Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Development and Optimization of Nefopam Hydrochloride Push-Pull Osmotic Pumps by Design of Experiments

Prashant Gorasiya,* Vipul Patel

Faculty of Pharmacy, RK University, Kasturbadham, Rajkot-360020, Gujarat, India

ARTICLE INFO

Article history:

Received: 27 May, 2021

Revised: 21 June, 2021

Accepted: 30 June, 2021

Published: 30 July, 2021

Keywords:

Cellulose acetate (CA), Design of Experiment (DoE), Nefopam hydrochloride (NFH), Polyethylene glycol (PEG) 3350, Push-pull osmotic pump (PPOP) tablet, Response surface central composite design.

DOI:

10.25004/IJPSDR.2021.130408

ABSTRACT

Nefopam hydrochloride (NFH) is one of the centrally acting NSAIDs drug used for pain management. The main objective of this research is to study the effect of ratio of Cellulose acetate: Polyethylene glycol (PEG) 3350, and %weight gain in extended release (ER) coating of push-pull osmotic pump (PPOP) tablets, optimized by the design of experiment (DoE) using response surface face center (α=1), the central composite design having two independent variables at three levels. PPOP tablets of NFH were administered once a day to reduce dosing frequency and improve patient compliance. PPOP tablets contain drug and push layers, compressed into bilayer tablets, coated with cellulose acetate (CA) as semipermeable membrane polymer, and PEG 3350 as a plasticizer or pore-forming agent. ER coated tablets mechanically drill ~0.50 mm on the drug layer part for the controlled release of the drug up to 24 hrs. Based on the results, the ratio of CA: PEG 3350 and % weight gain in ER coating of PPOP tablets shows a significant impact on % drug release. At lower % of PEG, burst release was observed due to cracking of ER coating layer, while at higher % of PEG, slightly rapid release of drug was observed. %Drug release is decreased with an increase in the %weight gain of tablets. PPOP Tablets with 10% PEG 3350 (Ratio of CA:PEG 3350, 90:10) and 8% weight gain exhibit zero-order kinetic drug release up to 24 hours.

Introduction

Currently, the most popular route for drug delivery is the oral route because of ease of self-administration, cost efficiency, and more patient acceptability.[1] Pain is defined as "an unpleasant sensational and emotional experience which one is associated with actual or potential damage of tissue" according to the international association for the study of Pain (IASP).[2] Acute and chronic pain is the primary type of pain. The central nervous system and peripheral nervous system involves in neuropathic pain.[3] In most developed countries, pain is a prevalent reason of physician consultation.[4,5] It is a major sign and symptom in most medical conditions that disturb a person's quality of life, daily activities, and general functioning.[6] Generally, analgesic and anesthetics classes of drugs are used for pain management by the physician in 20% to 70% of cases.[7]

Nefopam Hydrochloride falls under the category of non-steroidal anti-inflammatory diseases class drug used in treating acute and chronic pain, i.e., acute traumatic, post-operative, musculo-skeletal, dental, and cancer pain.[8,9] Nefopam Hydrochloride inhibit the reuptake of neurotransmitters serotonin, nor-epinephrine, and dopamine. Nefopam Hydrochloride also modulates sodium and calcium channels by inhibiting glutamate release, a key neurotransmitter for pain signaling.[10] Nefopam hydrochloride has a short half-life of approximately 3-4 hours, depending on response, one to three tablets three times per day are required. The recommended dose is two tablets three times a day. Long-term treatments require frequent medication per day by the patient, leading to patient incompliance, missed dose, fluctuation in drug plasma profile, and increased side effects.[11-13]

***Corresponding Author:** Prashant Gorasiya

Address: Faculty of Pharmacy, RK University, Kasturbadham, Rajkot-360020, Gujarat, India

Email ✉**:** pgorasiya114@gmail.com

Tel. : +91-9979365688

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Osmotic drug delivery system is more preferable for controlled release of drug at zero-order kinetic over a specific period using the principle of osmotic pressure, which is used as a driving force for the concentration-independent constant release of the drug throughout GI tract independent of pH from the delivery orifice, which is created on the drug layer part.[14] Push-pull osmotic tablets are biphasic systems containing drug layer and push layer, compressed into bilayer tablets that are further coated with semipermeable membrane polymer.[15] Design of Experiments (DoE) is a well-structured and organized method to determine the relationship between factors affecting a process and its output.[16,17]

In this research PEO N80 and PEO WSR 303 were used as the polymer in the drug layer part and push layer part respectively, NaCl was used as osmogen to prepare bilayer tablets. CA was used as semipermeable membrane polymer and PEG 3350 as a plasticizer or pore former in ER coating. ER coated tablets were mechanically drilled ~0.5 mm on the drug layer part. Tablets were evaluated for various physical and chemical parameters. Optimization of %PEG 3350 and %weight gain was carried out with the help of design expert 12 software, response surface central composite design.

Materials and Methods

Materials

Nefopam hydrochloride (NFH) was gifted from Emcure pharmaceutical limited, Pune, India. Polyethylene oxide (PEO) N80 and Polyethylene oxide (PEO) WSR 303 was gifted from DuPont Nutrition Ireland, Wallingstown, Irland. Sodium chloride (NaCl) and Butylated Hydroxy Toluene (BHT) was gifted from Merck KgaA, Darmstadt, Germany. Colour Iron oxide red and Iron oxide yellow was gifted from Koel colors pvt. ltd., Mumbai, India. Povidone (PVP) K 30 was gifted from BASF india ltd., Mumbai, India. Magnesium stearate was gifted from Peter Greven Nederland C.V., Nederland. Cellulose Acetate (CA) 398-10 was gifted from Eastman chemical company, Singapore. Polyethylene Glycol (PEG) 3350 was gifted from Clariant specialty chemicals, Vadodara, India, Aceton and Isopropyl alcohol was gifted from Finar chemicals, Ahmedabad, India. All other chemicals used for the study were analytical grades.

Methods

Preparation of Nefopam Hydrochloride Push-Pull Osmotic Tablets

NPH, PEO N80, NaCl (milled), and 100# pass Iron oxide yellow co-sifted through #20 ASTM sieve (drug layer part). PEO WSR 303, NaCl (milled), and 100# pass Iron oxide red co-sifted through #20 ASTM sieve (push layer part). BHT and PVP K-30 dissolved in the required quantity of isopropyl alcohol under stirring to obtained a clear homogeneous solution. Co-sifted material of drug layer part or push layer part transferred to RMG and granulated using BHT and PVP K-30 binder solution to obtain heavy wet mass. The wet mass was dried using FBD at inlet temperature 50°C till LOD was 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, repeat the milling process until all granules pass through the #20 ASTM sieve. Magnesium stearate sifted through #40 ASTM sieve and mixed with dried, sifted granules in double cone blender for 5 minutes at 12 RPM. The drug and push layer parts were compressed into bilayer tablets using cadmach CMB4-MT compression machine, 11.50 mm, Round shape, Biconvex, and plain D type tooling punches. Bilayer tablets coated using Neocota 5D coating machine with 5% w/w coating dispersion of CA and PEG 3350 in acetone: water (95:5) as per the parameter described in Table 1 until the desired weight gain is achieved. ER coated tablets were mechanically drilled (~0.5 mm) almost at the center of the drug layer part side using micromotor handpiece mechanical driller.[18,19] Formulation trial batch no. F1, F2, and F3 were prepared individually. Bilayer compressed tablets of batch no. F2 is further used for ER coating DoE trials for batch no. F4 to F11.

Process flow of Nefopam Hydrochloride push-pull osmotic Tablets presented in Fig. 1.

Development and Optimization of Nefopam Hydrochloride Push-Pull Osmotic Tablets

Response surface central composite design with three center points was used to study factors like pore former/plasticizer (ratio of CA: PEG 3350), i.e., % Polyethylene glycol 3350 and % weight gain on drug release. The goal

Table 1: ER coating parameter

Sr. No.	*Parameter*	*Pre-Warming*	*Coating*	*Curing*
1	Inlet temperature	30°C to 50°C	20°C to 40°C	40°C to 60°C
2	Bed temperature	35°C to 45°C	25°C to 35°C	35°C to 45°C
3	Pan speed	1 to 2 RPM	5 to 12 RPM	1 to 2 RPM
4	Duration	15 min	To be recorded	60 min
5	Atomization air pressure	NA	1.0 kg/cm^2 to 2.0 kg/cm^2	NA
6	Spray rate	NA	5 g/min to 20 g/min	NA

Table 2: Central composite face centered design for optimization of critical excipients level in extended release coating

		Levels		
Sr. No.	*Formulation Variables*	*-1*	*0*	*1*
1	Concentration of PEG 3350 (%)	5	10	15
2	Weight gain (%)	6	8	10
Response studied				
% Drug release at 1 hours				
% Drug release at 4 hours				
% Drug release at 8 hours				
% Drug release at 12 hours				
% Drug release at 20 hours				

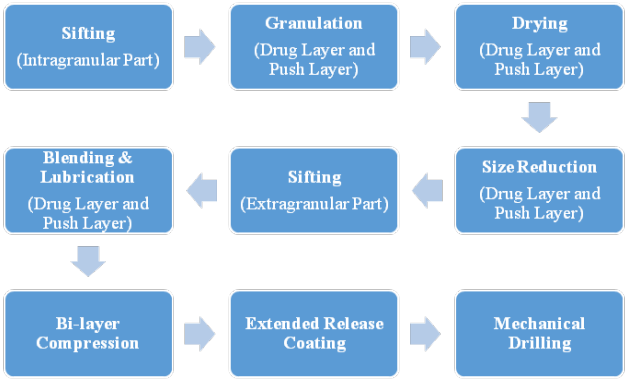

Fig. 1: Process flow of nefopam hydrochloride push-pull osmotic tablets

of the formulation development study was to understand if there is any interaction of these variables with drug product quality. This study also sought to establish the robustness of the proposed formulation. For this study, a central composite face-centered (CCF) 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 11 runs (batches).

Polyethylene glycol (PEG 3350) levels selected from 5% to 15% of the total extended-release coating component. The weight gain level selected for formulation studies was 6% to 10% according to the weight of the core tablets.

Table 2 summarized the factors and responses studied for optimization of critical excipients levels in the extended-release coating. Table 3 summarized the formulation composition of Nefopam Hydrochloride push-pull osmotic tablets, and Table 4 summarized the formulation batch summary for optimization of critical excipients level in the extended-release coating.

Evaluation of Nefopam Hydrochloride Push-Pull Osmotic Tablets in-process Stage

Dried Granules Stage (Drug Layer and Push Layer Part)

Loss on drying (LOD): About 1 gm of the drug was taken in a plate of halogen moisture analyzer (Make: Mettler Toledo, Model: Excellence HS 153) instrument. The temperature was set at 105°C. Record the percentage loss on drying. (Limit: NMT 2.0%w/w)

Lubricated Blend Stage (Drug Layer and Push Layer Part)

Bulk Density (BD): It is the ratio of total mass of powder to the bulk volume of powder.

$$Bulk\ \ Density = \frac{Mass\ \ of\ \ powder}{Bulk\ \ volume}$$

Bulk density of powder depends primarily on particle size distribution, particle shape, and the particles' tendency to adhere to one another.

Tapped Density (TD): It is the total mass of powder to the tapped powder volume.

$$Tapped\ \ Density = \frac{Mass\ \ of\ \ powder}{Tapped\ \ volume}$$

Tapped density was measured using the automated tap density tester USP-II method (Make: Electrolab, Model: ETD-1020X).

Compressibility Index (CI): The compressibility index and Hausner's ratio measure the propensity of powder to be compressed. The packing ability of the drug was evaluated from change in volume due to rearrangement of packing occurring during tapping. It was measured by following the formula.

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

Hausner's Ratio (HR): Hausner's ratio is an indirect index of ease of powder flow. It was calculated by following the formula.

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

Particle Size Distribution by Sieve Analysis: This method was used to determine the particle size distribution of granules of the test sample. This method was carried out by sifting a sample through a stack of wire mesh ASTM sieves of different sizes, i.e., #20, #30, #40, #60, #80, #100, and pan. A Sieve shaker (Make: Electrolab, Model: EMS-8 PLUS) was used to vibrate the sieve stack for a specific period and different amplitude with continuous or intermittent mode. Due to vibration, different size and shape particles were retained on respective sieve sizes and calculated % retain on each sieve. The particle size distribution data indicate flowability and uniformity of powder blend. It was also used for reverse engineering of powder mixtures. Powders with a broad size distribution tend to be poorer flowing than those with a narrow size distribution. %Retain on each sieve were calculated using the following equation.

$$\%Retain = \frac{Weight\ \ of\ \ sieve\ \ after\ \ test - Initial\ \ weight\ \ of\ \ sieve}{Weight\ \ of\ \ sample\ \ taken} \times\ 100$$

Table 3: Formulation composition of Nefopam Hydrochloride push-pull osmotic tablets

Sr. No.	*Ingredients*	*mg/tab*	*%w/w*	*%w/w*
	Drug layer			
1	Nefopam Hydrochloride IH (Emcure)	160.000	21.47	32.87
2	Polyethylene Oxide NF (PEO N80) (Dupont)	298.000	39.99	61.23
3	Sodium Chloride USP (Merck)	8.000	1.07	1.64
4	Iron Oxide Yellow IH (Koel)	1.400	0.19	0.29
5	Butylated Hydroxy Toluene NF (Merck)	0.200	0.03	0.04
6	Povidone USP (PVP K - 30) (BASF)	14.000	1.88	2.88
7	Isopropyl Alcohol USP* (Finar)	Q.S.	-	-
8	Magnesium Stearate USP/NF (Peter Greven)	5.100	0.68	1.05
Drug layer weight (mg)		486.700	-	100.00
	Push Layer			
1	Polyethylene Oxide NF (PEO WSR 303) (Dupont)	134.000	17.98	65.91
2	Sodium Chloride USP (Merck)	60.000	8.05	29.51
3	Iron Oxide Red IH (Koel)	0.700	0.09	0.34
4	Butylated Hydroxy Toluene NF (Merck)	0.100	0.01	0.05
5	Povidone USP (PVP K - 30) (BASF)	6.000	0.81	2.95
6	Isopropyl Alcohol USP* (Finar)	Q.S.	-	-
7	Magnesium Stearate USP/NF (Peter Greven)	2.500	0.34	1.23
Push Layer weight (mg)		203.300	-	100.00
Bi-layer core tablets weight (mg)		690.000	-	-
	Extended Release Coating			
1	Cellulose Acetate NF (CA398-10) (Eastman)	49.680	6.67	7.20
2	Polyethylene Glycol 3350 USP/NF (Clariant)	5.520	0.74	0.80
3	Purified Water USP*	Q.S.	-	-
4	Acetone USP/NF* (Finar)	Q.S.	-	-
Extended release tablets weight (mg)		745.200	100.00	8.00

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

Table 4: Formulation batch summary for optimization of critical excipients level in extended release coating

Sr. No.	*Ingredients*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*	*mg/tab*
Formulation Batch No.		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Core Tablets Batch No.		F1	F2	F3	F2	F2	F2	F2	F2	F2	F2	F2
	Extended Release Coating											
1	Core tablet weight	690.000	690.000	690.000	690.000	690.000	690.000	690.000	690.000	690.000	690.000	690.000
2	Cellulose Acetate CA398-10	49.680	49.680	49.680	39.330	58.650	65.550	35.190	37.260	62.100	52.440	46.920
3	PEG 3350	5.520	5.520	5.520	2.070	10.350	3.450	6.210	4.140	6.900	2.760	8.280
4	Purified Water*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
5	Acetone*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
ER coated tablets weight (mg)		745.200	745.200	745.200	731.400	759.000	759.000	731.400	731.400	759.000	745.200	745.200

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

a) Core tablets b) ER coated tablets c) Mechanically drilled tablets

Fig. 2: Nefopam Hydrochloride push-pull osmotic tablets

Compression Stage

- *Uniformity of Tablet Weight:* Accurately weighed individually 20 tablets taken at random and determined the average net weight. Not more than two of the individual tablet weights deviate more than 5.0% from its average weight and none of the tablets deviate more than 10.0% from its average weight.
- *Group Weight of Tablet:* Accurately weighed 20 tablets using weighing balance. Not more than 3.0% deviate from the theoretical weight of 20 tablets.
- *Thickness:* The thickness of 10 tablets measured by vernier calliper (Make: Mitutoyo, Model: CD-6" VC) and determined average, minimum and maximum thickness in mm.
- *Hardness:* It was used for the measurement of the crushing strength of tablets. The 10 tablets' hardness was measured by tablet hardness tester (Make: Erweka, Model: TBH 420TD) and determined average, minimum and maximum thickness in kp.
- *Friability:* Tablet Friability testing was performed during the compression stage to determine the durability of tablets during manufacturing, handling, coating, packing, and transportation which involves repeatedly dropping sample tablets over a fixed time and height with the help of a rotating drum having baffle. Tablets should not be break or separated during tests. Accurately weighed 10 tablets and placed the tablet in the drum of an automated tablet friabilator (Make: Electrolab, Model: EF-2W). Rotate the drum for 100 counts or 4 minutes at 25 rpm. After completion of the test, the tablets were removed. Removed any loose dust from the tablets and again accurately weighed. % friability should be NMT 1.0%. % friability calculated using the following equation.

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

- Extended-release Coating Stage
- Uniformity of Tablet Weight
- Group Weight of Tablet
- Thickness
- C*oating %Weight Gain:* It is Measured to determine % ER coating done on a compressed tablet, and calculated by the following equation.

$$\%Weight\ gain = \frac{Avg.\ weight\ of\ coated\ tablets - Avg.\ weight\ of\ core\ tablets}{Avg.\ weight\ of\ core\ tablets} \times 100$$

Finished Product Stage

In-vitro Dissolution

Apparatus: Dissolution test apparatus (Make: Lab India, Model: DS 8000^{+}), Dissolution condition: Medium: 6.8 pH phosphate buffer, Volume: 900 mL, Apparatus: Type II Paddle, Speed: 50 rpm, Time: 1, 4, 8, 12, 16, 20, 24 hours, Temperature: 37.0^{o}C ± 0.5^{o}C, Sampling volume: 10 mL. Filtered 10 mL samples were withdrawn at each time point through a 0.45 µ PVDF syringe filter. Discard the first 5 mL of filtrate and measured the absorbance in UV visible spectrophotometer at λ_{max} 266 nm using dissolution medium as a blank in the reference cell and calculated %drug release at each time point.

Assay

Took 5 tablets and weighed the individual tablets, and calculated the average weight of the tablet. Crushed all the 5 tablets and accurately weighed equivalent to 160 mg of label claim and transferred into 100 mL of the volumetric flask, add approximately 70 mL of acetonitrile-water as a diluent (50:50) and sonicate for 30 minutes to dissolve it and make up the volume with acetonitrile-water as a diluent (50:50). Pipette out 10 mL sample from it and transferred in to 100 mL of volumetric flask, make up the volume with acetonitrile-water as a diluent (50:50). Filtered 10 mL samples through 0.45 µ PVDF syringe filter. Discard the first 5 mL of filtrate and measure the absorbance in UV visible spectrophotometer at λ_{max} 2606 nm using acetonitrile-water (50:50) as a blank in the reference cell calculated % assay.

Stability Study

Stability study of optimized trial batch no. F2 has carried out in HDPE container as per ICH guideline at 40 ± 2^{o}C / 75 ± 5% RH for 1 month and 3 months and 25 ± 2^{o}C / 60 ± 5%

RH for 3 months. Tablets were analyzed for physical appearance, % Assay, and % Drug release.

Results and Discussion

In-process results of LOD at dried granules stage; bulk density, tapped density, compressibility index, hausner's ratio & PSD by sieve analysis at lubricated blend stage for drug and push layer parts are represented in Table 5. All results were found satisfactory and having good flow properties.

In-process results of compressed tablets were found satisfactory; no any critical problem was observed during the compression stage. In-process results of compressed tablets were summarized in Table 6.

In-process results of extended-release coated tablets were found satisfactory. No critical problem was observed during coating stage. In-process results of ER coated tablets were summarized in Table 7 and Table 8.

Assay results of Nefopam Hydrochloride push-pull osmotic tablets were found satisfactory and summarized in Table 9.

Batch details and analytical results for optimizing critical excipients levels in extended release coating are summarized in Table 10.

Discussion

(A) Significant Factors for %Drug Release at 1 Hour

Drug release was tested for tablets of all optimization batches. Fit summary and the analysis of variance (ANOVA) results are presented in the following Table.

The Model F-value of 31.58 implies that the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant.

The Lack of fit F-value of 1.28 implies that the lack of fit is insignificant relative to the pure error. There is a 50.14% 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 the %PEG 3350 and %weight gain has a significant effect on %drug release at 1 hour.

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

Drug release was tested for tablets of all optimization batches. Fit summary and the analysis of variance (ANOVA) results are presented in the following Table.

The model F-value of 24.60 implies that the model is significant. There is only a 0.04% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant.

The lack of fit F-value of 2.11 implies that the Lack of Fit is insignificant relative to the pure error. There is a 35.60% 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 the %PEG 3350 and %weight gain has a significant effect on %drug release at 4 hours.

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

Drug release was tested for tablets of all optimization batches. Fit summary and the analysis of variance (ANOVA) results are presented in the following Table.

Table 5: In-process results of drug layer part and push layer part

Batch No.	*D1*	*D2*	*D3*	*P1*	*P2*	*P3*
			Dried granules			
% LOD	1.03	1.25	1.12	1.26	1.05	1.26
			Lubricated blend			
BD in g/mL	0.571	0.588	0.556	0.556	0.526	0.571
TD in g/mL	0.667	0.690	0.667	0.625	0.625	0.667
CI in %	14.29	14.71	16.67	11.11	15.79	14.29
HR	1.17	1.17	1.20	1.13	1.19	1.17
			PSD by sieve analysis			
Sieve				% Retain		
#20	0.50	0.20	0.35	1.12	1.83	0.35
#30	3.25	3.24	3.83	5.43	8.71	6.23
#40	11.39	9.18	10.05	18.87	25.73	21.68
#60	20.43	17.37	17.52	21.46	21.92	17.30
#80	19.08	16.47	17.82	15.53	12.62	16.20
#100	9.29	12.48	10.30	9.13	5.84	8.08
Pan	47.75	36.06	35.66	23.61	41.07	40.12

The model F-value of 36.42 implies that 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. In this case, A, B are significant model terms. Values greater than 0.1000 indicate that the model terms are not significant.

The lack of fit F-value of 6.30 implies that the Lack of Fit is insignificant relative to the pure error. There is a 14.33% 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 the %PEG 3350 and %weight gain has a significant effect on %drug release at 8 hours.

(D) Significant Factors for %Drug Release at 12 Hours:

Drug release was tested for tablets of all optimization batches. Fit summary and the analysis of variance (ANOVA) results are presented in the following Table.

The model F-value of 44.09 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. In this case A, B are significant model terms. Values

Table 6: In-process results of compressed tablets

	Batch No.		
Test	*F1*	*F2*	*F3*
Individual Weight of Tablets (mg)	690 (683-695)	691 (682-697)	691 (680-696)
Group weight of 20 Tablets (g)	13.809	13.815	13.819
Thickness (mm)	7.25 (7.20-7.29)	7.54 (7.52-7.57)	7.41 (7.38-7.45)
Hardness (kp)	9.94 (8.96-10.91)	8.64 (7.96-9.51)	9.07 (8.23-9.84)
Friability Test (%w/w)	0.16	0.24	0.18

Table 7: In-process results of ER coated tablets trial batches F1 to F6

	Batch No.					
Test	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Individual Weight of Tablets (mg)	744 (735-751)	746 (739-752)	745 (732-755)	733 (724-743)	761 (754-770)	759 (749-768)
Group weight of 20 Tablets (g)	14.889	14.918	14.901	14.655	15.229	15.170
Thickness (mm)	7.71 (7.64-7.75)	7.72 (7.68-7.75)	7.72 (7.70-7.75)	7.87 (7.78-7.91)	8.11 (8.08-8.15)	8.14 (8.11-8.16)
Weight gain (%w/w)	7.93	8.11	8.04	6.05	10.28	10.09
Diameter (mm)	11.75 (11.71-11.78)	11.76 (11.72-11.78)	11.69 (11.63-11.72)	11.64 (11.60-11.68)	11.76 (11.73-11.78)	11.77 (11.75-11.79)

Table 8: In-process results of ER coated tablets trial batches F7 to F11

	Batch No.				
Test	*F7*	*F8*	*F9*	*F10*	*F11*
Individual Weight of Tablets (mg)	730 (720-741)	733 (724-745)	759 (750-770)	746 (736-758)	745 (734-754)
Group weight of 20 Tablets (g)	14.595	14.655	15.717	14.914	14.907
Thickness (mm)	7.92 (7.90-7.95)	7.87 (7.78-7.91)	8.14 (8.11-8.16)	7.71 (7.68-7.75)	7.74 (7.70-7.76)
Weight gain (%w/w)	5.81	6.11	10.16	8.07	7.93
Diameter (mm)	11.64 (11.62-11.67)	11.64 (11.60-11.68)	11.77 (11.74-11.79)	11.72 (11.69-11.75)	11.72 (11.69-11.75)

Table 9: Assay results of Nefopam Hydrochloride push-pull osmotic tablets

	Batch No.		
Test	*F1*	*F2*	*F3*
% Assay	99.5	100.2	99.8

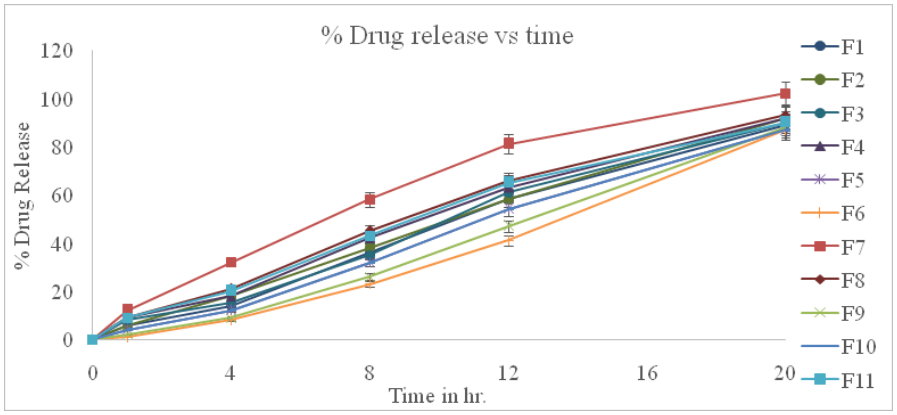

Fig. 3: *In-Vitro* dissolution results of trial batches

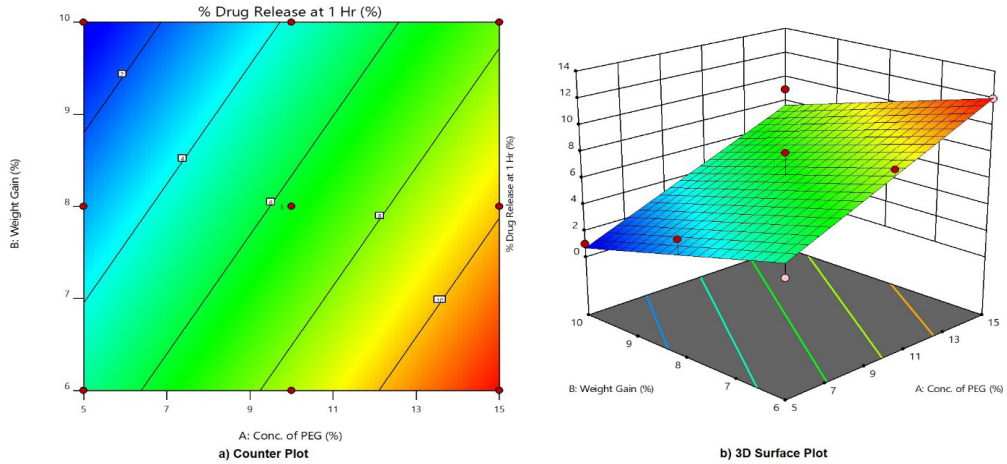

Fig. 4: Counter plot and 3D surface plot for the effect of %PEG 3350 and %weight gain on %drug release at 1 hour

Table 10: Batch details and analytical results for optimization of critical excipients level in the extended release coating

	Formulation variables (Independent variables)			*Responses (Dependent Variables)*				
B. No.	*Cellulose Acetate* (%)*	*A: PEG 3350 (%)*	*B: Weight gain (%)*	*% Drug release at 1 hour*	*% Drug release at 4 hours*	*% Drug release at 8 hours*	*% Drug release at 12 hours*	*% Drug release at 20 hours*
				NMT 10%	*Between 10-30%*	*Between 30-50%*	*Between 50-70%*	*NLT 85%*
F10	95	5	8	4	12	32	54	87
F7	85	15	6	**12**	**32**	**58**	**81**	102
F9	90	10	10	2	**9**	**26**	**47**	88
F5	95	5	6	4	12	32	54	87
F11	**85**	**15**	**8**	**9**	**20**	**43**	**65**	**90**
F6	95	5	10	1	8	23	41	87
F1	90	10	8	6	14	36	58	89
F8	90	10	6	9	21	45	66	93
F2	**90**	**10**	**8**	**6**	**18**	**38**	**58**	**92**
F4	85	15	10	9	18	42	63	92
F3	**90**	**10**	**8**	**8**	**15**	**35**	**61**	**90**

*For information only, NMT: Not more than, NLT: Not less than

Table 11: Fit summary results of all batches (% Drug Release at 1 hour)

Source	*Sequential p-value*	*Lack of Fit p-value*	*Adjusted R^2*	*Predicted R^2*	
Linear	0.0002	0.5014	0.8595	0.7816	Suggested
2FI	1.0000	0.4401			
Quadratic	0.8138	0.3175	0.7929	0.1350	
Cubic	0.1621	0.5063	0.8974	0.0036	Aliased

Table 12: ANOVA results of all batches (%Drug Release at 1 hour)

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	101.67	2	50.83	31.58	0.0002	significant
A-Conc. of PEG	73.50	1	73.50	45.66	0.0001	significant
B-Weight Gain	28.17	1	28.17	17.50	0.0031	significant
Residual	12.88	8	1.61			
Lack of Fit	10.21	6	1.70	1.28	0.5014	not significant
Pure Error	2.67	2	1.33			
Cor Total	114.55	10				

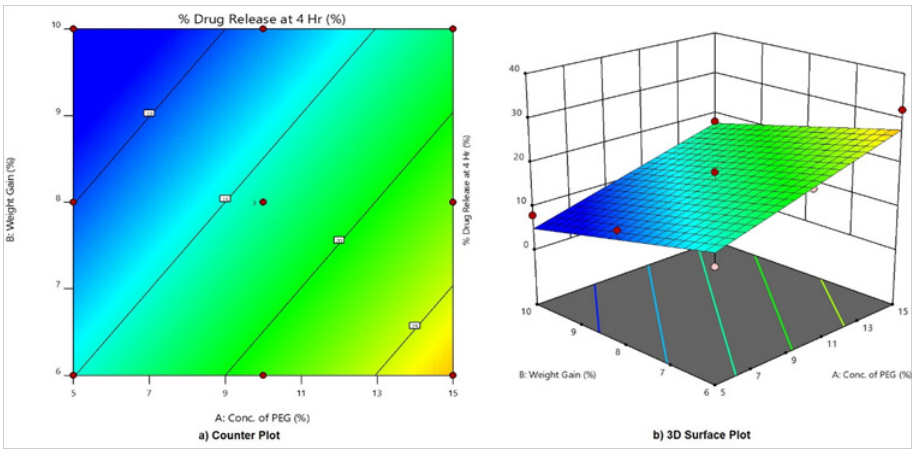

Fig. 5: Counter plot and 3D surface plot for the effect of %PEG 3350 and %weight gain on %drug release at 4 hours

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

Source	*Sequential p-value*	*Lack of Fit p-value*	*Adjusted R^2*	*Predicted R^2*	
Linear	0.0004	0.3560	0.8252	0.6601	Suggested
2FI	0.0705	0.4713	0.8789	0.6502	
Quadratic	0.5796	0.3889	0.8636	0.4695	
Cubic	0.2302	0.4951	0.9146	0.1354	Aliased

Table 14: ANOVA results of all batches (%Drug Release at 4 hours)

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	390.67	2	195.33	24.60	0.0004	significant
A-Conc. of PEG	240.67	1	240.67	30.31	0.0006	significant
B-Weight Gain	150.00	1	150.00	18.89	0.0025	significant
Residual	63.52	8	7.94			
Lack of Fit	54.85	6	9.14	2.11	0.3560	not significant
Pure Error	8.67	2	4.33			
Cor Total	454.18	10				

greater than 0.1000 indicate the model terms are not significant.

The Lack of Fit F-value of 4.79 implies that the Lack of Fit is insignificant relative to the pure error. There is an 18.27% 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 the %PEG 3350 and %weight gain has a significant effect on %drug release at 12 hours.

(E) Significant Factors for %Drug Release at 20 Hours:

Drug release was tested for tablets of all optimization batches. Fit summary and the analysis of variance (ANOVA) results are presented in the following Table.

The model F-value of 7.99 implies the model is significant. There is only a 1.24% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case, A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

The lack of fit F-value of 4.16 implies that the Lack of Fit is insignificant relative to the pure error. There is a 20.65% 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 the %PEG 3350 has a significant effect on %drug release at 24 hours, while %weight gain has no significant effect on %drug release at 24 hours.

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

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

Table 15: Fit summary results of all batches (%Drug Release at 8 hours)

Source	*Sequential p-value*	*Lack of Fit p-value*	*Adjusted R^2*	*Predicted R^2*	
Linear	< 0.0001	0.1433	0.8763	0.7734	Suggested
2FI	0.3366	0.1385	0.8773	0.6208	
Quadratic	0.5971	0.1048	0.8602	0.3136	
Cubic	0.0380	0.3917	0.9737	0.6196	Aliased

Table 16: ANOVA results of all batches (%Drug Release at 8 hours)

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	845.33	2	422.67	36.42	< 0.0001	significant
A-Conc. of PEG	522.67	1	522.67	45.03	0.0002	significant
B-Weight Gain	322.67	1	322.67	27.80	0.0008	significant
Residual	92.85	8	11.61			
Lack of Fit	88.18	6	14.70	6.30	0.1433	not significant
Pure Error	4.67	2	2.33			
Cor Total	938.18	10				

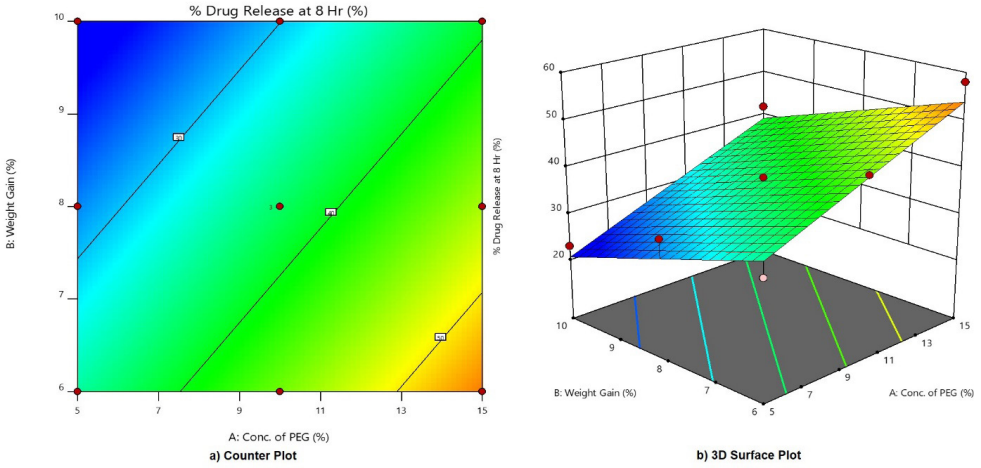

Fig. 6: Counter plots and 3D surface plots for the effect of % PEG 3350 and % weight gain on % drug release at 8 hours