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Research Article

A QbD Assisted Modified Release Formulation of Midodrine Hydrochloride for Management of Long-term Hypotension

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ABSTRACT

Midodrine Hydrochloride (MDH) is primarily utilized for the treatment of orthostatic hypotension. The main objective of this research work is to study the effect of the ratio of Methocel 4M to 100M, PVP K-30, and magnesium stearate in extended-release (ER) layer of bilayer tablets of MDH. Bilayer tablets of MDH were optimized by the design of experiment (DoE) using response surface face centre ($\alpha = 1$), the central composite design having three independent variables at three levels. Bilayer tablets of MDH were administered once a day to reduce dosing frequency and improve patient compliance. Midodrine Hydrochloride tablets contain a drug layer and extended-release layer, which is further compressed into bilayer tablets. Based on the results of *in-vitro* %drug release it can be concluded that the ratio of Methocel 4M to 100M in MDH bilayer tablets shows a significant impact on % drug release whereas the concentration of PVP K-30 and concentration of magnesium stearate does not shows significant impact on % drug release. As the increase in the ratio of Methocel 4M to 100M, increase in the % drug release and as a decrease in the ratio of Methocel 4M to 100M, decrease in the % drug release. The optimized formulation of MDH bilayer tablets with 6% of Methocel 4M as an extended-release polymer, 24% of Methocel 100M as an extended-release polymer, 5% of PVP K-30 as a binder and 0.5% of magnesium stearate as a lubricant exhibits extended drug release up to 12 hours.

Introduction

The oral route is the most popular route used for the administration of drugs into the body. Tablets are the most common dosage for taking medication. There are various types of tablet dosage forms available in the market. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase the drug's effectiveness by localization at the site of action, reducing the dose required, or providing uniform drug delivery.[1-4] The ideal extended-release drug delivery system should have the advantage of single-dose for the complete duration of treatment and it should deliver the active drug directly at a specific target. Extended-release tablets are provided to release their active ingredients at a controlled and predetermined rate to achieve and maintain optimum therapeutic blood levels of the drug. Therefore, this technology can provide better control of plasma drug levels over longer periods and less frequent dosing and improve patient compliance.[5]

Orthostatic hypotension means a decrease in blood pressure of at least 20 mm Hg for systolic blood pressure or a decrease in diastolic blood pressure 10 mm Hg within. minutes of standing up. In other words, orthostatic hypotension can describe the fall in blood pressure when a person is in a standing position.[6,7] MDH is a peripheral selective alpha-1-adrenergic agonist and it is mainly indicated for the treatment of orthostatic hypotension. MDH can also be prescribed to the patients with Postural Orthostatic Tachycardia Syndrome (POTS).[8]

MDH is a prodrug, after oral administration, it is rapidly absorbed and converts to its active metabolite

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desglymidodrine. The absolute bioavailability of Midodrine (measured as desglymidodrine) is 93% for the oral tablets. The bioavailability of desglymidodrine is not affected by food. Moreover, it has been found that MDH has a pH independent solubility and is absorbed throughout the gastro-intestinal tract. Due to its high water solubility and high permeability, MDH is classified as a BCS Class I drug.

The quality by design (QbD) approach can be applied to better understand the process and formulation variables, which can lead to better and robust quality into the product, assuring the target quality product profile. Based on risk assessment of process and formulation variables, design of experimentation (DoE) study need to conduct on critical parameters to establish a certain ranges for critical parameters within certain range to obtain design space (DS).[9-13] Design of Experiments (DoE) is a well-structured and organized method to determine the relationship between factors, which can affect a process and its output.[14,15]

Currently, MDH is only available as an immediate release tablet. Current research work aims to develop Bilayer tablets of MDH administer once a day to reduce dosing frequency and improve patient compliance. In this research, various concentrations of Methocel 4M prem DC2 and Methocel 100M prem DC2 were used in the extended release part of bilayer tablets. Tablets were evaluated for various physical and chemical parameters. Optimization of the ratio of Methocel 4M prem DC2 to Methocel 100M prem DC2 as an extended-release polymer, concentration of PVP K-30 as a binder and concentration of Magnesium stearate as a lubricant was carried out with the help of design expert 12 software, response surface central composite design.

Materials and Methods

Materials

Midodrine Hydrochloride (Emcure Pharmaceuticals Ltd) was used as a model drug. Pregelatinized Starch (Starch 1500), Lactose Monohydrate and Microcrystalline cellulose were used as diluents. Pigment Blend PB 530018 Orange used as colouring agent. PVP K-30 was selected as a binder. Methocel 4M prem DC2 and Methocel 100M prem DC2 were used as extended release polymer. Colloidal silicon dioxide used as Glidant. Magnesium stearate was used as lubricants. Purified water used as vehicle during process.

Methods

Preparation of Midodrine Hydrochloride Immediate Release Layer

Midodrine Hydrochloride, Microcrystalline cellulose (Avicel® PH 200 LM), Pregelatinized Starch (Starch 1500), PVP K-30 and 100# pass Pigment Blend PB 530018 Orange co-sifted through #25 ASTM sieve. Magnesium stearate sifted through #60 ASTM sieve and mixed with blend in double cone blender for 5 min at 20 RPM. Formulation trial # IR3 is finalized for the immediate release layer. Composition of Midodrine Hydrochloride drug layer part summarized in Table 1.

Preparation of Midodrine Hydrochloride Extended Release Layer

Midodrine Hydrochloride, Microcrystalline cellulose PH 101, Lactose Monohydrate, Methocel 4M prem DC2 and Methocel 100M prem DC2 co-sifted through #20 ASTM sieve. PVP K-30 dissolved in the required quantity of purified water under continuous stirring to obtained

Table 1: Composition of Midodrine Hydrochloride drug layer

Batch#		*IR1*		*IR2*		*IR3*	
Ingredient	*Category*	*Qty/Unit (mg)*	*%w/w*	*Qty/Unit (mg)*	*%w/w*	*Qty/Unit (mg)*	*%w/w*
Midodrine Hydrochloride	API	4.87	6.1	4.87	6.1	4.87	6.1
Microcrystalline cellulose PH101	Diluent	64.13	80.2	–	–	–	–
Microcrystalline cellulose PH102	Diluent	–	–	64.13	80.2	–	–
Microcrystalline cellulose PH200	Diluent	–	–	–	–	64.13	80.2
Pregelatinized Starch (Starch 1500)	Diluent	7.50	9.4	7.50	9.4	7.50	9.4
Pigment Blend PB 530018 Orange	Colouring Agent	0.50	0.6	0.50	0.6	0.50	0.6
Povidone (PVP K-30)	Binder/ disintegrant	1.50	1.9	1.50	1.9	1.50	1.9
Hydrophobic colloidal silica	Glidant	1.00	1.3	1.00	1.3	1.00	1.3
Magnesium stearate	Lubricants	0.50	0.6	0.50	0.6	0.50	0.6
Total		80.00	100.0	80.00	100.0	80.00	100.0

a homogeneous clear solution. Co-sifted material transferred in to rapid mixer granulator (RMG) and granulated using PVP K-30 binder solution to obtained wet mass. The wet mass was dried using a fluid bed dryer (FBD) at inlet temperature 50°C till LOD achieved (NMT 2.0%w/w). Dried granules sifted through #20 ASTM sieve. Mill the retained granules using multi-mill equipped with 1.0 mm screen at 1000 rpm knives forwarded setting. Milled granules passed through #20 ASTM sieve. If any retention is observed then repeat the milling process till all granules pass through #20 ASTM sieve. Magnesium stearate sifted through #60 ASTM sieve and mixed with dried sifted granules in double cone blender for 5 min at 20 RPM.[16]

Immediate release layer part and extended release layer part was compressed in to bilayer tablets using cadmach CMB4-MT compression machine, 9.0 mm, Round shape, plain/plain type-B tooling punches. Composition of Midodrine Hydrochloride modified release tablet summarized in Table 2.

Process flow of Midodrine hydrochloride bilayer tablets presented in Fig. 1 and Images of Midodrine hydrochloride bilayer tablets is presented in Fig. 2.

Quality Target Product Profile for Midodrine Hydrochloride Modified Release Tablets

Quality Target Product Profile (QTPP) was defined for proposed drug product which was summarized in Table 3.

Table 4 summarizes the quality attributes of the proposed drug product Midodrine Hydrochloride modified

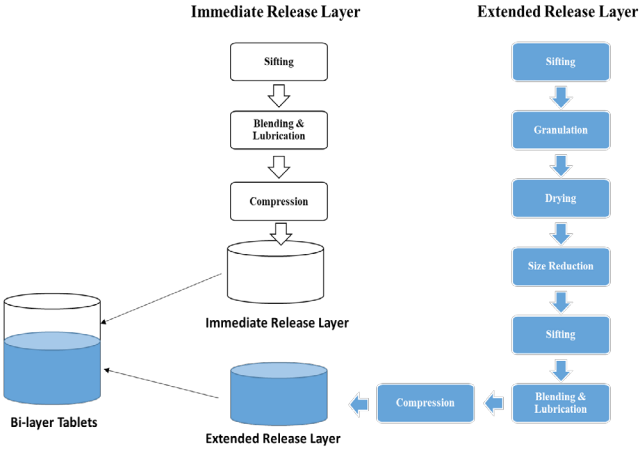

Fig. 1: Process flow of Midodrine Hydrochloride modified release bilayer Tablets

Table 2: Composition of Midodrine Hydrochloride Extended release layer

Batch#	*FER1*		*FER2*		*FER3*		*FER4*	
Ingredient	*Qty/Unit (mg)*	*%w/w*	*Qty/Unit (mg)*	*%w/w*	*Qty/Unit (mg)*	*%w/w*	*Qty/Unit (mg)*	*%w/w*
Immediate Release Layer								
Midodrine Hydrochloride	4.87	6.09	4.87	6.09	4.87	6.09	4.87	6.09
Microcrystalline cellulose PH200	64.13	80.16	64.13	80.16	64.13	80.16	64.13	80.16
Pregelatinized Starch (Starch 1500)	7.50	9.38	7.50	9.38	7.50	9.38	7.50	9.38
Pigment Blend PB 530018 Orange	0.50	0.63	0.50	0.63	0.50	0.63	0.50	0.63
Povidone (PVP K-30)	1.50	1.88	1.50	1.88	1.50	1.88	1.50	1.88
Hydrophobic colloidal silica	1.00	1.25	1.00	1.25	1.00	1.25	1.00	1.25
Magnesium stearate	0.50	0.63	0.50	0.63	0.50	0.63	0.50	0.63
Weight of IR layer	80.00	100.00	80.00	100.00	80.00	100.00	80.00	100.00
Extended Release Layer								
Midodrine Hydrochloride	10.13	8.44	10.13	8.44	10.13	8.44	10.13	8.44
Microcrystalline cellulose PH 101	48.67	40.56	48.67	40.56	48.67	40.56	48.67	40.56
Povidone USP (PVP K-30)	6.00	5.00	6.00	5.00	6.00	5.00	6.00	5.00
Methocel 4M prem DC2	18.00	15.00	14.40	12.00	10.80	9.00	7.20	6.00
Methocel 100M prem DC2	18.00	15.00	21.60	18.00	25.20	21.00	28.80	24.00
Colloidal silicon dioxide	0.60	0.50	0.60	0.50	0.60	0.50	0.60	0.50
Lactose Monohydrate	18.00	15.00	18.00	15.00	18.00	15.00	18.00	15.00
Magnesium stearate USP/NF	0.60	0.50	0.60	0.50	0.60	0.50	0.60	0.50
Purified water*	Q.S	–	Q.S	–	Q.S	–	Q.S	–
Weight of ER layer	120.00	100.00	120.00	100.00	120.00	100.00	120.00	100.00
Weight of bilayer tablets (mg)	200.00	–	200.00	–	200.00	–	200.00	–

*Evaporate during the process, does not remain in finished product.

release tablets and indicates which attributes were classified as drug product Critical Quality Attributes (CQAs).

Development and Optimization of Midodrine Hydrochloride modified release bilayer Tablets (Extended Release Layer)

Initial Risk Assessment of the Formulation Variables of extended release part

The initial risk assessment includes prior knowledge from the development of the product and experience with related formulations and information about drug substance from published literature and characterization. The result of the initial risk assessment of the drug layer formulation variables are presented in Table 5 and the justification for risk assessment is presented in Table 6.

To perform extend release part optimization, central composite design (CCD) with three center points was adopted for the ratio of Methocel 4M to Methocel 100M, PVP K-30 (Povidone) and Magnesium Stearate. Studies for drug layer formulation variables were performed by evaluating % drug release at different time points. Methocel 4M to Methocel 100M were investigated in the range from 0.15 to 0.35%. Binder concentrations selected for formulation studies were 3 to 7%, Magnesium Stearate was evaluated 0.30 to 0.50%.

The goal of the formulation development study was to understand if there is any interaction of these variables with drug product quality. For this study, a central composite face centered (CCD) design was chosen to allow a quadratic model fit while evaluating three levels for each factor. The design had three center points, α=1.0 and total 13 runs (batches).

Summary of factors and responses studied for optimization of critical excipients for extended release layer part presented in Table 7 and formulation composition of Midodrine Hydrochloride bilayer tablets presented in Table 8.

Evaluation of Midodrine Hydrochloride Modified release Bilayer Tablets[17]

In-process stage

Bulk density (BD): Bulk density was measured with a glass-measuring cylinder. A pre-defined weight of the API was transferred in the measuring cylinder softly and then the volume occupied by the API was measured. Bulk density was calculated using the following formula:

$$\rho = m/V$$

Where,

ρ = density in g/mL,
m = Weight in g
V = volume in mL

Tapped density (TD): Tapped density is measured as the fraction of total mass of the powder to the tapped volume of the powder.

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped Volume}}$$

Compressibility Index (CI): The compressibility was measured by following formula.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio (HR): Hausner's ratio was calculated by following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 3 : Quality Target Product Profile for Midodrine Hydrochloride Modified Release Tablets.

QTPP Elements		*Target*	*Justification*
Dosage form		Tablets	Tablet is commonly accepted unit oral dosage form.
Dosage design		Modified release Tablets	Faster onset of action followed by longer duration
Dosage strength		15 mg	It is the unit dose of Midodrine HCl which needs to be incorporated for once a daily administration
Route of administration		Oral	Oral route is most accepted route for administration of dosage form
Stability		At least 12 months at room temperature	To maintain therapeutic potential of the drug during storage period
Drug product quality attributes	Physical attributes Assay Content uniformity Dissolution	Pharmaceutical equivalent requirement	Pharmaceutical equivalence requirement: must meet the same compendial or other applicable quality standards.
Container Closure System		Suitable for storage and stability formulation.	Need to achieve target shelf life and to ensure tablets integrity during shipping.

Table 4: Critical Quality Attributes of Midodrine Hydrochloride Modified Release Tablets

Quality attributes of the drug product		*Target*	*Is this CQA?*	*Justification*
Physical Attributes	Appearance	Colour of tablet acceptable to the patient.	No	Colour and appearance are not directly linked to safety and efficacy. Therefore, they are not critical.
	Odor	No unpleasant odour	No	In general, a noticeable odour is not directly linked to safety and efficacy, but odour can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odour.
	Size	Size of tablet acceptable to the patient.	No	For ease of swallowing as well as patient acceptance the target for tablet dimensions for product targeted is 9mm punch for easy of swallowing.
Assay		90–110% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development and based on USP monograph.
Dissolution		Media: 0.1N HCl followed by pH 6.8 buffer Apparatus: USP- II (Paddle) Volume:900 mL Speed: 50 rpm Time (hours) – % Drug Release 2 – NMT.5% 4 – Between 40–50% 8 – Between 60–75% 12 – NLT 85%	Yes	The drug release profile is important for development of Modified release of Dosage form of Midodrine Hydrochloride. Both formulation as well as process related parameters may affect dissolution of Midodrine Hydrochloride from tablet dosage form. This CQA will be investigated throughout formulation and process development.

Table 5: Initial Risk Assessment for the Formulation Variables of extended release part

	Formulation Attributes		
Drug Product CQA	*Ratio of Methocel 4M to Methocel 100M*	*PVP K-30*	*Magnesium Stearate*
Assay	Low	Low	Low
Dissolution	High	Medium	High

Table 6: Justification for Initial Risk Assessment of extended release part

Formulation Variables	*Drug Product CQAs*	*Justifications*
Ratio of Methocel 4M to Methocel 100M	Assay	Assay is mainly determined after compression of the tablets. Therefore, there is no impact of pore former polymer level on assay of pellets. Hence, risk is low.
	Dissolution	If the polymer ration is suboptimal, ER formulation will not have the desired extended release profile. Ratio of Methocel 4M to Methocel 100M may affect drug release from bilayer tablets. Therefore, risk is high.
Povidone USP (PVP K-30)	Assay	Hydrophilic binder concentration does not influence assay of the products. Therefore, risk is low.
	Dissolution	Change in concentration of binder may affect drug release of the product. Therefore, risk is medium.
Magnesium Stearate	Assay	Low concentration of lubricant does not have significant impact on Assay. Therefore, risk is low.
	Dissolution	Over-lubrication due to excessive concentration of hydrophobic lubricant may retard dissolution. The risk is High.

Table 7: Central composite face centered design for optimization of critical excipients level in extended release part

Sr. No.	*Formulation Variables*	*Levels*		
		-1	*0*	*1*
1	Ratio of Methocel 4M to Methocel 100M	0.15	0.25	0.35
2	Povidone USP (PVP K-30)	3	5	7
3	Magnesium Stearate	0.30	0.50	0.7

Response Studied
% Drug release @2 hr
% Drug release @4 hr
% Drug release @8 hr
% Drug release @12 hr

Fig. 2: Images of Midodrine hydrochloride bilayer tablets

Compression Stage

- *Uniformity of tablet weight:* Precisely weighed 20 tablets were taken separately and determined the average net weight. Not more than (NMT) two of the individual tablet weights deviate more than 5.0% from their average weight and none of the tablets deviates more than 10.0% from their average weight.
- *Group weight of tablet:* 20 tablets accurately weighed using weighing balance. Not more than (NMT) 3.0% deviate from the theoretical weight of 20 tablets.
- *Thickness:* It was measured during compression stage. Select 10 tablets randomly and measure thickness by vernier calliper.
- *Hardness:* Hardness of the tablet was measured during compression stage. Select 10 tablets randomly and measure hardness by tablet hardness tester.
- *Friability:* Friability testing of tablets was done during the compression stage. Precisely weighed 10 tablets and employed the tablet in the drum of automatic tablet friabilator (Make: Electrolab, Model: EF-2W). Rotate the drum for 100 counts at 25 rpm. After completion of the test, removed the tablets and measure weight. Friability should be not more than (NMT) 1.0%. The following equation is used for the calculation of % friability.

$$\%\text{Friability} = \frac{\text{Initial weight of tablets} - \text{Weight of tablets after rotation}}{\text{Initial weight of tablets}} \times 100$$

Table 8: Formulation composition of Midodrine Hydrochloride bilayer tablets (Batch Number: MHT)

Sr. No.	*Ingredients*	*Immediate Release Layer*	
		Qty/Tab (mg)	*%w/w*
1	Midodrine Hydrochloride USP	4.87	6.09
2	Microcrystalline cellulose PH200 USP/NF	64.13	80.16
3	Pregelatinized Starch (Starch 1500)	7.50	9.38
4	Pigment Blend PB 530018 Orange	0.50	0.63
5	Povidone USP (PVP K-30)	1.50	1.88
6	Hydrophobic colloidal silica USP/NF	1.00	1.25
7	Magnesium stearate USP/NF	0.50	0.63
Weight of IR layer		80.00	100.00
	Extended Release Layer		
1	Midodrine Hydrochloride USP	10.13	8.44
2	Microcrystalline cellulose PH 101 USP/NF	48.67	40.56
3	Povidone USP (PVP K-30)	6.00	5.00
4	Methocel 4M prem DC2 (HPMC 2208)	7.20	6.00
5	Methocel 100M prem DC2 (HPMC 2208)	28.80	24.00
6	Colloidal silicon dioxide	0.60	0.50
7	Lactose Monohydrate	18.00	15.00
8	Magnesium stearate USP/NF	0.60	0.50
9	Purified water*	Q.S	--
Weight of ER layer		120.00	100.00
Weight of bilayer tablets (mg)		200.00	--

*Evaporate during the process, does not remain in finished product.

Finished product stage[18]

In-Vitro Dissolution: Apparatus: Dissolution test apparatus (Make: Lab India, Model: DS 8000$^+$), Dissolution condition: Medium: 0.1N HCl followed by 6.8 pH phosphate buffer, Volume: 900 mL, Apparatus: Type II Paddle, Speed: 50 rpm, Time: 2, 4, 8, 12 hours., Temperature: 37.0°C ± 0.5°C, Sampling volume: 10 mL. Filtered 10mL samples withdrawn at each time points through 0.45 µ PVDF syringe filter. Discard first 5 mL of filtrate and measured area of absorbance with HPLC method at 283 nm and calculated % drug release at each time point.

Stability Study

Stability study of the final formulation of batch no. MDT has been carried out in HDPE container as per ICH guideline at 40±2°C / 75 ± 5% RH for 1 month and 3 months and 25 ± 2°C / 60±5% RH for 3 months. Tablets were analyzed for physical appearance, % Assay, and % Drug release.

Results and Discussion

In-process results of bulk density, tapped density, compressibility index, Hausner's ratio & PSD by sieve analysis at lubricated blend stage for drug layer part presented in Table 9. All results were found satisfactory and having good flow properties.

In-process results of compressed tablets found satisfactory, no any critical problem observed during compression stage. In-process results of compressed tablets were summarized in Table 10.

Batch details and analytical results for optimization of critical excipients level in extended release layer summarized in Table 11 and graphically presented in Fig. 3 and 4.

Discussion

(A) Significant factors for % drug release at 2 hours

Drug release was tested for tablets of all optimization batches. The analysis of variance (ANOVA) results presented in Table 12 and counter plot is shown in Fig. 5.

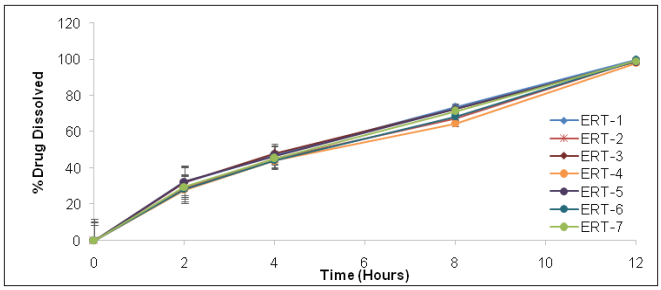

Fig. 3: *In-Vitro* dissolution results of trial batches optimization of critical excipients level in extended release layer (Batch No. ERT-1 to ERT-7)

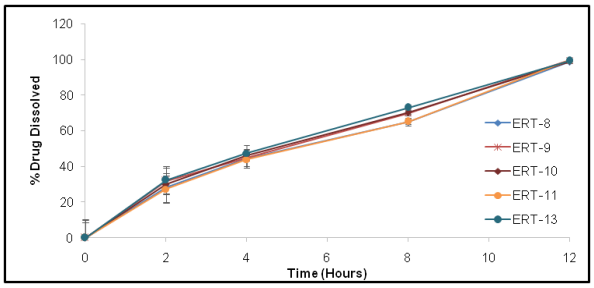

Fig. 4: *In-Vitro* dissolution results of trial batches optimization of critical excipients level in extended release layer (Batch No. ERT-8 to ERT-13)

Table 9: In-process results of drug layer part and extended release part

Batch#	*IR1*		*IR2*		*IR3*	
Flow properties						
Bulk density (g/mL)	0.41		0.42		0.53	
Tapped density (g/mL)	0.53		0.49		0.62	
Carr's Index (%)	22.64		21.01		14.52	
Hausner's ratio	1.293		1.17		1.17	
% Assay	99.5		99.2		99.1	
Sieve analysis						
Sieve#	*%R*	*%CR*	*%R*	*%CR*	*%R*	*%CR*
20	2.16	2.14	2.25	2.25	2.32	2.30
30	6.45	8.55	6.55	8.80	6.68	8.93
40	15.24	23.68	12.69	21.49	22.87	31.61
60	11.68	35.28	9.91	31.40	11.62	43.13
Pan	65.19	100.00	68.6	100.00	57.34	100.00

%R – Retention in percentage, %CR –cumulative retention in percentage

Table 10: In-process results of compressed tablets

	Batch No.			
Test	*FER1*	*FER2*	*FER3*	*FER4*
Individual Weight of Tablets (mg)	201 (197-203)	199 (196-203)	202 (199-204)	201 (198-204)
Group weight of 20 Tablets (g)	4.020	3.980	4.040	4.021
Thickness (mm)	4.55 (4.51-4.57)	4.51 (4.48-4.55)	4.59 (4.55-4.62)	4.53 (4.50-4.59)
Hardness (kp)	8.92 (7.78-9.11)	8.34 (7.14-9.56)	9.09 (8.29-9.91)	8.56 (7.57-9.21)
Friability Test (%w/w)	0.11	0.09	0.10	0.12

The Model F-value of 13.00 implies the model is significant. There is only a 0.03% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

Table 11: Batch details and analytical results for optimization of critical excipients level in extended release layer

	Formulation variables (Independent variables)			*Responses (Dependent Variables)*			
Batch No	*Ratio of Methocel 4M to Methocel 100M*	*Povidone (PVP K-30) (%)*	*Magnesium Stearate (%)*	*% Drug Release @2 hours*	*% Drug Release @4 ours*	*% Drug Release @8 hours*	*% Drug Release @12 hours*
ERT-1	0.35	7	0.3	32.1	47.2	73.7	99.7
ERT-2	0.25	5	0.3	28.9	45.1	67.2	99.1
ERT-3	0.35	3	0.7	31.9	48.1	72.9	98.7
ERT-4	0.15	7	0.7	27.9	44.1	64.7	97.9
ERT-5	0.25	5	0.7	32.4	46.7	72.5	98.5
ERT-6	0.25	7	0.5	28.3	44.2	68.4	99.3
ERT-7	0.25	5	0.5	29.5	45.3	71.3	99.2
ERT-8	0.15	3	0.3	28.2	44.6	64.9	98.6
ERT-9	0.25	5	0.5	31.8	44.8	69.9	99.4
ERT-10	0.25	5	0.5	29.9	46.2	70.2	98.8
ERT-11	0.15	5	0.5	27.2	43.9	65.1	99.3
ERT-12	0.35	5	0.5	33.1	47.2	72.8	98.7
ERT-13	0.25	3	0.5	32.3	47.4	72.9	99.1

Table 12: ANOVA results of all batches (%Drug Release at 2 hours)

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	47.20	6	7.87	13.00	0.0033	significant
A-Ratio of Methocel 4M to Methocel 100M	17.40	1	17.40	28.77	0.0017	
B-Povidone	8.00	1	8.00	13.22	0.0109	
C-Magnesium Stearate	6.13	1	6.13	10.12	0.0190	
AB	4.69	1	4.69	7.75	0.0319	
AC	5.20	1	5.20	8.60	0.0262	
BC	1.27	1	1.27	2.09	0.1979	
Residual	3.63	6	0.61			
Lack of Fit	0.61	4	0.15	0.10	0.9717	not significant
Pure Error	3.02	2	1.51			
Cor Total	50.83	12				

Table 13: ANOVA results of all batches (% Drug Release at 4 hours)

					p-value	
Source	*Sum of Squares*	*Df*	*Mean Square*	*F Value*	*Prob > F*	*Comments*
Model	20.53	3	6.84	13.92	0.0010	significant
A-Ratio of Methocel 4M to Methocel 100M	16.34	1	16.34	33.23	0.0003	
B-Povidone	3.53	1	3.53	7.17	0.0253	
C-Magnesium Stearate	0.67	1	0.67	1.36	0.2741	
Residual	4.42	9	0.49			
Lack of Fit	3.42	7	0.49	0.97	0.5949	not significant
Pure Error	1.01	2	0.50			
Cor Total	24.95	12				

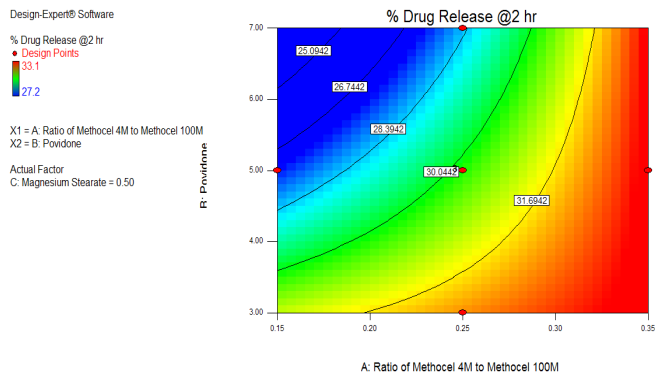

Fig. 5: Counter plot for the effect of ratio of methocel 4M prem DC2 to methocel 100M prem and povidone at 2 hours

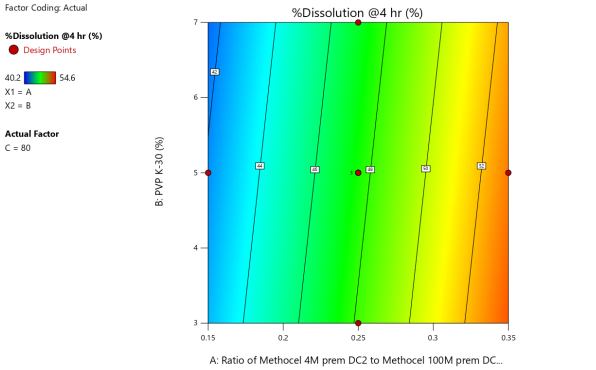

Fig. 6: Counter plot for the effect of ratio of methocel 4M prem DC2 to methocel 100M prem and povidone at 4 hours

Table 14: ANOVA results of all batches (% Drug Release at 8 hours)

Source	*Sum of Squares*	*df*	*Mean Square*	*F value*	*p-value Prob > F*	*Comments*
Model	126.41	6	21.07	16.85	0.0016	significant
A-Ratio of Methocel 4M to Methocel 100M	29.64	1	29.64	23.71	0.0028	
B-Povidone	10.13	1	10.13	8.10	0.0294	
C-Magnesium Stearate	14.04	1	14.04	11.23	0.0154	
AB	11.21	1	11.21	8.97	0.0242	
AC	7.68	1	7.68	6.14	0.0479	
BC	0.21	1	0.21	0.17	0.6939	
Residual	7.50	6	1.25			
Lack of Fit	6.42	4	1.60	2.95	0.2687	not significant
Pure Error	1.09	2	0.54			
Cor Total	133.91	12				

The Lack of Fit F-value of 0.10 implies the Lack of Fit is not significant relative to the pure error. There is a 97.17% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good and hence the model can be used to fit the response under study.

Based on ANOVA results, it can be concluded that increasing in Ratio of Methocel 4M prem DC2 to Methocel 100M prem with an increase in binder concentration shows faster % drug release at 2 hours.

(B) Significant Factors for % Drug Release at 4 hours

Drug release was tested for tablets of all optimization batches. The analysis of variance (ANOVA) results presented in Table 13 and counter plot is shown in Fig. 6.

The Model F-value of 13.92 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

The Lack of Fit F-value of 0.97 implies the Lack of Fit is not significant relative to the pure error. There is a 59.49% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good and hence the model can be used to fit the response under study.

Based on ANOVA results, it can be concluded that increasing in Ratio of Methocel 4M prem DC2 to Methocel 100M prem with an increase in binder concentration shows faster % drug release at 4 hours.

(C) Significant Factors for % Drug Release at 8 hours

Drug release was tested for tablets of all optimization batches. The analysis of variance (ANOVA) results presented in Table 14 and counter plot is shown in Fig. 7.

The Model F-value of 16.85 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

The Lack of Fit F-value of 2.95 implies the Lack of Fit is not significant relative to the pure error. There is a 26.87% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good and hence the model can be used to fit the response under study.

Based on ANOVA results, it can be concluded that increasing in Ratio of Methocel 4M prem DC2 to Methocel

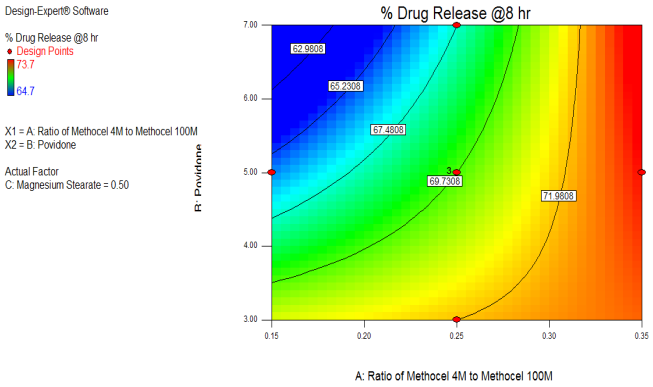

Fig. 7: Counter plot for the effect of Ratio of Methocel 4M prem DC2 to Methocel 100M prem and Povidone at 8 hours

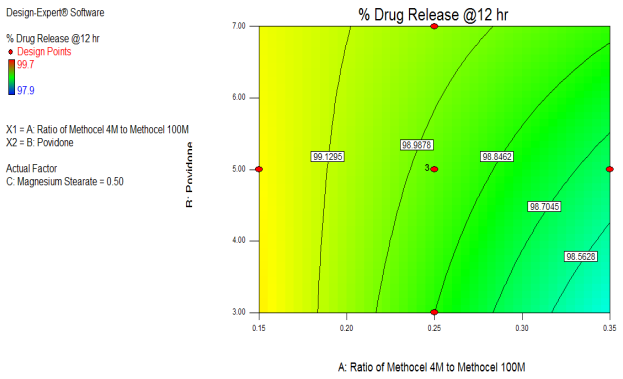

Fig. 8: Counter plot for the effect of Ratio of Methocel 4M prem DC2 to Methocel 100M prem and Povidone at 12 hours

Table 15: ANOVA results of all batches (%Drug Release at 12 hours)

					p-value	
Source	*Sum of Squares*	*df*	*Mean Square*	*F Value*	Prob > F	*Comments*
Model	2.03	6	0.34	3.05	0.1003	not significant
A-Ratio of Methocel 4M to Methocel 100M	0.18	1	0.18	1.62	0.2496	
B-Povidone	0.020	1	0.020	0.18	0.6858	
C-Magnesium Stearate	0.18	1	0.18	1.62	0.2496	
AB	0.021	1	0.021	0.19	0.6797	
AC	8.333E-004	1	8.333E-004	7.521E-003	0.9337	
BC	0.80	1	0.80	7.23	0.0361	
Residual	0.66	6	0.11			
Lack of Fit	0.48	4	0.12	1.28	0.4827	not significant
Pure Error	0.19	2	0.093			
Cor Total	2.69	12				

100 M prem with an increase in binder concentration shows faster % drug release at 8 hours.

(D) Significant Factors for % Drug Release at 12 hours

Drug release was tested for tablets of all optimization batches. The analysis of variance (ANOVA) results presented in Table 15 and counter plot is shown in Fig. 8.

The Model F-value of 0.05 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant.

The Lack of Fit F-value of 1.28 implies the Lack of Fit is not significant relative to the pure error. There is a 48.27% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good and hence the model can be used to fit the response under study.

Based on ANOVA results, it can be concluded that increasing in Ratio of Methocel 4M prem DC2 to Methocel 100M prem with an increase in binder concentration shows faster % drug release at 12 hours.

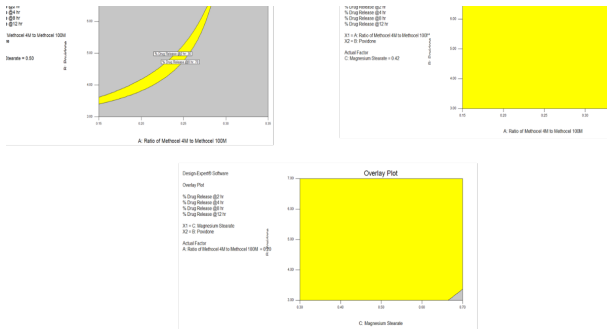

Fig. 9: Overlay plot of effect of PVP K-30, Magnesium stearate and Ratio of Methocel 4M prem DC2 to Methocel 100M prem DC2

The DoE models were used to establish acceptable ranges for formulation variables. Finally, the overlay plots of selected independent variable upons the response under study are shown in Fig. 9.

The yellow zone indicates the design space, where all selected response was estimated to be within desired acceptance criteria.

The overlay plots proved that the center point of the selected design was found to be within the design space