | 12.3 | 17.8 | 13.1 | 3.6 | 4.3 | 9.8 | 11.8 | 19.5 | 1.1 | 15.9 | 16.6 | 13.9 | 14.1 | 17.1 | 12.4 | 1.5 |
| 4 | 16.3 | 32.3 | 48.2 | 35.6 | 12.5 | 17.4 | 30.6 | 31.5 | 50.1 | 14.5 | 42.8 | 43.6 | 28.1 | 33.1 | 45.4 | 32.7 | 10.2 |
| 8 | 52.5 | 64.2 | 83.1 | 73.2 | 47.8 | 50.1 | 67.3 | 71.4 | 82.8 | 46.9 | 78.6 | 80.1 | 73.9 | 65.4 | 82.7 | 72.3 | 44.8 |
| 12 | 71.7 | 97.9 | 98.5 | 97.7 | 64.1 | 69.6 | 99.1 | 98.3 | 98.4 | 65.8 | 99.1 | 98.5 | 97.5 | 96.8 | 98.8 | 96.5 | 62.7 |

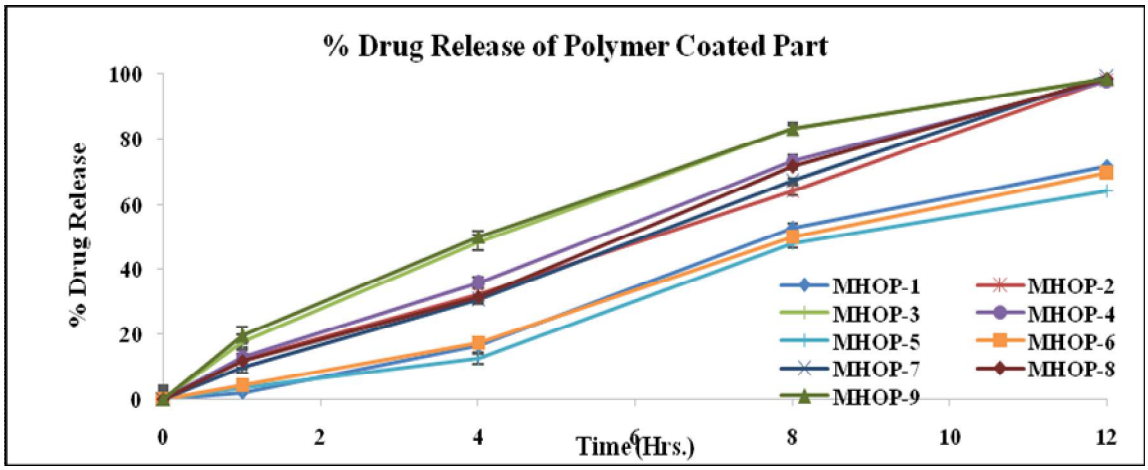


**Figure 3. % drug release of optimize formulation of extended release coating pellets (Batch no. MHOP-1 to MHOP-9)**

 

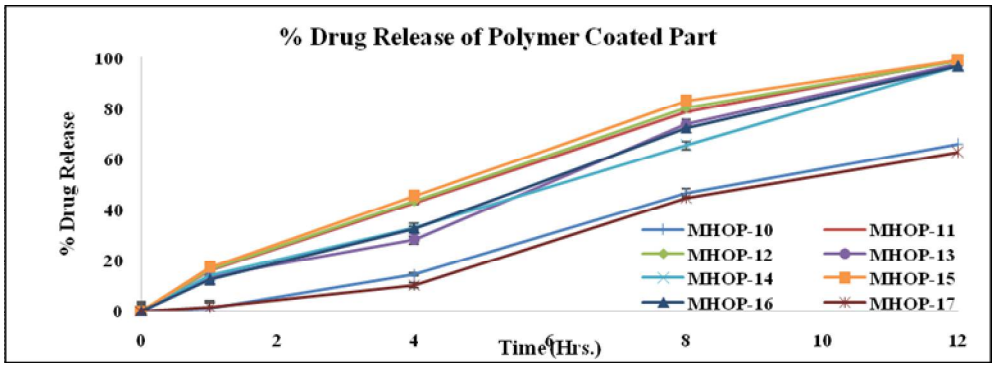


**Figure 4. % drug release of optimize formulation of extended release coating pellets (Batch no. MHOP-10 to MHOP-17)**

**Table 12: Dissolution of final products in different media.**

| Time (Hrs) | Limit | 0.1N HCl followed by pH 6.8 phosphate buffer | 0.1 N HCL | pH 4.5 phosphate buffer | pH 6.8 phosphate buffer |
|---|---|---|---|---|---|
| 2 | Note more than 35% | 29.5 ± 1.3 | 31.3 ± 3.7 | 26.8 ± 3.7 | 32.6 ± 4.6 |
| 4 | Between 40 to 50% | 44.5 ± 2.3 | 47.1 ± 2.7 | 42.3 ± 1.6 | 49.4 ± 3.5 |
| 8 | Between 60 to75% | 70.4 ± 1.9 | 65.7 ± 2.1 | 73.2 ± 1.3 | 72.5 ± 2.1 |
| 12 | Note less than 85% | 96.2 ± 0.7 | 92.4 ± 1.1 | 97.4 ± 1.1 | 95.1 ± 1.5 |

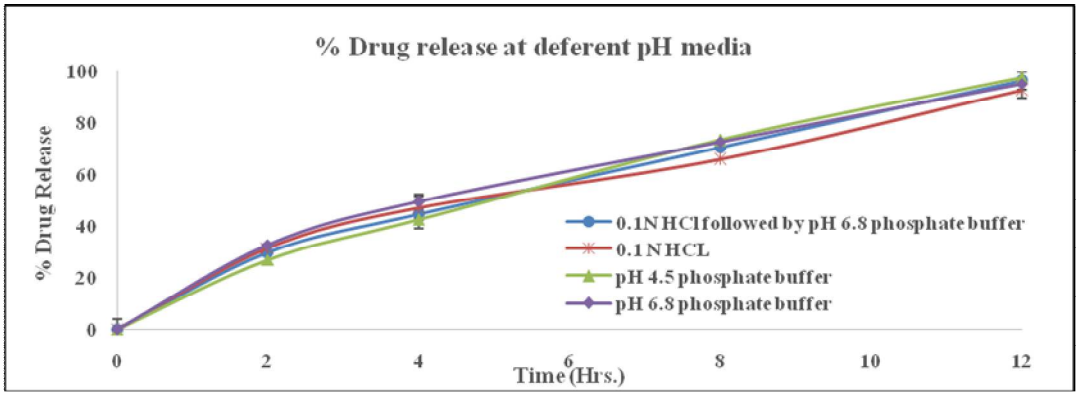


**Figure 5. % drug release of final formulation in different media**

**Table 13: Stability studies of final formulation**

| Time (Hrs) | Limit | Initial | 40/75°C (1 M) | 25/60°C (1 M) | 40/75°C (3 M) | 25/60°C (3 M) |
|---|---|---|---|---|---|---|
| 2 | Note more than 35% | 29.5 ± 1.3 | 27.1 ± 4.3 | 32.1 ± 3.5 | 27.5 ± 4.7 | 32.1 ± 4.7 |
| 4 | Between 40 to 50% | 44.5 ± 2.3 | 42.6 ± 3.1 | 47.1 ± 1.8 | 43.1 ± 3.2 | 45.3 ± 3.3 |
| 8 | Between 60 to75% | 70.4 ± 1.9 | 63.9 ± 2.3 | 69.7 ± 1.5 | 64.6 ± 2.5 | 70.2 ± 2.9 |
| 12 | Note less than 85% | 96.2 ± 0.7 | 93.2 ± 1.5 | 95.3 ± 0.6 | 94.5 ± 1.7 | 96.1 ± 1.9 |

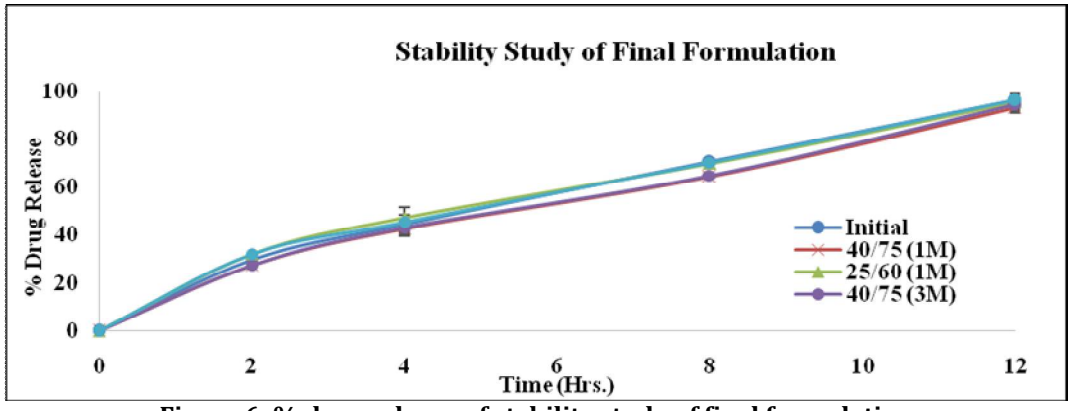


**Figure 6. % drug release of stability study of final formulation**

 

## DISCUSSION

### Drug Layering:

Concentration of binder play critical role for good adhesion of drug on the inner core. Lesser binder concentration leads poor adhesion of drugs and leads loss of the drug during process. This ultimately may results into lower assay of the drug pellets. More binder concentration leads good adhesion of the drug onto the inner pellets but may increase chance of agglomeration. To avoid more agglomeration, talc used in the formulation with different ration (30-40% of API). Results shows that there was increase in process efficiency with increase in the binder and talc concentration. Increasing in binder concentration, 3 % to 5 % leads to good process efficiency and increasing talc in 30% to 40%leads to reduce static charge and also minimize generation of agglomeration during the process.

### Extended Release Coating:

Extended release coating is important for controlling release of drug from the drug layer pellets. The preliminary trials were taken with different % of weight gain, different ration of Hypropellose: Ethyl cellulose and change in ratio of Triethyl citrate as plasticizer. Base on trials 20% of weight gain, ratio of Ethyl cellulose: Hypromellose (90:10) and 10% of plasticizer shows optimum release over 12 hours.

### Optimization of Extended Release Coating:

To perform polymer layer optimization, central composite design (CCD) was adopted for pore former level, Plasticizer level and % weight gain. Studies for polymer layer formulation variable were performed by evaluating dissolution of polymer coated pellets. Fit summary of different dependent parameters were summarized in below table.

**Table 14: Fits summary of optimization batches for dependent parameters**

| Source | Sum of Squares | df | Mean Square | F Value | p-value Prob > F | Comments |
|---|---|---|---|---|---|---|
| **Response Y1: Drug release at 2 hrs** | | | | | | |
| Mean vs Total | 2355.29 | 1 | 2355.29 | | | |
| Linear vs Mean | 399.09 | 3 | 133.03 | 57.28 | < 0.0001 | Suggested |
| 2FI vs Linear | 5.31 | 3 | 1.77 | 0.7114 | 0.5671 | |
| Quadratic vs 2FI | 8.38 | 3 | 2.79 | 1.19 | 0.3821 | |
| Cubic vs Quadratic | 6.15 | 4 | 1.54 | 0.4462 | 0.7743 | Aliased |
| **Response Y2: Drug release at 4 hrs** | | | | | | |
| Mean vs Total | 16207.06 | 1 | 16207.06 | | | |
| Linear vs Mean | 2571.13 | 3 | 857.04 | 136.24 | < 0.0001 | Suggested |
| 2FI vs Linear | 1.04 | 3 | 0.3479 | 0.0431 | 0.9874 | |
| Quadratic vs 2FI | 27.82 | 3 | 9.27 | 1.23 | 0.3692 | |
| Cubic vs Quadratic | 50.58 | 4 | 12.64 | 16.18 | 0.0227 | Aliased |
| **Response Y3: Drug release at 8 hrs** | | | | | | |
| Mean vs Total | 76058.61 | 1 | 76058.61 | | | |
| Linear vs Mean | 2800.78 | 3 | 933.59 | 73.17 | < 0.0001 | |
| 2FI vs Linear | 3.90 | 3 | 1.30 | 0.0804 | 0.9692 | |
| Quadratic vs 2FI | 107.28 | 3 | 35.76 | 4.58 | 0.0447 | Suggested |
| Cubic vs Quadratic | 12.22 | 4 | 3.06 | 0.2159 | 0.9136 | Aliased |
| **Response Y4: Drug release at 20 hrs** | | | | | | |
| Mean vs Total | 1.343E+05 | 1 | 1.343E+05 | | | |
| Linear vs Mean | 2563.46 | 3 | 854.49 | 11.55 | 0.0006 | |
| 2FI vs Linear | 31.26 | 3 | 10.42 | 0.1120 | 0.9511 | |
| Quadratic vs 2FI | 922.28 | 3 | 307.43 | 269.10 | < 0.0001 | Suggested |
| Cubic vs Quadratic | 3.91 | 4 | 0.9785 | 0.7190 | 0.6327 | Aliased |

**Table 15: ANOVA result of optimization batches for dependent parameters($Y_1$: drug release at 2hr)**

| Source | Sum of Squares | df | Mean Square | F Value | p-value Prob > F | Comments |
|---|---|---|---|---|---|---|
| **Model** | 399.09 | 3 | 133.03 | 57.28 | < 0.0001 | Significant |
| A-Pore former level (HPMC content in EC:HPMC) | 373.32 | 1 | 373.32 | 160.76 | < 0.0001 | Significant |
| B-Plasticizer Level (Triethyl citrate) | 12.77 | 1 | 12.77 | 5.50 | 0.0356 | Significant |
| C-% Weight Gain | 13.00 | 1 | 13.00 | 5.60 | 0.0342 | Significant |
| **Residual** | 30.19 | 13 | 2.32 | | | |
| Lack of Fit | 26.69 | 11 | 2.43 | 1.39 | 0.4922 | Not significant |
| Pure Error | 3.50 | 2 | 1.75 | | | |
| **Cor Total** | 429.28 | 16 | | | | |

 

The p-value suggests that the model was found to be significant. As depicted in Table 15, the effect of Pore former level, Plasticizer Level and % Weight Gain were found to be significant whereas other model terms were found to be insignificant. Further, the Model F-value of 57.28 implies the model is significant. Moreover, the value of adequate precision was found to be 22.6732 which indicates an adequate signal to noise ratio and hence the model can be used to navigate the design space. Final equation for the response $Y_1$ is : 11.77 + 6.11*A – 1.13*B – 1.14*C.

**Table 16: ANOVA result of optimization batches for dependent parameters ($Y_2$: drug release at 4hr)**

| Source | Sum of Squares | df | Mean Square | F Value | p-value Prob > F | Comments |
|---|---|---|---|---|---|---|
| **Model** | 2571.13 | 3 | 857.04 | 136.24 | < 0.0001 | significant |
| A-Pore former level (HPMC content in EC:HPMC) | 2534.46 | 1 | 2534.46 | 402.88 | < 0.0001 | significant |
| B-Plasticizer Level (Triethyl citrate) | 4.62 | 1 | 4.62 | 0.7350 | 0.4068 | not significant |
| C-% Weight Gain | 32.04 | 1 | 32.04 | 5.09 | 0.0419 | significant |
| **Residual** | 81.78 | 13 | 6.29 | | | |
| Lack of Fit | 80.33 | 11 | 7.30 | 10.10 | 0.0935 | not significant |
| Pure Error | 1.45 | 2 | 0.7233 | | | |
| **Cor Total** | 2652.91 | 16 | | | | |

The p-value suggests that the model was found to be significant. As depicted in Table 16, the effect of Pore former level and % Weight Gain were found to be significant whereas other model terms were found to be insignificant. Further, the Model F-value of 136.24 implies the model is significant. Moreover, the value of adequate precision was found to be 30.2308 which indicates an adequate signal to noise ratio and hence the model can be used to navigate the design space. Final equation for the response $Y_2$ is: 30.88 + 15.92*A – 0.68*B – 1.79*C.

**Table 17: ANOVA result of optimization batches for dependent parameters ($Y_3$: drug release at 8hr)**

| Source | Sum of Squares | Df | Mean Square | F Value | p-value Prob > F | Comments |
|---|---|---|---|---|---|---|
| **Model** | 2911.96 | 9 | 323.55 | 41.42 | < 0.0001 | significant |
| A-Pore former level (HPMC content in EC:HPMC) | 2729.10 | 1 | 2729.10 | 349.40 | < 0.0001 | significant |
| B-Plasticizer Level (Triethyl citrate) | 5.63 | 1 | 5.63 | 0.7202 | 0.4242 | not significant |
| C-% Weight Gain | 66.05 | 1 | 66.05 | 8.46 | 0.0227 | significant |
| AB | 2.20 | 1 | 2.20 | 0.2823 | 0.6116 | |
| AC | 0.9800 | 1 | 0.9800 | 0.1255 | 0.7336 | |
| BC | 0.7200 | 1 | 0.7200 | 0.0922 | 0.7702 | |
| $A^2$ | 83.35 | 1 | 83.35 | 10.67 | 0.0137 | |
| $B^2$ | 15.08 | 1 | 15.08 | 1.93 | 0.2073 | |
| $C^2$ | 1.42 | 1 | 1.42 | 0.1815 | 0.6829 | |
| **Residual** | 54.68 | 7 | 7.81 | | | |
| Lack of Fit | 28.59 | 5 | 5.72 | 0.4384 | 0.8023 | not significant |
| Pure Error | 26.09 | 2 | 13.04 | | | |
| **Cor Total** | 2966.64 | 16 | | | | |
| **Model** | 2911.96 | 9 | 323.55 | 41.42 | < 0.0001 | significant |

The p-value suggests that the model was found to be significant. As depicted in Table 17, the effect of Pore former level and % Weight Gain were found to be significant whereas other model terms were found to be insignificant. Further, the Model F-value of 41.42 implies the model is significant. Moreover, the value of adequate precision was found to be 18.5818 which indicates an adequate signal to noise ratio and hence the model can be used to navigate the design space. Final equation for the response $Y_3$ is: 69.20 + 16.52*A –0.75*B – 2.57*C + 0.525*AB + 0.35*AC – 0.30*BC – 5.58*$A^2$ + 2.37*$B^2$ – 0.7275*$C^2$.

 

**Table 18: ANOVA result of optimization batches for dependent parameters ($Y_4$: drug release at 12hr)**

| Source | Sum of Squares | Df | Mean Square | F Value | p-value Prob > F | Comments |
|---|---|---|---|---|---|---|
| **Model** | 3517.01 | 9 | 390.78 | 342.06 | < 0.0001 | significant |
| A-Pore former level (HPMC content in EC:HPMC) | 2540.84 | 1 | 2540.84 | 2224.06 | < 0.0001 | significant |
| B-Plasticizer Level (Triethyl citrate) | 1.60 | 1 | 1.60 | 1.40 | 0.2753 | not significant |
| C-% Weight Gain | 21.03 | 1 | 21.03 | 18.40 | 0.0036 | significant |
| AB | 2.20 | 1 | 2.20 | 1.93 | 0.2073 | |
| AC | 28.88 | 1 | 28.88 | 25.28 | 0.0015 | |
| BC | 0.1800 | 1 | 0.1800 | 0.1576 | 0.7032 | |
| $A^2$ | 594.37 | 1 | 594.37 | 520.27 | < 0.0001 | |
| $B^2$ | 0.0239 | 1 | 0.0239 | 0.0209 | 0.8892 | |
| $C^2$ | 0.0053 | 1 | 0.0053 | 0.0046 | 0.9477 | |
| **Residual** | 8.00 | 7 | 1.14 | | | |
| Lack of Fit | 7.25 | 5 | 1.45 | 3.88 | 0.2173 | not significant |
| Pure Error | 0.7467 | 2 | 0.3733 | | | |
| **Cor Total** | 3525.00 | 16 | | | | |

The p-value suggests that the model was found to be significant. As depicted in Table 18, the effect of Pore former level and % Weight Gain were found to be significant whereas other model terms were found to be insignificant. Further, the Model F-value of 342.06 implies the model is significant. Moreover, the value of adequate precision was found to be 44.8054 which indicates an adequate signal to noise ratio and hence the model can be used to navigate the design space. Final equation for the response $Y_4$ is: $97.73 + 15.94*A - 0.40*B - 1.45*C + 0.525*AB + 1.90*AC + 0.15*BC - 14.89*A^2 + 0.0944*B^2 - 0.0444*C^2$.

The overlay plots of selected independent variable upon the response under study are shown in figure 7, figure 8, and figure 9. The yellow zone indicate the design space where all selected response were estimated to be within desired acceptable criteria. The overlay plot can be used to establish the acceptable range for selected process variable. The overlay plots demonstrated that the centre points of the selected design was found to be within the design space.

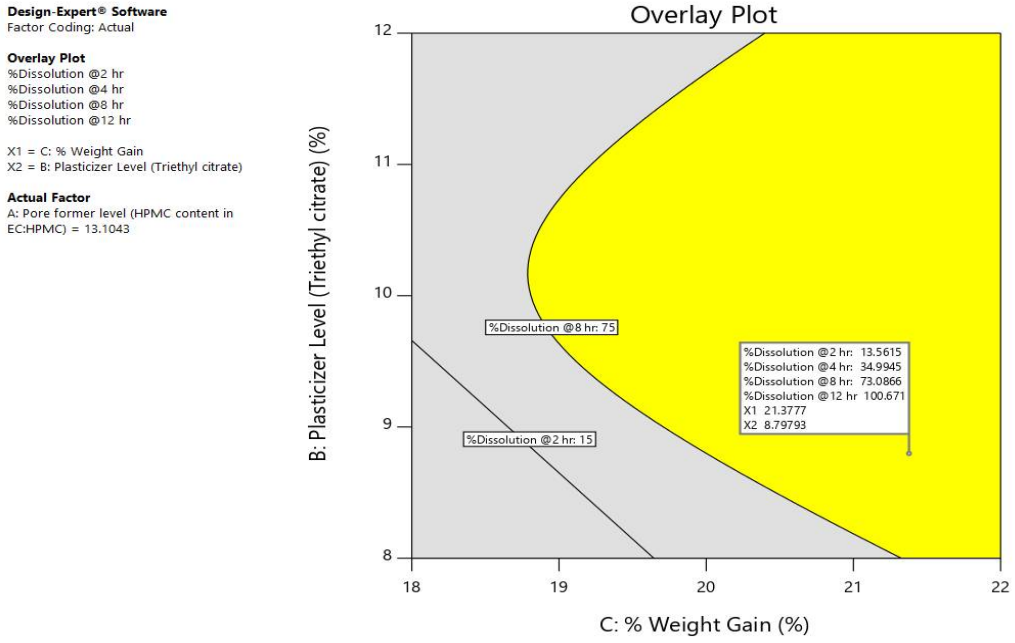


**Figure 7. Overlay Counter Plot of Plasticizer and % Weight Gain**

 

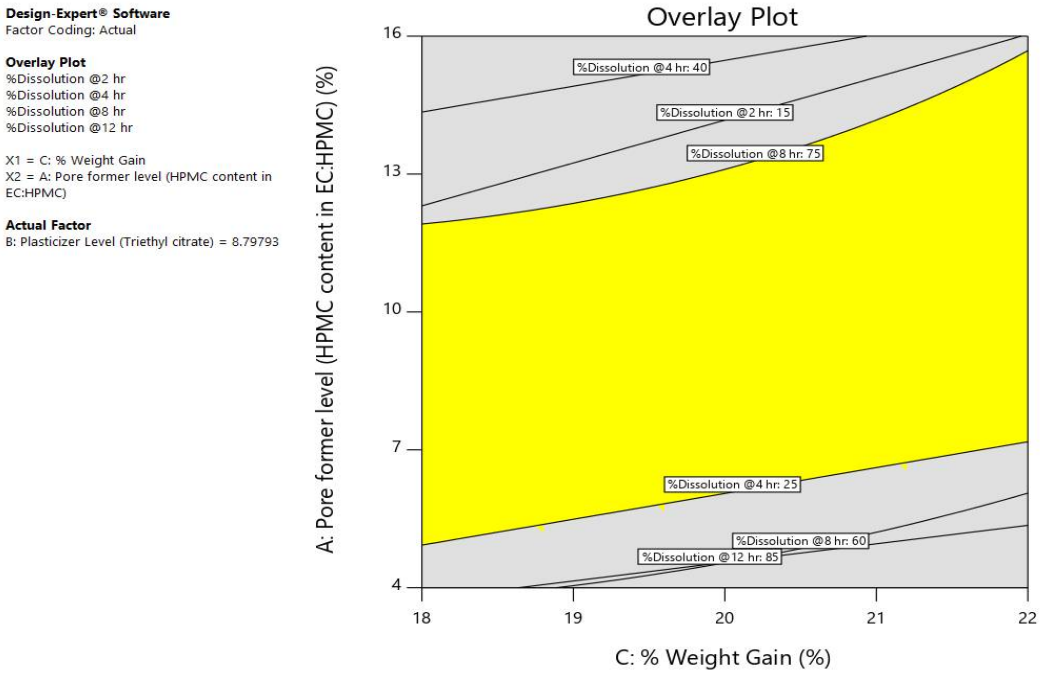


**Figure 8. Overlay Counter Plot of Pore former level and % Weight Gain.**

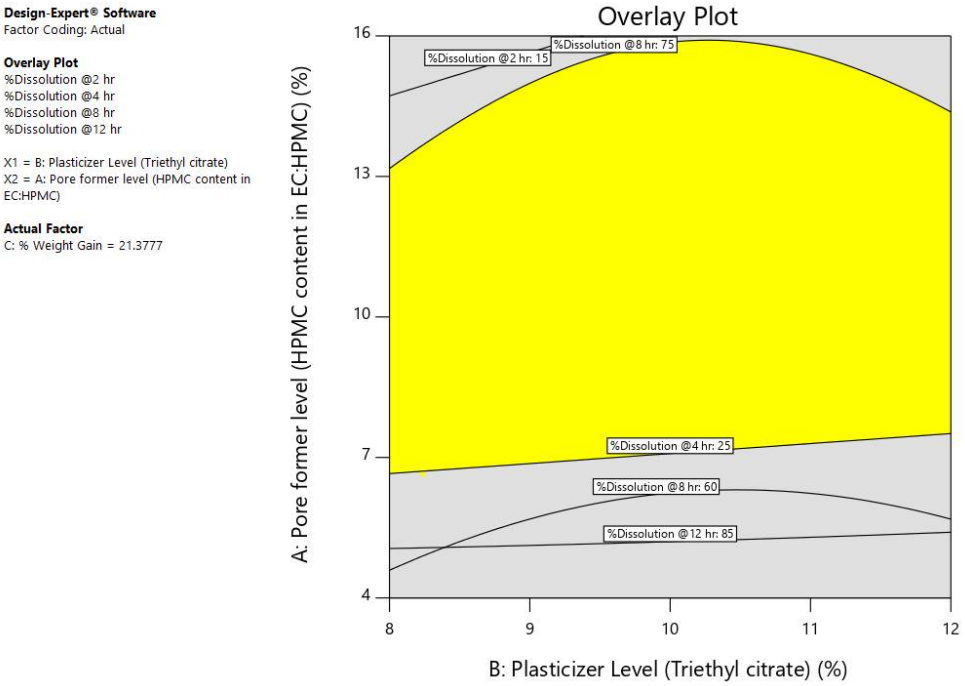


**Figure 9. Overlay Counter Plot of effect of Plasticizer and Pore former level.**

## CONCLUSION

Based on the present research work it was concluded that, MIDH extended release capsules was successfully developed using quality by design approach. Central composite design (CCD) was used to optimize MIDH pellets selecting independent variables (Pore former level, Plasticizer level and % weight gain) and responses (% drug release at 2, 4, 8 and 12 hrs). Overlay plot of studied variables shows that range of 19% to 22% of weight gain gives extend of drug release over 12 hours. Stability study carried out for final formulation and there is no any major changes observed for% drug release over 12 hours.

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