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QbD Enabled Development of Press Coated Tablet of Nifedipine: Optimization, *In-vitro* Release and Stability Studies

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Abstract

The study aimed to develop a time-controlled release drug delivery system using the press coating method for chronotherapeutic treatment of hypertension and angina pectoris. The formulation intended to administer the drug at night, with the intention of relieving symptoms in the morning. The research concluded that, the drug's identification test verified it as Nifedipine, demonstrating good flowability. Different polymers, including various viscosity grades of HPC, influenced properties positively. Combining polymers in different ratios yielded distinct release kinetics at specific intervals. Hydrophilic and gellable polymers combined in the outer shell led to productive time release, whereas hydrophilic with erodible polymers extended the release over 6 to 11 hours. Rupturable and gellable polymer combinations achieved release from 6 to 10 hours, while erodible with rupturable polymers ranged from 6 to 8 hours due to composition differences. Excipient concentration impacted release kinetics, with hydrophilic and hydrophobic nature also influencing core tablet release kinetics. pH-independent release demonstrated practicality, especially with non-ionic HPC and EC polymers. The study revealed diverse release kinetics based on polymer and excipient integration in core and outer compositions. Understanding polymeric behaviours improved drug targeting accuracy. Data analysis indicated a mixed release kinetic involving erosion, diffusion, and swelling mechanisms. Overall, the study contributes insights into dosage form behaviour and polymeric influences on drug release.

Keywords: *Design of experiments, Press coated tablet, Nifedipine, Stability, Hypertension*

1. Introduction

Angina pectoris is a type of chest pain caused by reduced blood flow to the heart. It is a symptom of coronary artery disease (CAD), which is a narrowing of the arteries that supply blood to the heart[1,2]. The pain of angina is usually described as a squeezing or tightness in the chest, and it can also radiate to the arms, neck, jaw, or back. It typically comes on with exertion or stress and goes away with rest[3]. Angina can affect a person's life in a number of ways. It can limit their physical activity, make it difficult to work, and cause anxiety and depression. In some cases, it can also lead to a heart attack. Oral dosage forms are widely preferred for drug delivery because it increases the patient compliance in case of child and old ages. It is an ideal dosage form that sustain in the plasma conc. for prolong to treat disease condition of patients[4]. Oral dosage form consists of solid form such as tablets and capsules which are easy to administer. These dosage form marketed into different shape, size and colours so that they increase the patient compliance and easy to remember for layman[5]. Due to these characteristic properties, it develops lots of interest in developing such dosage form that optimized the therapeutic effect and minimize the side effects as well. This delivery system not only increases the therapeutic effect but also decrease the multiple dosing of the drugs also. Oral administration of drug

is very effective in all the cases because it's easily available in different form in market and having cost effective in nature. Tablets are the solid dosage forms that are pharmaceutical products which are meant for marketed use[6]. These are the widely used dosage forms that are easily available in the market in different shape, size and colours that are easy to use. The route of administration for different variety of tablets is oral route which is most common. As we all know, tablets are developed by the compression of powder in the confined spaces between dies. A tablet is comprising of one or more APIs and other excipients used in developing complete formulation[7]. These are widely used for systemic drug delivery as well as for local drug actions. In systemic delivery, tablets dissolved in the mouth, stomach and gastrointestinal tract so that the drug release in the fluid and absorbed in the systemic circulation. In local delivery, tablets are used to administer to the mouth or gastrointestinal tract that can be used to increase the stomachic pH[8].

Press coated system is used to formulate the oral drug by direct compression method in which the polymers prevent the drug from the core so that the drug release does not occurs until the polymeric shell get eroded or swollen. Press coated system works on press coating that help in the achieving the delayed release and intermittent release formulation. Press coating is also known as compressional coating which is simple and cheap that involve in direct compression of both core and coat[9]. Hydrophilic cellulose derivatives are used for compression on the laboratory scale. These polymers are used in the formulation of the drug such as ibuprofen, salbutamol etc so that the bioavailability should be satisfactory. Over the time, due to imbalance in the circadian rhythm causes so much problem to the patients and they have to take lots of medication at certain intervals of time so to overcome such use of drugs chronobiological studies are performed on the different functions to observe their circadian rhythm such as blood pressure, heart beat, body temperature, gastric pH, plasma concentration of various hormones, renal functions etc to develop the appropriate drug dosage to treat the disease and overcome the use of lots of medicine and minimize the toxicity and side effect of it over the body. So these methods demonstrate the potential benefits in the management of number of disease. It shows great deals of interest in particular patient suffering from allergic rhinitis, cardiovascular disorders, cancer, asthma, peptic ulcer etc. It seems that the person who suffers from allergic rhinitis got its worst symptoms in the morning while he wakes up[2].

In the formulation and development of press coated tablet, the controlled release techniques were used to develop the chronotherapeutic drugs that help in the disease treatment. Controlled release method was widely used to prepare the matrix tablet, drug moieties trapped in matrix and released at specific interval of time[10].

2. Materials And Methods

Materials

Nifedipine was purchased from sigma Aldrich, USA. Ac-Di-Sol, HPC, HPMC, microcrystalline cellulose and lactose monohydrate and all other excipients and reagent utilized were of analytical grade.

Methods

Preparation of core tablet

The inner core tablet was prepared by the direct compression method in order to perform the different kinetic release profile due to the involvement of different release mechanisms in it. Accurately weighed the Nifedipine by the help of electrical weighing balance and poured in the mortal and then we added the other excipients such as Ac-Di-Sol, microcrystalline cellulose and lactose monohydrate and triturated perfectly for 10 minutes and then pass the blended powder through the sieve no. 60 and then we added the magnesium stearate which passed through 80 no. sieve and mixed them perfectly and then the blended powder get compressed in to tablet (having average weight of 100mg) by the rotary tablet machine having 6mm concave faced punches and applied sufficient pressure so that the tablets occupied 5 kg/cm2 hardness[11].

Formulation development of Nifedipine press coated tablet and its optimization

In this press coated tablets we used different polymers in various ratio. All the powders were mixed well in mortar and passed through sieve no. 44. The powder blend was divided into two equal halves so that it is used for upper and lower shell. These tablets were prepared by the help of rotary tablet machine in which the half powder was used to make the powder bed in die and then we manually put the core tablet in the centre of the dies, then remaining die was filled with the half powder blend. Then we run the machine so that the powders compressed under the sufficient compressional force in the 10 mm diameter concave punch to keep the hardness of 10 kg/cm2 for each press coated tablets. Press coated tablets were prepared by the data obtained from total run by BBD method. A total of 25 runs with 5 centre points were taken in consideration and number of excipients were selected as obtained by BBD. Predefined amounts of excipients were taken and mixed with the blended phase containing water[12].

Experimental design of drug loaded formulation

Nifedipine loaded press coated tablets were taken for quality optimization by RSM with the help of Design expert ® (10.0.4, Stat-Ease Incorporation) software. The RSM of the previously mentioned computer program incorporates basically BBD was selected for further research[13].

Characterization of optimized nifedipine press coated formulation

Weight Variation

Weight variation of the tablets were studied as prescribed in the USP/NF, the weight variation of random 20 tablets were taken and then calculate their average weight of it and then compared the weight of individual tablets with the average weight.

Thickness and Diameter

Thickness and diameter of the tablets were measured with the help of vernier calliper and after that we obtained the mean (n=3) and standard deviation of all.

Hardness

In the study of hardness, we took random 5 tablets and measured by the help of Monsanto Hardness tester and then the mean (n=3) and standard deviation of all the tablets were obtained.

Friability

Pre-weighed 20 tablets and placed them in the Roche Friabilator apparatus and then the apparatus for 100 revolutions at 25 rpm and after completing its revolution took out all the tablets and de-dusted them and then weighed them again. The tablets were considered for acceptance when they losses less than 1.0 % of their weight.

In vitro drug release of press coated tablet

The dissolution studies were carried out in USP Dissolution Basket assembly at 50, 100 and 150 rpm at 37 ± 0.5 °C in 0.1 N HCl, the stimulated gastric fluid (1st fluid) and then in phosphate buffer solution of pH 6.8, stimulated intestinal fluid (2nd fluid) that were used as the dissolution medium. At specific interval of time, withdraw 5ml of sample from the dissolution media and poured equal amount of fresh dissolution medium in it. And then run the UV spectrophotometer at the wavelength of 236nm for all the withdraw samples respectively for 0.1N HCl and Phosphate buffer (pH 6.8)[14].

"The lag time was defined as the intersection on the time axis as part of the straight line of the dissolution curve extended to the time axis, and the dissolution rate of Nifedipine was calculated from the slope of the straight line. All the dissolution studies were performed in triplicate to obtained mean and standard deviation."

Infra-red spectroscopic analysis (IR) of press coated tablet

For IR Spectrum, we first of all dried potassium bromide (KBr) powder for 1 hour in hot air oven at 130˚C and after that we mixed the dried Nifedipine powder with the KBr powder and kept it in the desiccator to prevent them from moisture. Then the pellet was prepared by the help of the hydraulic

pump and kept it in the desiccator again. We put the prepared pellet in the pellet holder of the IR Spectroscopy and then run the spectrum and record the spectra and mark the peaks[15].

Differential scanning calorimetry (DSC) of press coated tablet

To identify possible interactions among the nifedipine and the excipients differential scanning calorimetry studies was conducted. This gives us an appropriate data to find any interaction and track change in the crystallinity of the drug. A less than 5 mg of nifedipine was taken inside the punctured metal panel and began from 50-200 °C range of temperature. The heating rate was 10 °C/min. Nitrogen gas was used as clean air, and liquid nitrogen cooled the system. The thermal differential analyser was used for determination of DSC[16].

Stability Studies of press coated tablet

Stability and stability testing of pharmaceutical components and finished pharmaceutical products are covered under the FDA's Current Good Manufacturing Practice rules. Stability studies are the final stage evaluation parameters of the tablets in which we check the stability of the tablet by placing then in different storage condition and then observe the changes occurs in them after certain interval of time. Stability testing of drugs and medicinal products is essential at every stage of development. From the prepared press coated tablet we choose the appropriate formulation that shows the appropriate drug release[17]. The press coated tablet of nifedipine that prepared by the direct compression method was subjected to be proceed for the stability studied as per the U.S. FDA stability guidelines as well as the ICH Guidelines too as the short term of the testing procedure that was carried out at different temperature such as 25˚C/60% RH, 30˚C/65% RH and 40˚C/70% as well as in hot air oven at 60˚C. At the interval of 15, 30 and 45 days the sample that are stored get analyzed on the basis of its physical appearance and drug content the result should be given[18].

3. Results and Discussion

Preparation of drug loaded formulation and qualitative optimization of method of preparation

The inner core of the press coated tablet was mainly prepared by direct compression method in order to perform the different release kinetic of the drug through different release mechanism involved in it and evaluated for thickness, diameters, hardness, weight variation, friability and drug content. All the formulations of press coated tablets were prepared as mentioned in the method of preparation in order to study the effect of core and coated tablets that designed on lag time and time-controlled release of the drug and then evaluated all the designed formulations for weight variations, thickness, diameter, hardness, friability, *in-vitro* dissolution study and erosion study[19]. In the figure 7, we have shown the morphological view of optimized press coated tablet by taking its transverse and cross-section of the tablet through which we can assumed that the core is perfectly coated by the coating material[20].

Table 1: Experimental runs obtained after applying Box-Behnken Design

	Factor 1	Factor 2	Factor 3	Factor 4	Response 1	Response 2	Response 3
Run	A: HPMC K4M (mg)	B: EC-N20 (mg)	C: HPC-EXF (mg)	D: HPC-LXF (mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)
1	125	100	120	120	9.6	0.23	5.32
2	125	100	85	85	9.6	0.24	5.33
3	200	50	85	85	9.9	0.27	5.42
4	125	100	50	50	9.5	0.23	5.32
5	125	100	50	120	9.7	0.24	5.32
6	125	100	120	50	9.8	0.28	5.37
7	200	150	85	85	10	0.28	5.41
8	200	100	50	85	10	0.27	5.37
9	125	150	85	50	9.7	0.27	5.37
10	125	50	85	120	9.8	0.28	5.38
11	50	50	85	85	9.5	0.24	5.36
12	50	100	85	50	9.6	0.23	5.32
13	125	50	85	50	9.6	0.24	5.32
14	125	150	50	85	9.7	0.25	5.33

15	50	100	50	85	9.6	0.23	5.33
16	50	100	85	120	9.6	0.24	5.34
17	50	150	85	85	9.7	0.25	5.34
18	125	150	85	120	9.6	0.25	5.35
19	125	50	120	85	9.7	0.26	5.35
20	50	100	120	85	9.7	0.27	5.38
21	200	100	120	85	10	0.28	5.41
22	125	50	50	85	9.6	0.25	5.37
23	125	150	120	85	9.7	0.27	5.38
24	200	100	85	120	9.8	0.28	5.41
25	200	100	85	50	9.8	0.28	5.4

Experimental design: model fitting and optimization of parameters

After formulation development the model fitting was done with the help of Design exert software DX11 (State Ease Incorporation). Response surface methodology was employed and quality by design approach was utilized. The results were found to be in the range of 9.5-10, 0.23-0.28 and 5.32-5.41 for hardness, friability and thickness, respectively (Table 1). The predicted R square values were in the arrangement with the adjusted R square value (table 2). 3-D response surface analysis was done to determine the effect of various factors on the response as given in the figure 1, 2 and 3^{20}.

Table 2: ANOVA for Quadratic model of Hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.4522	14	0.0323	5.96	0.0037	significant
A-HPMC K4M	0.2700	1	0.2700	49.85	< 0.0001	
B-EC-N20	0.0075	1	0.0075	1.38	0.2666	
C-HPC-EXF	0.0133	1	0.0133	2.46	0.1477	
D-HPC-LXF	0.0008	1	0.0008	0.1538	0.7031	
AB	0.0025	1	0.0025	0.4615	0.5123	
AC	0.0025	1	0.0025	0.4615	0.5123	
AD	5.551E-17	1	5.551E-17	1.025E-14	1.0000	
BC	0.0025	1	0.0025	0.4615	0.5123	
BD	0.0225	1	0.0225	4.15	0.0689	
CD	0.0400	1	0.0400	7.38	0.0217	
A^2	0.0502	1	0.0502	9.27	0.0124	
B^2	0.0059	1	0.0059	1.10	0.3200	
C^2	0.0096	1	0.0096	1.77	0.2125	
D^2	0.0000	1	0.0000	0.0090	0.9261	
Residual	0.0542	10	0.0054			
Cor Total	0.5064	24				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 5.96 implies the model is significant. There is only a 0.37% 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, CD, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation of Hardness in Terms of Coded Factors = + 9.60 + 0.1500A + 0.0250B + 0.0333C + 0.0083D - 0.0250AB - 0.0250AC + 0.0000AD - 0.0250BC - 0.0750BD - 0.1000CD + 0.1333A^2 + 0.0458B^2 + 0.0583C^2 - 0.0042D^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are

coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients (Table 3).

Table 3: Actual vs Predicted Value Report of Hardness

Run Order	Actual Value	Predicted Value	Residual	Leverage
1	9.60	9.60	0.0042	0.583
2	9.60	9.60	0.0000	1.000
3	9.90	9.93	-0.0292	0.583
4	9.50	9.51	-0.0125	0.583
5	9.70	9.73	-0.0292	0.583
6	9.80	9.78	0.0208	0.583
7	10.00	9.93	0.0708	0.583
8	10.00	9.93	0.0667	0.583
9	9.70	9.73	-0.0333	0.583
10	9.80	9.70	0.1000	0.583
11	9.50	9.58	-0.0792	0.583
12	9.60	9.57	0.0292	0.583
13	9.60	9.53	0.0667	0.583
14	9.70	9.72	-0.0208	0.583
15	9.60	9.58	0.0167	0.583
16	9.60	9.59	0.0125	0.583
17	9.70	9.68	0.0208	0.583
18	9.60	9.60	0.0000	0.583
19	9.70	9.74	-0.0375	0.583
20	9.70	9.70	0.0000	0.583
21	10.00	9.95	0.0500	0.583
22	9.60	9.62	-0.0208	0.583
23	9.70	9.74	-0.0375	0.583
24	9.80	9.89	-0.0875	0.583
25	9.80	9.87	-0.0708	0.583

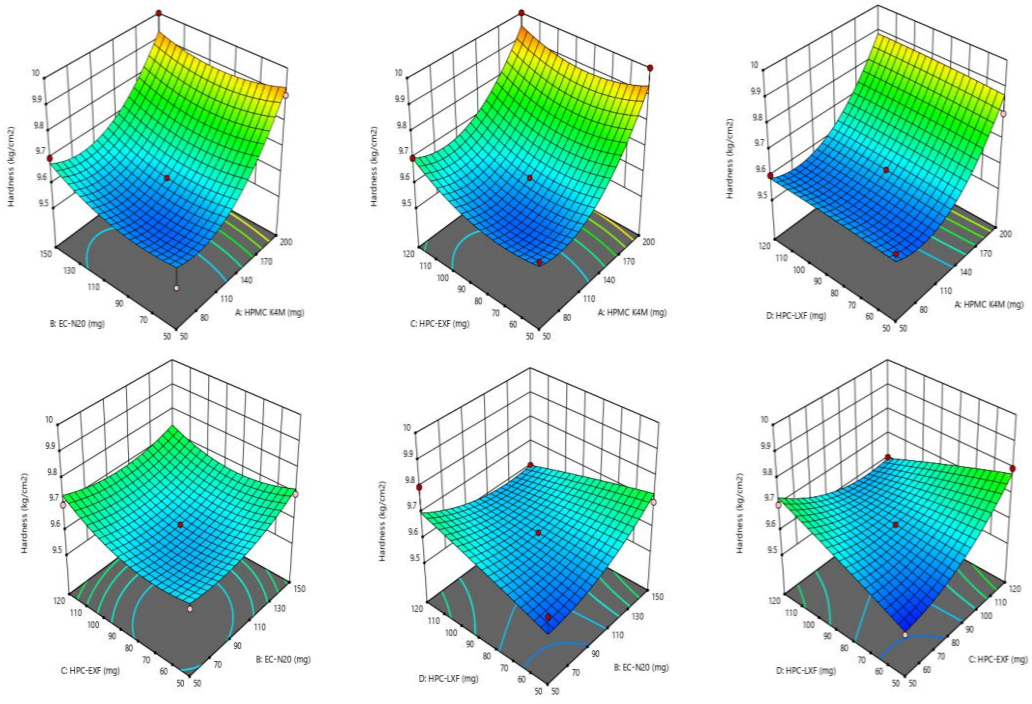

Figure 1: 3D response surface plot representing the effect of factors on the hardness

Table 4: ANOVA for 2FI model of Friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0067	10	0.0007	4.97	0.0035	significant
A-HPMC K4M	0.0033	1	0.0033	24.77	0.0002	
B-EC-N20	0.0001	1	0.0001	0.5572	0.4677	
C-HPC-EXF	0.0012	1	0.0012	8.92	0.0098	
D-HPC-LXF	8.333E-06	1	8.333E-06	0.0619	0.8071	
AB	0.0000	1	0.0000	0.0000	1.0000	
AC	0.0002	1	0.0002	1.67	0.2170	
AD	0.0000	1	0.0000	0.1857	0.6730	
BC	0.0000	1	0.0000	0.1857	0.6730	
BD	0.0009	1	0.0009	6.69	0.0216	
CD	0.0009	1	0.0009	6.69	0.0216	
Residual	0.0019	14	0.0001			
Cor Total	0.0086	24				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 4.97 implies the model is significant. There is only a 0.35% chance that an F-value this large could occur due to noise (Table 4).

P-values less than 0.0500 indicate model terms are significant. In this case A, C, BD, CD are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model[21].

The **Predicted R^2** of 0.3279 is in agreement with **Adjusted R^2** of 0.6233 as one might normally expect; i.e., the difference is less than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.797 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation of Friability in Terms of Coded Factors= + 0.2564 + 0.0167A + 0.0025B + 0.0100C - 0.0008D + 0.0000AB - 0.0075AC - 0.0025AD + 0.0025BC - 0.0150BD - 0.0150CD

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients (Table 5).

Table 5: Actual vs Predicted Value Report of Friability

Run Order	Actual Value	Predicted Value	Residual	Leverage
1	0.2300	0.2506	-0.0206	0.457
2	0.2400	0.2564	-0.0164	0.040
3	0.2700	0.2706	-0.0006	0.457
4	0.2300	0.2322	-0.0022	0.457
5	0.2400	0.2606	-0.0206	0.457
6	0.2800	0.2822	-0.0022	0.457
7	0.2800	0.2756	0.0044	0.457
8	0.2700	0.2706	-0.0006	0.457
9	0.2700	0.2747	-0.0047	0.457
10	0.2800	0.2681	0.0119	0.457
11	0.2400	0.2372	0.0028	0.457
12	0.2300	0.2381	-0.0081	0.457
13	0.2400	0.2397	0.0003	0.457

14	0.2500	0.2464	0.0036	0.457
15	0.2300	0.2222	0.0078	0.457
16	0.2400	0.2414	-0.0014	0.457
17	0.2500	0.2422	0.0078	0.457
18	0.2500	0.2431	0.0069	0.457
19	0.2600	0.2614	-0.0014	0.457
20	0.2700	0.2572	0.0128	0.457
21	0.2800	0.2756	0.0044	0.457
22	0.2500	0.2464	0.0036	0.457
23	0.2700	0.2714	-0.0014	0.457
24	0.2800	0.2697	0.0103	0.457
25	0.2800	0.2764	0.0036	0.457

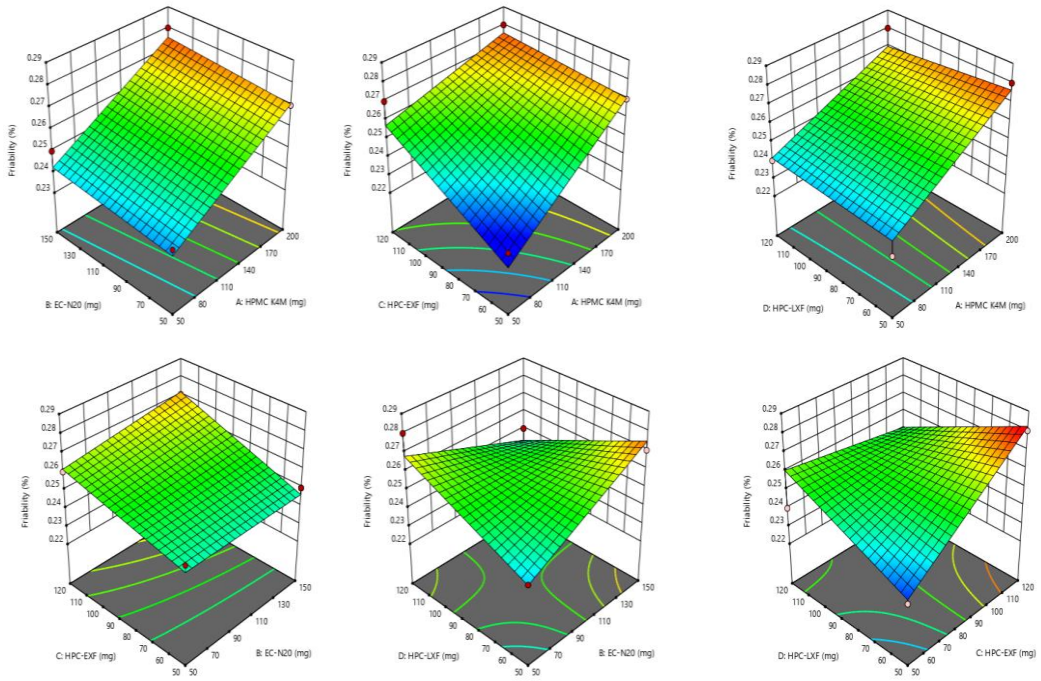

Figure 2: 3D response surface plot representing the effect of factors on the Friability

Table 6: ANOVA for Quadratic model of Thickness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0230	14	0.0016	5.39	0.0055	significant
A-HPMC K4M	0.0102	1	0.0102	33.56	0.0002	
B-EC-N20	0.0000	1	0.0000	0.1096	0.7474	
C-HPC-EXF	0.0024	1	0.0024	7.92	0.0184	
D-HPC-LXF	0.0000	1	0.0000	0.1096	0.7474	
AB	0.0000	1	0.0000	0.0822	0.7802	
AC	0.0000	1	0.0000	0.0822	0.7802	
AD	0.0000	1	0.0000	0.0822	0.7802	
BC	0.0012	1	0.0012	4.03	0.0726	
BD	0.0016	1	0.0016	5.26	0.0447	
CD	0.0006	1	0.0006	2.05	0.1822	
A^2	0.0035	1	0.0035	11.37	0.0071	
B^2	0.0013	1	0.0013	4.19	0.0678	
C^2	0.0001	1	0.0001	0.2321	0.6404	
D^2	4.412E-06	1	4.412E-06	0.0145	0.9065	

Residual	0.0030	10	0.0003
Cor Total	0.0260	24	

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 5.39 implies the model is significant. There is only a 0.55% chance that an F-value this large could occur due to noise (Table 6).

P-values less than 0.0500 indicate model terms are significant. In this case A, C, BD, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 8.019 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation of Thickness in Terms of Coded Factors = + 5.33 + 0.0292A - 0.0017B + 0.0142C + 0.0017D + 0.0025AB - 0.0025AC - 0.0025AD + 0.0175BC - 0.0200BD - 0.0125CD + 0.0350A^2 + 0.0212B^2 + 0.0050C^2 + 0.0013D^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients (table 7).

Table 7: Actual vs Predicted Value Report of Thickness

Run Order	Actual Value	Predicted Value	Residual	Leverage
1	5.32	5.34	-0.0196	0.583
2	5.33	5.33	0.0000	1.000
3	5.42	5.41	0.0054	0.583
4	5.32	5.31	0.0121	0.583
5	5.32	5.34	-0.0162	0.583
6	5.37	5.36	0.0088	0.583
7	5.41	5.42	-0.0062	0.583
8	5.37	5.39	-0.0175	0.583
9	5.37	5.37	0.0008	0.583
10	5.38	5.38	0.0042	0.583
11	5.36	5.36	-0.0012	0.583
12	5.32	5.33	-0.0129	0.583
13	5.32	5.33	-0.0125	0.583
14	5.33	5.32	0.0071	0.583
15	5.33	5.32	0.0058	0.583
16	5.34	5.34	-0.0012	0.583
17	5.34	5.35	-0.0129	0.583
18	5.35	5.33	0.0175	0.583
19	5.35	5.35	-0.0046	0.583
20	5.38	5.36	0.0225	0.583
21	5.41	5.41	-0.0008	0.583
22	5.37	5.36	0.0088	0.583
23	5.38	5.39	-0.0062	0.583
24	5.41	5.39	0.0154	0.583
25	5.40	5.40	0.0038	0.583

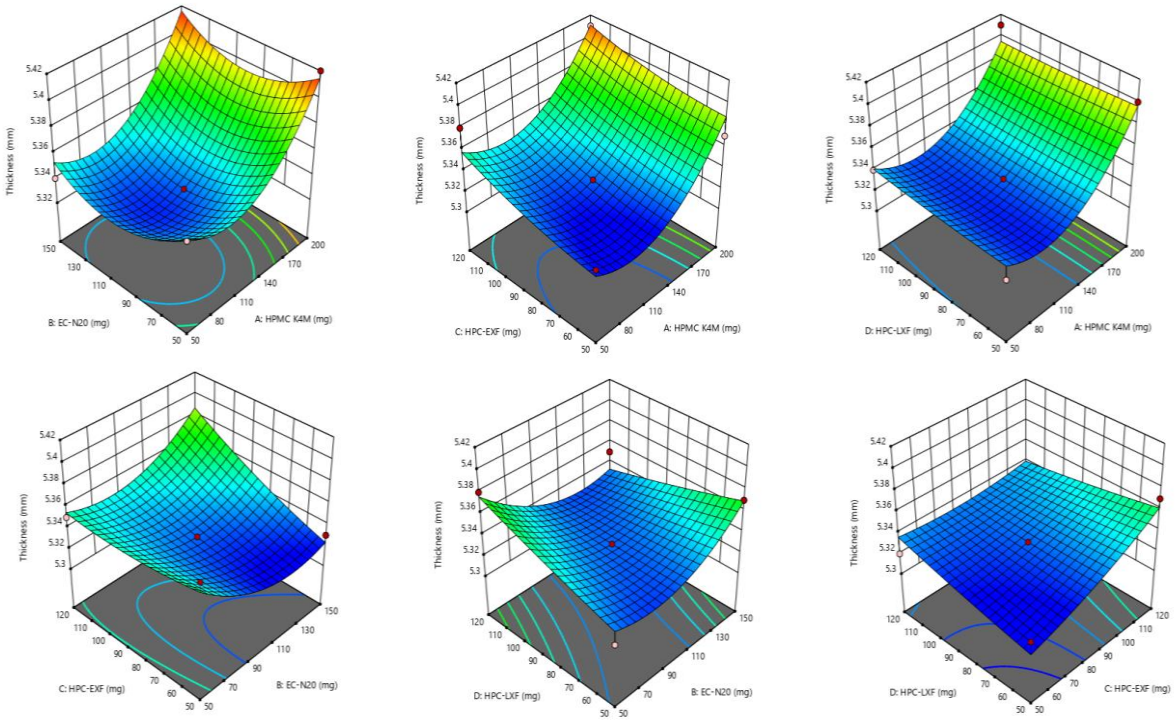

Figure 3: 3D response surface plot representing the effect of factors on the Thickness

Desirability analysis

As the results indicated in the figure 5, the desirability of the optimized system was found to be more than 0.73, which is considered as suitable for the selection and consideration will be based the data presented in the figure 4.

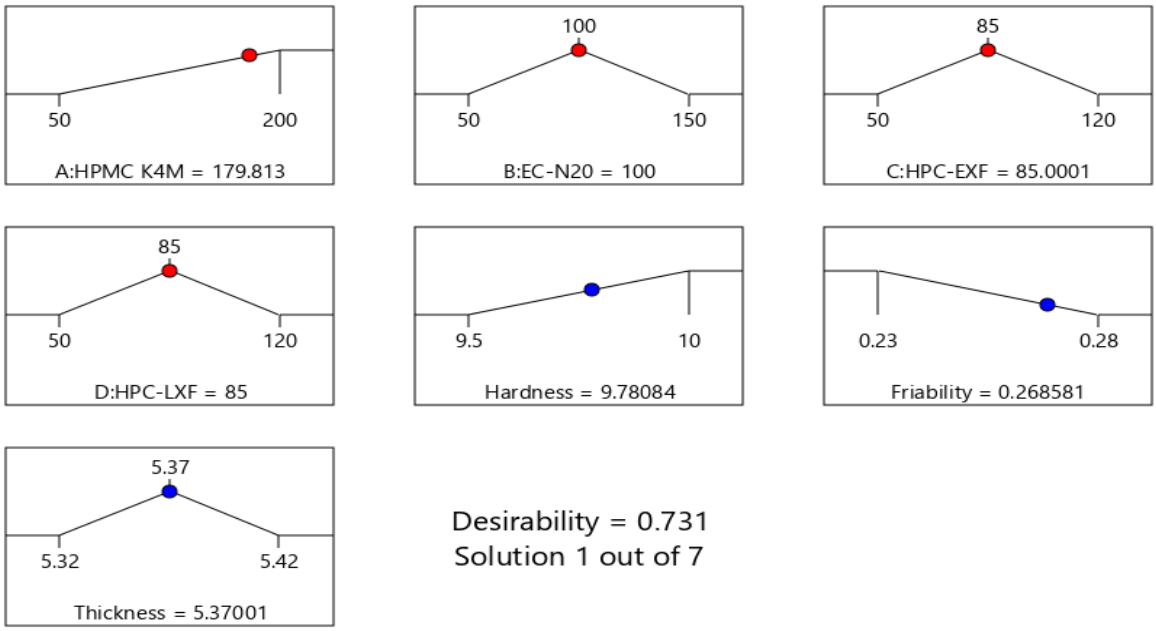

Figure 4: Desirability of different optimization parameters of factors and response

Confirmation location and data suitability

The results obtained after applying numerical and graphical optimization tool, it was found out that the desirable results will be obtained when following concentration of factors will be taken (Table 8) and the results will be finalized as obtained in table 9.

Table 8: Confirmation Location

HPMC K4M	EC-N20	HPC-EXF	HPC-LXF
179.813	99.9999	85	85

Table 9: Results Obtained of final obtained confirmation location

S. No.	Hardness	Friability	Thickness
1.	9.7	0.26	5.37
2.	9.8	0.27	5.36
3.	9.7	0.27	5.37

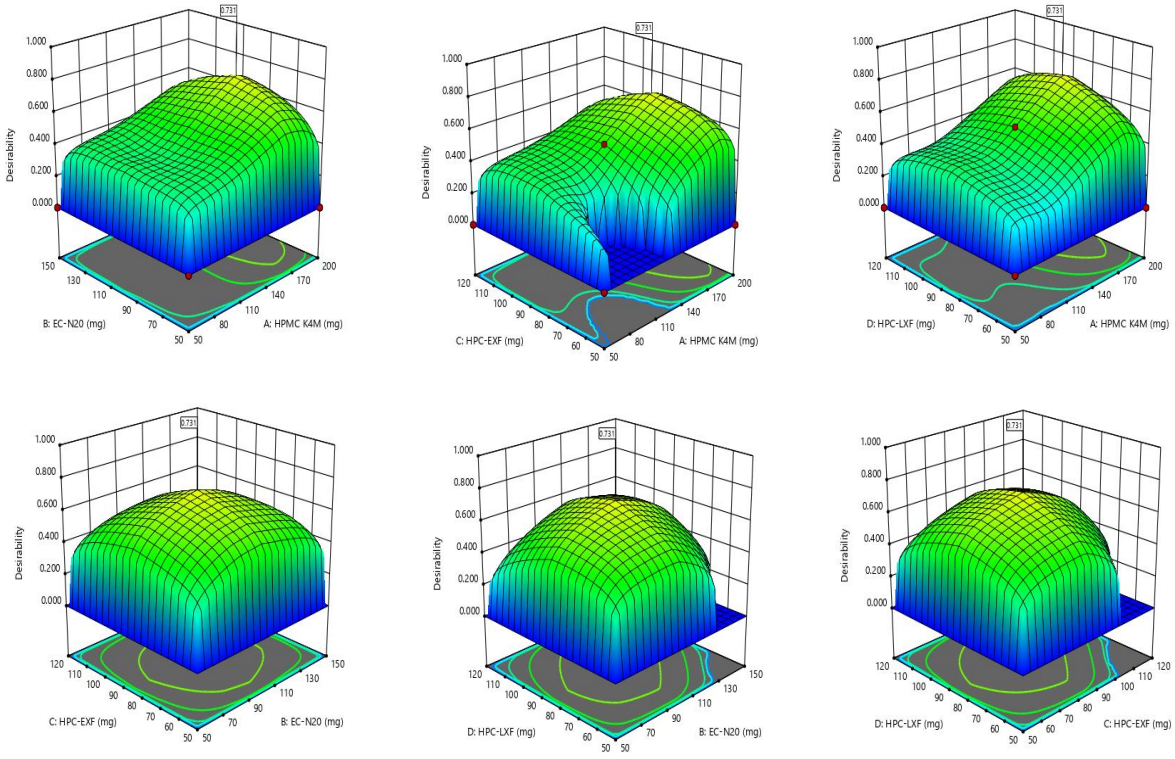

Figure 5: Desirability plot of optimized system

Overlay plot analysis

The overlay plot suggested that the developed and optimized parameters are very well fitted in the boundaries of the system and can be used to evaluate the data (Figure 6).

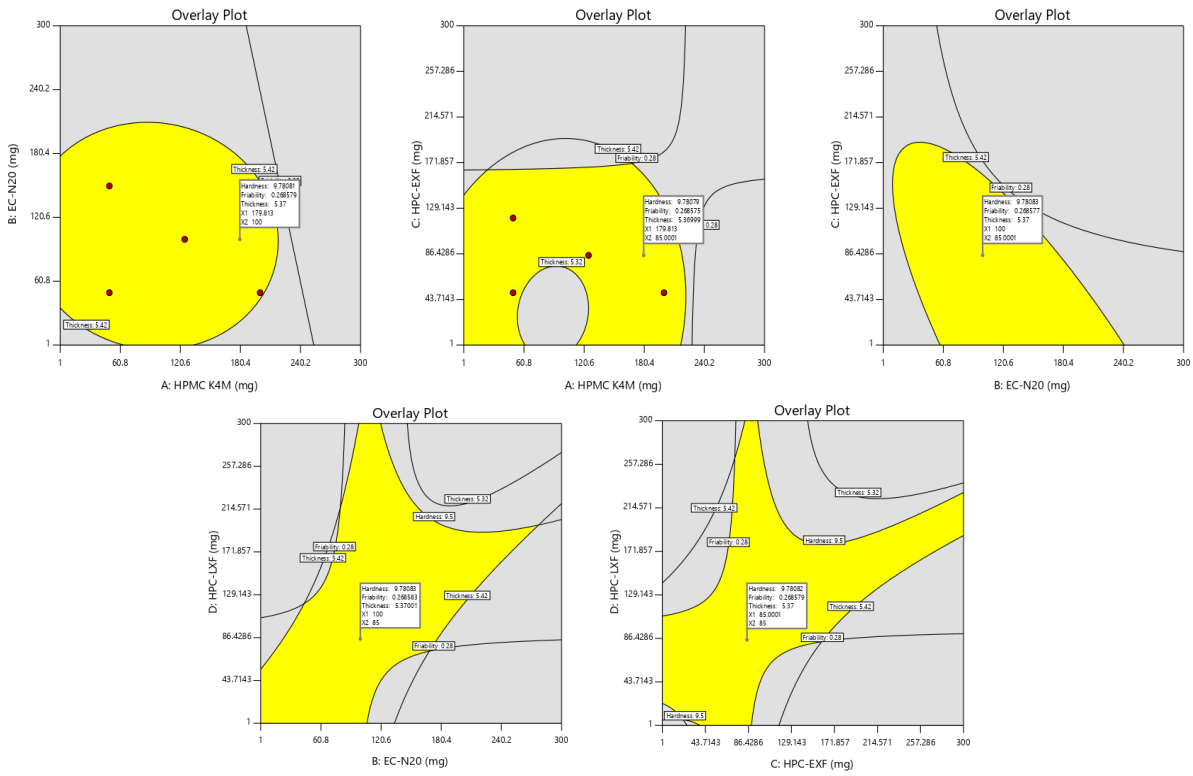

Figure 6: Overlay plot of all the factors and responses

In-vitro drug release patterns of Nifedipine core tablets

The study of release patterns of the press tablets basically we put the tablets into the beaker that contains dissolution medium and then took the images of the tablets. Figure 7 shows that the formulation containing high amount of the Ac-DI-Sol® get swell when contact with the dissolution medium and get disintegrate after few minutes. In this study, it was observed that the formulation having less amount of Ac-DI-Sol® remains for long time than the high amount containing Ac-DI-Sol® that means the C3 formulation disintegrate faster than the C1 & C3 formulations[22–24].

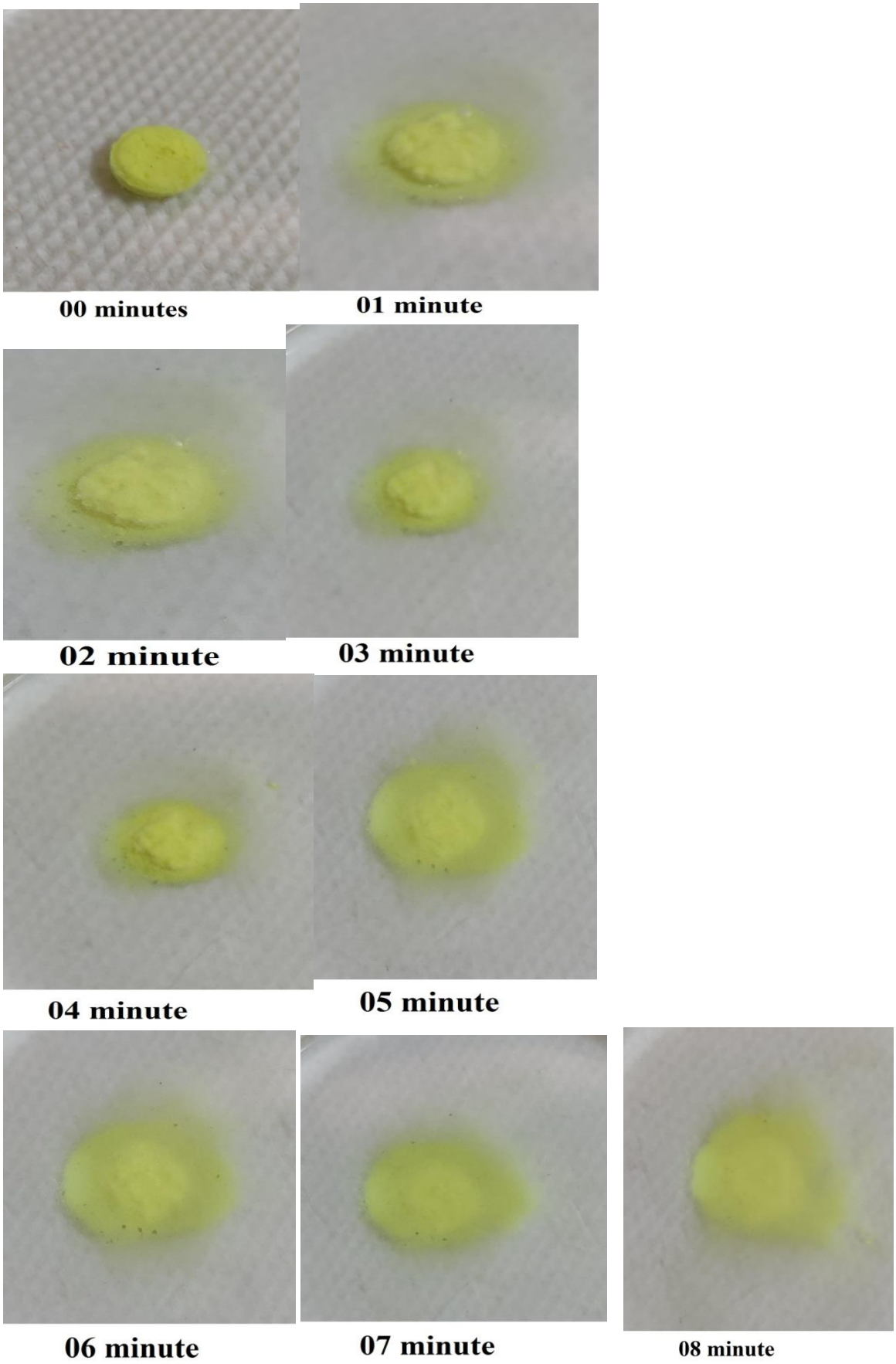

Figure 7: In-Vitro Release patterns of Nifedipine core tablets

Effect of Dissolution Medium pH on Dissolution Profile of Nifedipine from Core tablets

In order to study the effect of dissolution medium pH on release of the drug profile of Nifedipine we tested for the formulation which was carried out in both the solution 1st stimulated gastric fluid i.e., 0.1N HCL and 2nd stimulated intestinal fluid i.e., pH 6.8 Phosphate buffer solution. All the dissolution data that were performed on the core tablet was given in the following table 10 and figure 8 show the significant effect of the dissolution pH that it causes any changes in the release profile or not. Basically, the Nifedipine is freely soluble in both the solution 1st stimulated gastric fluid i.e., 0.1N HCL and 2nd stimulated intestinal fluid i.e., pH 6.8 Phosphate buffer solution and other excipients that were present in the core are also shows pH independent solubility as well[25].

Table 10: Effect of Dissolution medium pH on the dissolution profile of the core tablet

TIME (min)	% DRUG RELEASE	
	pH 1.2	pH 6.8
00	00	00
1	58.23±0.17	54.42±0.20
2	65.25±0.17	61.62±0.21
3	86.49±0.26	74.71±0.32
4	94.38±0.16	84.40±0.23
5	97.24±0.12	87.54±0.11
6	97.63±0.24	88.26±0.15
7	98.24±0.10	89.70±0.30
8	98.53±0.11	97.27±0.07
9	99.49±0.25	98.24±0.65
10	99.82±0.05	99.22±0.10
11	99.95±0.07	99.64±0.10
12	100.02±0.01	99.94±0.05

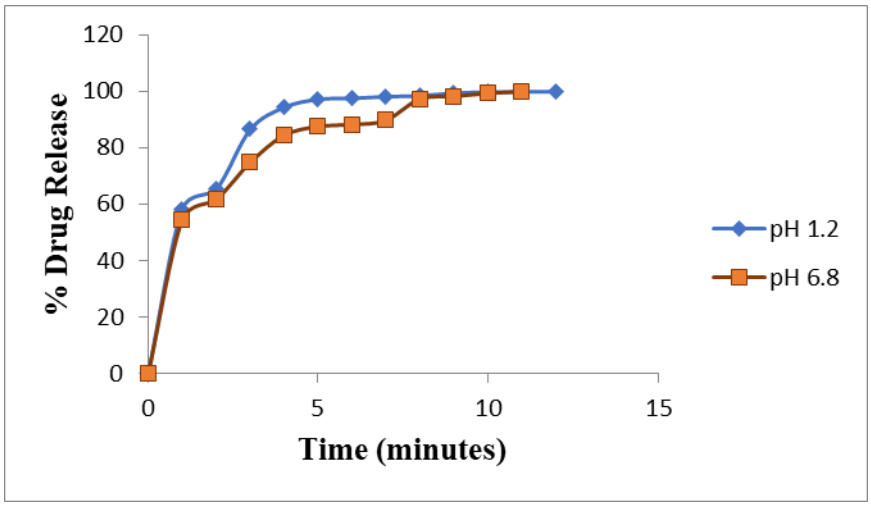

Figure 8: Effect of Dissolution medium pH on the dissolution profile of the core tablet

In-vitro drug release patterns of Nifedipine press coated tablets

Different viscosity grade of HPC polymers were used in the press coating material that were used as the outer shell of the tablets. In the table 1, we have shown the two different grades of HPC i.e., HPC-EXF and HPC-LXF in different amounts in three different formulations through which we easily determined the dissolution behaviour of the tablets. As we all known that the polymers purse different mechanisms through which the release of the drug took place, here the HPC-EXF exhibits the erodible properties while HPC-LXF exhibits the rupturable properties through which the drug release. In a study which was done by Nakano et. al. that was performed on the theophylline having HPC matrix tablets in a result it was founded that due to the presence on the HPC polymer increase in the

viscosity of the polymer the release of the drug also extended for long period of time. So, this studied suggested that the release of the polymer completely depends upon the dissolution rate of the polymer that was used in the tablets. So, if we increased the amount of the HPC in any formulation it will increase the dissolution rate through which the release of the press coated tablets also extend prolong in the body. It's also seemed that there were so many complicated factors that affect the release of the drug from the matrix tablets such as the water penetration, gelation of polymers, erodible nature of the polymers due to which the effect was seen in the drug release. In this formulation we add some amount of the drug in the outer shell so that the drug release from starting until the lag time of the core tablet were also obtained. In this formulation due to the nature of the polymers when the reputation and erosion occurs the drug from the outer shell also release which provide the immediate relief from the disease and when the complete erosion of the polymers pursued then the drug from core also seem. Due to use of the combination of these both polymers in different ratio we founded that due to the nature of the polymers it extends the release of drug for long period of times. From the following figure 9, it is clear that the press coated tablet followed extended-release pattern at pH 6.8 whereas at pH 1.2, the complete drug release was occurred within 7 hrs[18,20].

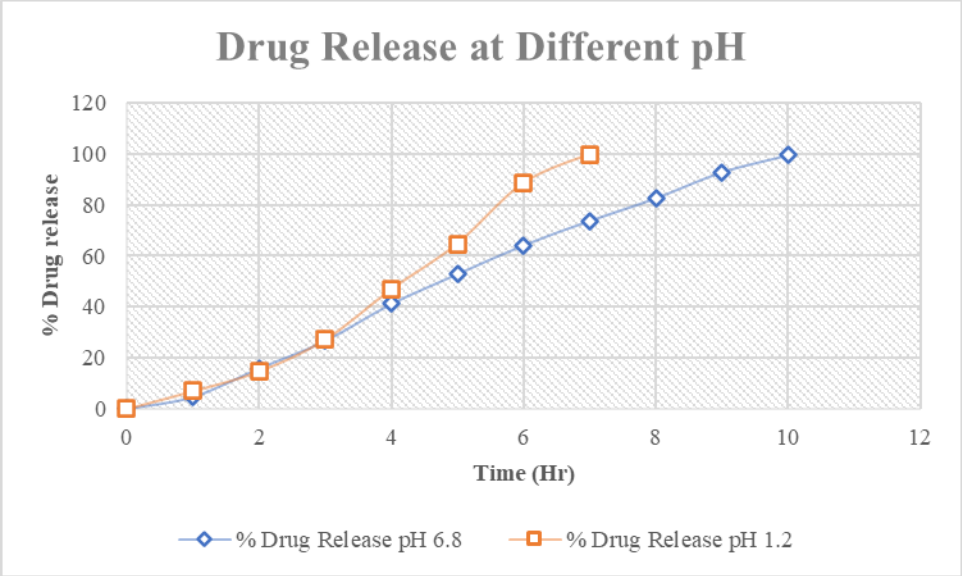

Figure 9: Drug release pattern from press coated tablet at different pH

Infra-red spectroscopic analysis

FT-IR Spectroscopy was used for the identification of the drug and different functional group peaks was observed that were similar to the standard peak value as given in the USP/IP[26]. The peaks of different functional group were observed in the spectrum that was mentioned in the figure 10. The FTIR analysis revealed no interaction and all the excipients were found to be non-interactive in nature[14,27].

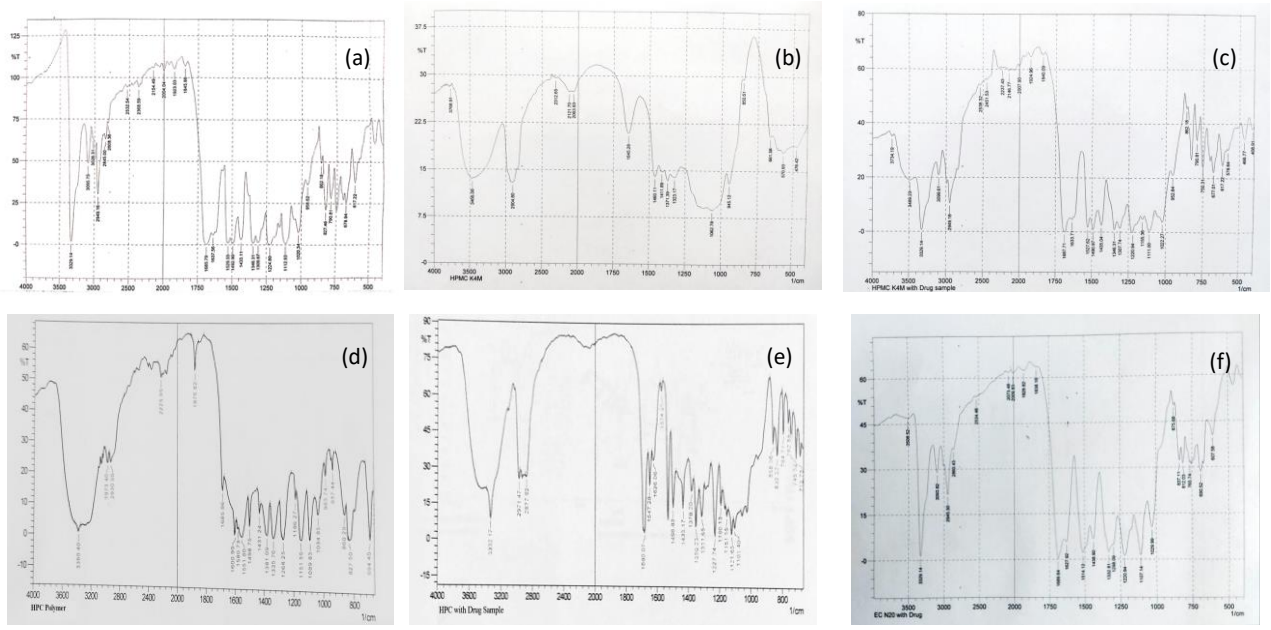

Figure 10: FTIR analysis of (a) Nifedipine, (b) HPMC K4M, (c) Mixture of Nifedipine and HPMC, (d) HPC, (e) HPC with Nifedipine and (f) EC with Nifedipine

Differential scanning calorimetry (DSC)

The DSC experiments have been carried out to assess the drug's crystallinity and impurity on the basis of its melting point. Due to the polymorphous shape of Nifedipine, the DSC thermo gram showed one exothermic peak at 174.5°C. The exothermic peak of Nifedipine at 174.5°C was shifted to 174.6°C, which suggest the no molecular interaction of Nifedipine into HPMC matrix during formulation development (Figure 11)[28].

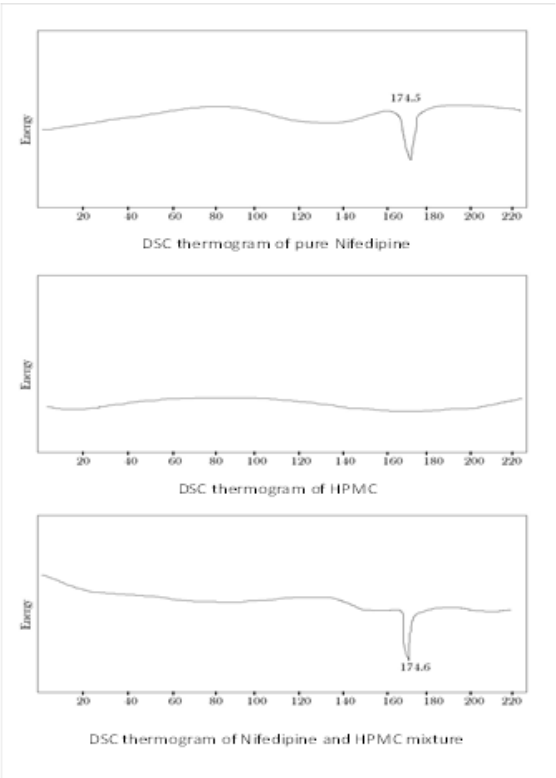

Figure 11: DSC Thermogram of pure Nifedipine, HMPC and its mixture

Storage stability of optimized formulation

The term stability defines itself as the time lapse at which the drug retains the same characteristic properties that possessed at the time of manufacturing process. These studies were performed on the optimized formulation by exposing it to the different temperatures as prescribed in the U.S. FDA and ICH Guidelines. The formulation was kept at different temperature such as 25˚C/60% RH, 30˚C/65% RH and 40˚C/7% for the 15, 30 and 45 days. The stored sample was analyzed for the determination of the changes that occurs in the physical properties, hardness, drug content and compatibility at the specific interval of time.

The result the of the optimized formulation was showing good stability after storing them in different condition no any significance changes were seem in the tablets. The result of the stability studies that were performed on the formulation illustrated in the table 11 which include the physical appearance, thickness and hardness where the compatibility studies were carried out with the help of FT-IR Spectrum[29].[30]

Table 11: Stability Studies that performed on optimized formulation

Formulation	Parameters/Observations								
	Colour			Hardness			Friability		
	15 Days	30 Days	45 Days	15 Days	30 Days	45 Days	15 Days	30 Days	45 Days
Opt. Tablet	No Change	No Change	No Change	9.8	9.8	9.7	0.26	0.26	0.27

4. Conclusion

Box-Behnken architecture was used in the development of the optimal nifedipine press coated tablet, a statistical method. Largely responses and factors were chosen, and the reformulation was fully prepared, accurately described and analyzed the data for ex-vivo permeation. In particular, the different release kinetic of the drug was observed with different polymer and excipient incorporating in the outer and in core composition. By studied more about the polymeric materials we got more behaviour knowledge in the dosage forms and their applications in the dry coating of the different core formulation that was proposed in this present study, safe and more accurate targeting of the drug from the dosage form that can be achieved. The different polymeric properties also effect on the release of the drug.

In the final we study the release mechanism using the data analysis in which we run the dissolution data of the optimized formulation in all four-release model in the result we observed that the formulation comprises of the anomalous transportation of the drug using the erosion, diffusion and swelling mechanism release kinetic that means the formulation shows mixed release kinetic. After overall analysis, it was observed that the design of experiment analysis reduced the efforts and time required to finalize all the data and played crucial role in the selection of optimized parameters based on the results obtained.

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References:

1. Freedman, B. (1987). Treating Angina. Choosing the Most Appropriate Therapy. *Current Therapy (Seaforth)*, *28*(11).
2. Astuti, S. H., Rahma, W. A., & Budianto, E. (2020). Biodegradable Microcapsules from D,L–PLA/PCL as Controlled Nifedipine Drug Delivery Carrier. *Macromolecular Symposia*, *391*(1). https://doi.org/10.1002/masy.201900132.
3. Hansen, J. F., Hagerup, L., Sigurd, B., Pedersen, F., Mellemgaard, K., & Bjergaard, O. P. (1997). Treatment with Verapamil and Trandolapril in Patients with Congestive Heart Failure and Angina Pectoris or

Myocardial Infarction. *American Heart Journal*, *134*(2 II). https://doi.org/10.1016/S0002-8703(97)70008-5.

4. Solanki, P., Singh, R., & Singh, Vishnu Dutt. (2016). Formulation And Evaluation Of Fast Dissolving Tablet: A Review. *World Journal of Pharmacy Research*, *5*(10). https://doi.org/10.20959/wjpr201610-7147.
5. Jeevanandam, J., Chan, Y. S., & Danquah, M. K. (2016). Nano-Formulations of Drugs: Recent Developments, Impact and Challenges. *Biochimie*, *128–129*, 99–112. https://doi.org/10.1016/j.biochi.2016.07.008.
6. Aderibigbe, B., Aderibigbe, I., & Popoola, P. (2017). Design and Biological Evaluation of Delivery Systems Containing Bisphosphonates. *Pharmaceutics*, *9*(1), 1–24. https://doi.org/10.3390/pharmaceutics9010002.
7. Ali, B. H., Inuwa, I., Al Za'Abi, M., Al Bahlani, S., Al Issaei, H., Ramkumar, A., Madanagopal, T., Nemmar, A., Malheiros, D. M., & Zatz, R. (2014). Renal and Myocardial Histopathology and Morphometry in Rats with Adenine-Induced Chronic Renal Failure: Influence of Gum Acacia. *Cellular Physiology and Biochemistry*, *34*(3), 818–828. https://doi.org/10.1159/000363045.
8. Jayaprakash, R., & Natesan, S. K. (2017). Stability Indicating Rp-HPLC Method Development And Validation For The Simultaneous Determination Of Vildagliptin And Metformin In Pharmaceutical Dosage Form. *International Journal of Pharmacy and Pharmaceutical Sciences*, *9*(3). https://doi.org/10.22159/ijpps.2017v9i3.16233.
9. De Abreu Engel, R. E., Thomas Barden, A., Chagas Campanharo, S., Olegário, N., Volpato, N. M., & Scherman Schapoval, E. E. (2019). Evaluation of Linagliptin Dissolution from Tablets Using HPLC and UV Methods. *Drug Analysis Research*, *3*(2). https://doi.org/10.22456/2527-2616.97847.
10. Müller, M., & Keßler, B. (2012). Release of Pamidronate from Poly(Ethyleneimine)/Cellulose Sulphate Complex Nanoparticle Films: An in Situ ATR-FTIR Study. *Journal of Pharmaceutical and Biomedical Analysis*, *66*, 183–190. https://doi.org/10.1016/j.jpba.2012.03.047.
11. Xing, M., Yan, X., Guo, J., Li, W., Li, Z. J., Dong, C., Guo, J., Qu, K., & Luo, Y. (2023). Banzhilian Formula Alleviates Psoriasis-like Lesions via the LCN2/MMP-9 Axis Based on Transcriptome Analysis. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1055363.
12. Shakeel, F., Haq, N., El-Badry, M., Alanazi, F. K., & Alsarra, I. A. (2013). Ultra Fine Super Self-Nanoemulsifying Drug Delivery System (SNEDDS) Enhanced Solubility and Dissolution of Indomethacin. *Journal of Molecular Liquids*, *180*, 89–94. https://doi.org/10.1016/j.molliq.2013.01.008.
13. Solanki, P., Ansari, M. D., & Aqil, M. (2022). Formulation and Development of Pam-PLc Complex Loaded Self Nano-Emulsifying Drug Delivery System (SNEDDS) for the Treatment of Osteoporosis. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.4004050.
14. Solanki, P., Ansari, M. D., Anjali, Khan, I., Jahan, R. N., Nikita, Pandit, J., Aqil, M., Ahmad, F. J., & Sultana, Y. (2021). Repurposing Pentosan Polysulfate Sodium as Hyaluronic Acid Linked Polyion Complex Nanoparticles for the Management of Osteoarthritis: A Potential Approach. *Medical Hypotheses*, *157*. https://doi.org/10.1016/j.mehy.2021.110713.
15. Pankaj, M., Pavitra, K., Mangla, B., & Aggarwal, G. (2022). Formulation Development, Optimization by Box–Behnken Design, and In Vitro Characterization of Gefitinib Phospholipid Complex Based Nanoemulsion Drug Delivery System. *Journal of Pharmaceutical Innovation*. https://doi.org/10.1007/s12247-022-09690-6.
16. Solanki, P., Ansari, M. D., Alam, M. I., Aqil, M., Ahmad, F. J., & Sultana, Y. (2022). Precision Engineering Designed Phospholipid-Tagged Pamidronate Complex Functionalized SNEDDS for the Treatment of Postmenopausal Osteoporosis. *AAPS PharmSciTech*. https://doi.org/10.1007/s13346-022-01259-7.
17. Rathee, A., Solanki, P., Verma, S., Vohora, D., Ansari, M. J., Aodah, A., Kohli, K., & Sultana, Y. (2023). Simultaneous Determination of Posaconazole and Hemp Seed Oil in Nanomicelles through RP-HPLC via a Quality-by-Design Approach. *ACS Omega*. https://doi.org/10.1021/acsomega.3c02097.
18. Khan, I., Pandit, J., Ahmed, S., Zameer, S., Nikita, Ahmad, S., Bano, S., Ansari, M. D., Solanki, P., Jahan, R. N., Waheed, A., Aqil, M., & Sultana, Y. (2022). Development and Evaluation of Biodegradable Polymeric Lomustine Nanofibres for the Efficient Tumor Targeting: In Vitro Characterization, Ex Vivo Permeation and Degradation Study. *Journal of Drug Delivery Science and Technology*, *75*(August), 103685. https://doi.org/10.1016/j.jddst.2022.103685.
19. Dutta, M., Solanki, P., Chaudhary, G., Sahoo, P. K., & Dutt, R. (2023). A Simple Comprehensive Validated Liquid Chromatographic (HPLC) Methodology For Simultaneous Estimation Of 5-Fluorouracil And Cannabidiol. *European Chemical Bulletin*, *12*(12), 2058–2068.
20. Ansari, M. D., Saifi, Z., Pandit, J., Khan, I., Solanki, P., Sultana, Y., & Aqil, M. (2022). Spanlastics a Novel Nanovesicular Carrier: Its Potential Application and Emerging Trends in Therapeutic Delivery. *AAPS PharmSciTech*, *23*(4). https://doi.org/10.1208/s12249-022-02217-9.

21. Dutta, M., Solanki, P., Chaudhary, G., Sahoo, P. K., & Dutt, R. (2023). Development and Validation of HPLC Method for the Simultaneous Estimation. *European Chemical Bulletin*, *12*(12), 10–12.
22. Solanki, P., Sultana, Y., & Singh, S. (2021). Traditional Medicine: Exploring Their Potential in Overcoming Multi-Drug Resistance. In *Strategies to Overcome Superbug Invasions: Emerging Research Opportunities* (pp. 118–129). https://doi.org/10.4018/978-1-7998-0307-2.ch006.
23. Ansari, M. D., Khan, I., Solanki, P., Pandit, J., Jahan, R. N., Aqil, M., & Sultana, Y. (2022). Fabrication and Optimization of Raloxifene Loaded Spanlastics Vesicle for Transdermal Delivery. *Journal of Drug Delivery Science and Technology*, *68*(January), 103102. https://doi.org/10.1016/j.jddst.2022.103102.
24. Ossipov, D. A. (2015). Bisphosphonate-Modified Biomaterials for Drug Delivery and Bone Tissue Engineering. *Expert Opinion on Drug Delivery*, *12*(9), 1443–1458. https://doi.org/10.1517/17425247.2015.1021679.
25. Taha, E. I., Al-Saidan, S., Samy, A. M., & Khan, M. A. (2004). Preparation and in Vitro Characterization of Self-Nanoemulsified Drug Delivery System (SNEDDS) of All-Trans-Retinol Acetate. *International Journal of Pharmaceutics*, *285*(1–2), 109–119. https://doi.org/10.1016/j.ijpharm.2004.03.034.
26. Singh, V. D., & Solanki, P. (2016). Isolation and Standardization of Antioxidant Activity of Bhallatak (Semecarpus Anacardium Linn.). *World Journal of Pharmacy Research*, *5*(10), 1021–1028. https://doi.org/10.20959/wjpr201610-7145.
27. Tiwari, R., Kumar, A., Solanki, P., Dhobi, M., Sundaresan, V., Kalaiselvan, V., & Raghuvanshi, R. S. (2021). Analytical Quality-by-Design (AQbD) Guided Development of a Robust HPLC Method for the Quantification of Plumbagin from Plumbago Species. *Journal of Liquid Chromatography & Related Technologies*. https://doi.org/10.1080/10826076.2021.1973027.
28. Solanki, P., Singh, R., & Singh, S. (2013). Evaluation of Antioxidant Activity of Brinjal (Solanum Melongena). *Journal of Current Science*, *1*(1), 1211–1220.
29. Yin, Q., Tang, L., Cai, K., Tong, R., Sternberg, R., Yang, X., Dobrucki, L. W., Borst, L. B., Kamstock, D., Song, Z., Helferich, W. G., Cheng, J., & Fan, T. M. (2016). Pamidronate Functionalized Nanoconjugates for Targeted Therapy of Focal Skeletal
30. Bandyopadhyay, S., Katare, O. P., & Singh, B. (2012). Optimized Self Nano-Emulsifying Systems of Ezetimibe with Enhanced Bioavailability Potential Using Long Chain and Medium Chain Triglycerides. *Colloids and Surfaces B: Biointerfaces*, *100*, 50–61. https://doi.org/10.1016/j.colsurfb.2012.05.019.