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Research Article

Formulation and Evaluation of Colchicine Sustained release tablet by using factorial designs

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Abstract

The study on the effect of polymer concentration on *in vitro* drug release profile revealed that there is a change *in vitro* drug release parameters (t_{50}, t_{80}, and MDT) with a change in polymer concentration. Fraction of HPMC K4M, HPMC K 100 M, and Ethyl Cellulose were required to be 15, 10, and 7 mg respectively for designing optimized batch F7. The release rate of Colchicine decreased proportionally with an increase in the concentration of ethyl Cellulose and HPMC K100 M. Also the high amount of HPMC K4M leads to the less initial release and sustain effect. A theoretical drug release profile was generated using pharmacokinetic parameters of Colchicine. The value of t_{50} and t_{80} of theoretical drug release profile was found to be 242 min and 529 min respectively. The similarity factor f_2 was applied between the *in vitro* drug release profile of optimizing batches and theoretical profile, which indicate a decent similarity between all *in vitro* drug release profiles (f_2 = 68.28 for F7). All the batches except F1shows the value of f2 value within a range. Batch F7 showed the highest f_2 (f_2 = 68.28) among all the batches and this similarity was also reflected in t_{50} (≈ 256 min) and t_{80} (≈ 554 min) values. A 2^3 full factorial design was applied to systemically optimize *in vitro* drug release profile. The HPMC K4M (X_1), Concentration of HPMC K100 M (X_2), and concentration of EC (X_3) were selected as independent variables. The time required for 50% drug released (t_{50}), the time required for 80% drug release (t_{80}), similarity factor f_2, and mean dissolution time (MDT) were selected as dependent variables. The results of full factorial design indicate that the HPMC K4M (X_1), Concentration of HPMC K100 M (X_2), and concentration of EC (X_3) have a significant effect on *in vitro* drug release profile. To find out the release mechanism the *in vitro* release data were fitted in the Korsmeyer-Peppas equation. All Batches except F1 and F3 show Anomalous diffusion-controlled release (combined mechanism of diffusion and case II transport).

Keywords: Colchicine, Sustained release tablet, 2^3 full factorial design, Similarity factor.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which is characteristic of the conventional intermittent dosage regimen [1]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament to achieve better selectivity and a longer duration of action. Colchicine is a major alkaloid from *Colchicum autumnale L.* and is found also in other Colchicum species. Its primary therapeutic use is in the treatment of gout, but it has been used also in the therapy of familial Mediterranean fever (periodic disease). Although the precise mode of action of colchicine in the treatment of gout is unknown, it is considered to act against the inflammatory response to urate crystals, by possibly

inhibiting the migration of granulocytes into the inflamed area [2].

MATERIALS AND METHOD

Colchicine was a gift sample, provided by Himedia Private Limited, Mumbai Hydroxypropylmethylcellulose K4M, Hydroxypropylmethylcellulose K100M was a gift sample provided by Jaxani Pharmaceutical, Ahmedabad, India. Ethylcellulose, Dicalcium Phosphate, Lactose, Poly Vinyl Pyrrolidone K-30, Iso Propyl Alcohol, Talc, and Magnesium Stearate were used as filler purchased from S.D. Fine Chem. Ltd, Mumbai, India.

METHODOLOGY

Quantity of Colchicine, HPMC K4M, HPMC K100 M, Ethyl Cellulose, Dicalcium Phosphate, and Lactose as per formula was passed through 60 # and were mixed properly [Table 1]. For the preparation of the binder, PVP K -30 was dispersed in IPA. The drug and other excipients were granulated using the above-prepared binder solution. The mass was granulated using 20 #. The granules were dried at 40 ^{o}C. Dried granules were passed through 20 # sieve and the fines were separated using 40 # sieve to obtain 20-40 # granules. These granules were lubricated with a mixture of talc and magnesium Stearate (2:1). The lubricated granules were compressed into tablets using Minipress tablet compression machine [3].

Table 1: Composition of Colchicine Sustained release tablet

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8
Colchicine (mg)	6	6	6	6	6	6	6	6
HPMC K4M (mg)	10	15	20	30	10	15	20	30
HPMC K100 M (mg)	5	15	5	15	5	15	5	15
Ethyl cellulose (mg)	5	5	5	5	10	10	10	10
DCP (mg)	30	30	30	30	30	30	30	30
Lactose (mg)	61	46	51	31	56	41	46	26
PVP K- 30 (%)	5	5	5	5	5	5	5	5
Talc (%)	2	2	2	2	2	2	2	2
Mag. Stearate (%)	1	1	1	1	1	1	1	1

DSC Study

The physicochemical compatibilities of the drug and the used excipients were tested by differential scanning calorimetric analysis [4]. The DSC analysis of the drug alone elicited a peak at 159 °C, very close to the reported value of Colchicine melting point, which is 155-157 °C as shown in Figures 1 and 2.

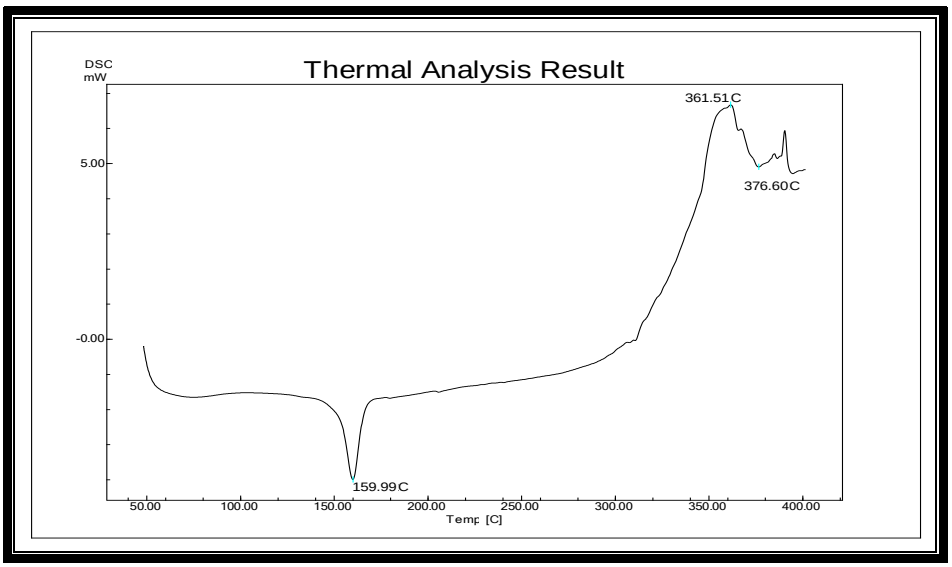

Figure 1: DSC Spectrum of Pure Colchicine

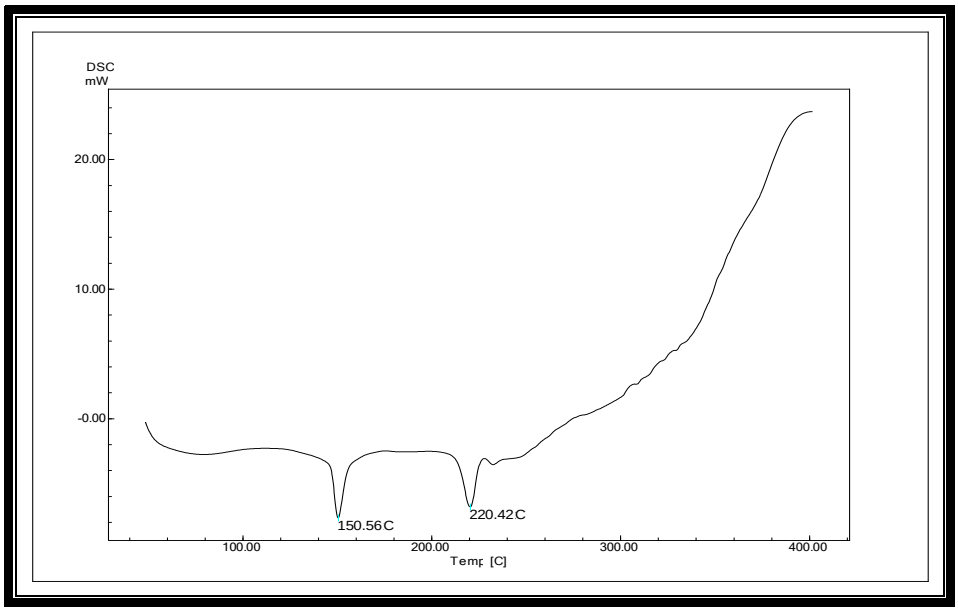

Figure 2: DSC Spectrum of Colchicine & excipients mixture

Evaluation parameters of Granules

Angle of repose [4] : θ = $\tan^{-1}$ (h/r)

Bulk density [5]= Weight of powder/ Bulk volume

Tapped density = Weight of powder/ Tapped volume

Compressibility Index: The Granules was determined by Carr's compressibility index [6].

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Hausner's Ratio: It was determined by the following Equation:

Hausner's Ratio = Tapped Density / Bulk Density

Evaluation of Tablets

Weight variation test: To study weight variation, twenty tablets of the formulation were weighed using a Sartorius electronic balance [7].

Drug content: Five tablets were weighed individually, and powdered. The drug was extracted in 0.1 N HCl and Phosphate buffer pH 6.8, and the solution was filtered through the Whatman filter. The absorbance was measured at 350 nm [8].

Hardness: The five tablets was determined using the Monstan hardness tester [9].

Thickness: The tables were determined by using vernier calipers [10].

Friability: Friability was checked using the Roche friabilator. Pre weighed 10 tablets were rotated for 4 min at 25 RPM [11].

***In-vitro* drug release studies:** Drug release studies were carried out using a USP type -II dissolution rate test apparatus for 2 hr in 0.1 M HCl (900 ml). At the end of the period, 10 ml of the samples were taken and analyzed for Colchicine content [12]. The sample was analyzed using a UV spectrophotometer at 350 nm.

Data Analysis: To analyze the mechanism of drug release from the matrix tablets, the release data were [13] fitted to the following equations:

Zero-order kinetics: $Q_t = Q_o + K_o t$

First-order kinetics: $Q_t = \log Q_o + K_1 t/2.303$

Higuchi model: $Q_t = K_H \cdot t^{1/2}$

Korsmeyer-Peppas release model: $Mt / M_\infty = K \cdot t^n$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, K is a kinetic constant incorporating structural and geometric characteristics of the tablet, and n is the diffusional exponent indicative of the drug release mechanism.

Comparison of dissolution profiles: The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile [14]. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. This similarity factor is calculated by the following formula,

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\}$$

Where n is the number of dissolution times and R_t and T_t are the reference and test dissolution values at time t. The mean dissolution time (MDT) of all batches was calculated using the following equation [15].

$$MDT = \frac{\int_0^\infty t\, dM(t)}{\int_0^\infty dM(t)}$$

Where t is the midpoint between two sampling points and dM(t) is the additional mass in time.

RESULT AND DISCUSSION

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content [Table 2]. All the formulations show values within acceptable limits. Drug Released from Trial Batches after 12 hr Dissolution Study had been shown in the following table 3. It has revealed that

the polymer concentration has a significant effect on the drug release profile. From all these data, it can be seen that Batch T3 and T7 show the release profile matching with the theoretical Profile. Batch T3 shows the F2 Value of 55.58 and batch T7 shows 53.46. Batches T1, T3, T5, and T7 show More than 80 % Drug release after 12 hr. Batches T1 and T5 show initial high release of drug and it release around 80 % drug after 3 hours. So for matching with the theoretical profile, the optimum concentration of all these three polymers is necessary. The average concentration of HPMC K4 M (between 15-30 mg) with less concentration of HPMC K100 M (between 5- 10 mg) and EC (between 5- 10 mg) shows a promising Approach for the development of sustained release dosage form of Colchicine.

Table 2: Evaluation of Preliminary Trial batches for various parameters

Batch	T1	T2	T3	T4	T5	T6	T7	T8
Angle of Repose (θ)	38.65	28.35	26.00	30.75	39.80	24.94	29.05	32.73
Bulk Density (gm/cc)	0.55	0.52	0.50	0.56	0.54	0.52	0.51	0.55
Tapped density (gm/cc)	0.71	0.66	0.58	0.72	0.68	0.62	0.62	0.72
Carr's Index (%)	22.53	21.12	13.79	22.22	20.59	16.13	17.74	23.61
Hausner's Ratio	1.29	1.26	1.16	1.29	1.26	1.19	1.21	1.30
Avg. Weight (mg)	121.04±0.64	120.74±0.65	120.18±0.79	120.19±0.62	120.94±0.77	120.83±0.24	120.87±1.59	120.65±0.49
Drug Content (%)	98.17±0.33	98.58±1.32	98.41±0.83	98.27±1.02	98.25±0.41	99.39±0.99	98.65±0.70	98.44±0.56
Hardness (kg/cm²)	5.66±0.28	5.73±0.11	5.73±0.30	5.66±0.11	5.66±0.41	5.80±0.40	5.86±0.50	5.60±0.20
Friability (%)	0.56	0.34	0.36	0.47	0.52	0.43	0.41	0.38

Table 3: Cumulative percentage drug release from Colchicine Sustained release tablets

Time (Hr)	T1	T2	T3	T4	T5	T6	T7	T8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	35.03	18.41	15.55	13.58	29.13	19.22	15.85	13.04
2	61.09	26.08	26.97	27.33	58.69	26.07	27.29	24.10
3	89.24	36.10	36.93	38.54	79.24	30.03	36.07	31.81
4	89.84	40.62	44.89	43.02	81.84	34.99	43.75	37.03
6	90.05	52.60	56.32	52.72	83.05	47.30	60.22	45.86
8	89.58	62.51	70.53	61.53	86.06	58.29	70.62	55.17
10	89.14	70.79	78.51	68.58	86.58	67.62	77.97	62.59
12	89.07	76.09	87.45	73.12	87.07	74.37	81.95	71.72

Optimization of sustained-release tablet formulation using 2^3 full factorial Designs: It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. The response/s (Yi) is/are measured for each trial and then either simple linear, interactive, or Quadratic Model is fitted by carrying out multiple regression analysis and F-statistics to identify statistically significant terms. A statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$Y = b_o + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1^*X_2 + b_{23}X_2^*X_3 + b_{13}X_1^*X_3 + b_{123}X_1^*X_2^*X_3$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the eight runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1, X_2, and X_3) represent the average result of changing one factor at a time from its low to high value [Table 4].

Formulation of Colchicine Sustained release tablet using 2^3 full factorial designs: Different tablets formulations of Colchicine were prepared by wet granulation method. Drug, hydrophilic polymer, and a hydrophobic polymer, diluents were mixed. PVP K30 was used as the binder in wet granulation [Figure 4 &5]. PVP K30 dissolved in IPA and used as a binder. Bind the above dry mixture with PVP K30 solution till granules are obtained. Pass granules through 20 mesh sieve and dry in the oven at 40 °c for removal of moisture.

Table 4: Formulation and in vitro drug release characteristics of batches in 2^3 Full Factorial Design

Batches	HPMC K4M	HPMC K100M	EC	t_{50}	t_{80}	f_2	MDT
F_1	-1	-1	-1	117	450	43.91	153
F_2	1	-1	-1	268	542	64.44	244
F_3	-1	1	-1	129	496	52.4	178
F_4	1	1	-1	334	630	52.05	265
F_5	-1	-1	1	220	556	54.79	186
F_6	1	-1	1	265	566	66.83	242
F_7	-1	1	1	256	554	68.28	239
F_8	1	1	1	292	590	60.95	255

Independent variable	Real value		
	Low (-1)	Medium (0)	High (1)
HPMC K4M (X1)	15	20	25
HPMCK100M(X2)	3	6.5	10
EC(X3)	3	5	7

Table 5: Composition of Factorial Design batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Colchicine	6	6	6	6	6	6	6	6
HPMC K4 M	15	25	15	25	15	25	15	25
HPMC K100 M	3	3	10	10	3	3	10	10
Ethyl cellulose	3	3	3	3	7	7	7	7
DCP	30	30	30	30	30	30	30	30
Lactose	60	50	53	43	56	46	49	39
PVP K- 30 in IPA	5 %	5 %	5 %	5 %	5 %	5 %	5 %	5 %
Talc	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %
Mag. Stearate	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %

In vitro drug release Study: The *in vitro* release profile of formulations for 12 hours was tested according to the procedure described earlier. The *in vitro* drug release profiles of factorial batches are shown in Table 6. The statistical analysis of the factorial design batches was performed by multiple linear regression analysis. The t_{50}, t_{80}, f_2, and MDT values for the 8 batches (F1 to F8) showed a wide variation. The values of the correlation coefficient indicate a good fit.

Table 6: % Drug Release of Factorial Design batches after 12 Hr

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F8	THR
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	27.62	18.73	32.02	16.53	21.78	22.98	24.59	18.73	31.00
2	38.83	31.59	47.49	27.93	36.03	34.29	33.00	32.35	37.27
3	61.93	43.11	58.64	35.51	50.12	42.81	44.14	42.18	43.54
4	76.72	50.10	64.87	41.85	59.91	49.74	51.12	47.51	49.81
6	88.10	67.54	77.41	56.21	75.78	64.56	66.31	60.20	62.36
8	91.54	79.52	83.56	70.50	81.63	77.54	78.27	73.39	74.90
10	92.69	87.65	89.02	77.23	83.14	84.39	86.71	82.13	87.45
11	92.77	90.35	90.13	82.12	84.53	86.85	88.45	85.22	93.72
12	93.23	92.10	91.49	83.87	85.89	89.97	90.98	88.34	100.00

The F2 shows less initial release compared to F6 and F7 because it contains a higher amount of HPMC K4M which sustains the profile. From Batches F2, F6, and F7, batch F7 shows higher similarity than others with the theoretical profile. also, it shows a higher f2 value than all other batches. (68.28) and it shows higher release in the initial period and sustains the release till 12 hrs matching with theoretical profile [Table 7].

Table 7: Summary of Regression analysis of Colchicine tablet

Coefficients	t_{50}	t_{80}	f2	MDT
b_o	235.125	548	57.95625	220.25
b_1	54.625	34	3.11125	31.25
b_2	17.625	19.5	0.46375	14
b_3	23.125	18.5	4.75625	10.25
b_{12}	5.625	8.5	-5.03125	-5.5
b_{23}	-1.875	-14	1.43875	2.5
b_{13}	-34.375	-22.5	-1.93375	-13.25
b_{123}	-7.875	-2.0	-1.93	-4.5
R^2	0.9939	0.9992	0.9997	0.9932

Comparison of *In-vitro* Drug Release Profile: The similarity factor, f_2, given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profiles. The f_2 value for 68.28 of batch F7 indicates less difference *in vitro* drug release profile with theoretical release profile [Table 8 & 9]. The similarity between the theoretical release profile and the *in vitro* drug release profile of F7.

Table 8: Comparison of checkpoints between F7 batch and Theoretical profile

Check Points	Theoretical value	Batch F7
t_{50} (min)	242	256
t_{80} (min)	529	554
f_2	50 - 100	68.28
MDT (min)	278	239

Table 9: Comparison of % Drug Release of various batches after 12 Hr.

Time (Hr)	F2	F6	F7	THEORETICAL
0	0.00	0.00	0.00	0.00
1	18.73	22.98	24.59	31.00
2	31.59	34.29	33.00	37.27
3	43.11	42.81	44.14	43.54
4	50.10	49.74	51.12	49.81
6	67.54	64.56	66.31	62.36
8	79.52	77.54	78.27	74.90
10	87.65	84.39	86.71	87.45
11	90.35	86.85	88.45	93.72
12	92.10	89.97	90.98	100.00

Kinetic Modeling and Mechanism of Drug Release

All batches showed a higher correlation with the Higuchi plot than zero order and first order. Batch F1 and F3 showed Fickian diffusion-controlled release whereas other batches show the anomalous effect (combined mechanism of diffusion and case II transport). For Higuchi Model, all the batches except F1 show an r^2 value of more than 0.925 [Table 10]. .

Table 10: Kinetic modeling of Factorial Design batches: R^2 Value, n value, and Release Mechanism

Batch	Zero-order r^2	First-order r^2	Higuchi r^2	Korsmeyer- Peppas		Release Mechanism
				r^2	n	
F1	0.768	0.434	0.925	0.905	0.496	Fickian Diffusion
F2	0.941	0.542	0.989	0.991	0.643	Anomalous Diffusion
F3	0.817	0.411	0.971	0.976	0.412	Fickian Diffusion
F4	0.962	0.569	0.987	0.997	0.657	Anomalous Diffusion
F5	0.841	0.472	0.965	0.951	0.543	Anomalous Diffusion
F6	0.934	0.509	0.996	0.997	0.558	Anomalous Diffusion
F7	0.931	0.505	0.995	0.994	0.554	Anomalous Diffusion
F8	0.945	0.533	0.994	0.993	0.609	Anomalous Diffusion

Formulation and Evaluation of optimized Batch

Tablets were prepared by the wet granulation method as discussed earlier and evaluated for various evaluation tests like Flow properties, Hardness, Friability, Average weight, *In-vitro* Drug Release. Results have been shown in the following table 11 & 12.

Table 11: Evaluation Parameters of Factorial Design Batches

Parameters	Value		Parameters	Value
Angle of Repose	26.75		Hardness	5.66 ± 0.34
Bulk Density	0.53		Friability	0.58
Tapped Density	0.62		Avg. Wt	120.18 ± 0.98
Carr's Index	14.51		Drug content	98.42 ± 1.04
Hausner's Ratio	1.16			

Table 12: % Drug release of optimized batch after 12 Hr

Time (Hr)	A1	A2	A3	A4	A5	A6	THR
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	23.78	24.16	24.35	23.87	22.89	25.88	31.00
2	32.84	32.00	34.56	33.56	32.16	36.69	37.27
3	44.36	45.97	45.90	45.84	43.54	45.65	43.54
4	50.59	52.63	51.57	52.21	53.21	53.25	49.81
6	65.40	66.98	65.23	68.43	67.23	68.11	62.36
8	72.66	80.11	79.86	79.62	78.87	78.97	74.90
10	87.38	86.86	87.50	87.84	89.39	86.39	87.45
11	89.42	89.23	89.45	90.19	90.85	90.85	93.72
12	90.41	90.87	90.67	91.82	92.51	90.64	100.00

Optimized batch shows very good flow properties. It shows all the value within its range. The hardness varies in the range of 5-6 kg/cm^2. All six tablets show a good dissolution profile, matching well with the theoretical profile. It shows more than 90 % drug release after 12 Hrs.

CONCLUSION

After the trial work, it was concluded that batch T3 showing a promising future for factorial design to optimize the concentration of sustained-release polymer with hardness at 5-6 Kg/cm^2. The release rate of Colchicine decreased proportionally with an increase in polymer viscosity and polymer concentration. A 2^3 full factorial design was applied to systemically optimize *in vitro* drug release profile. The HPMC K 4 M (X_1), HPMC K100M (X_2), and Ethyl Cellulose(X_3) were selected as independent variables. The time required for 50% drug released (t_{50}), the time required for 80% drug release (t_{80}), similarity factor f_2, and mean dissolution time (MDT) were selected as dependent variables. The similarity factor f_2 was applied between the *in vitro* drug release profile of factorial design batches and the theoretical drug release profile. Batch F7 showed the highest f_2 (f_2 = 68.28) among all the batches. All the batches show good linearity with Highchi's equation. From *in vitro* drug release profile of all batches, batch F7 indicates similarity with desired release profile.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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