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Factorial Design Experiments for Preparing Sustained Release Matrix Tablets of Meclizine HCl

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ABSTRACT

Aim: Aim of this work was to formulate and evaluate the sustained release matrix tablet of drug, Meclizine HCl. **Methods:** In this present study sustained release matrix tablets of meclizine HCl were prepared by direct compression method using Carbopol 934 and HPMC K4M in different concentrations. Optimization was performed as per 3^2 factorial design. The concentrations of HPMC K4M and Carbopol 934 were chosen as independent variables with levels coded as -1, 0 and +1, while drug release and swelling index were chosen as dependent variables. **Result:** The results for pre compression parameters showed that tablet have good flowability and all the results obtained for pre compression and post-compression parameters were in range as per IP. In F1 to F9 formulation the F7 that is (60:30) (HPMC K4 M and Carbopol934) formulation gives the more sustained release as compared to other formulations. As it has higher concentration of HPMC K4M in it. **Conclusion:** The sustained release matrix tablets of Meclizine HCl were formulated using Carbopol 934 and HPMC K4 M polymer gives the sustained release.

INTRODUCTION

Sustained release system is a type of modified drug delivery system that can be used as an alternative to a conventional system. Among different dosage forms, matrix tablets are widely accepted for oral sustained release [2]. Matrix tablets may be defined as the, oral solid dosage form in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serve as release rate retardants. Matrix tablets release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion-controlled mechanisms**.**

The present study is aimed to formulate and develop Meclizine hydrochloride (MCZ) sustained release matrix tablet using direct compression technique. MCZ is first generation antihistamine piperazine class drug. which is used in the treatment of motion sickness.(1) Matrix tablet is one of the most convenient approach for preparation of sustained release dosage forms. In actual practice direct compression of drug, retardant material, and additives is done to form a tablet in which drug particles are embedded in the matrix core of the retardant.(2)

With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for a prolonged period. The design of an efficient dosage form is an important element in achieving this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, and depot dosage forms are terms used to describe drug delivery systems that are intended to provide a long-term therapeutic benefit. (3)

In the case of an oral sustained-release dosage form, the effect lasts for several hours, depending on the formulation's residence period in the GIT. A physician can achieve several desirable therapeutic advantages by prescribing a sustained release dosage form (3).

Advantages:

- Decreased local and systemic side effects.
- Better drug utilization
- Better patient compliance

Disadvantages

- Dose Dumping
- Reduced potential for dose adjustment
- SR dosage form are expensive.

POLYMERS USED IN MATRIX TABLET [23]

1. **Hydrophilic Polymer-** Hydrophilic Polymers are those polymers that dissolve in or are swollen by water.eg-Polythene glycol, Polyvinyl pyrrolidone.
2. **Hydrophobic Polymer-** Are material that are not soluble in water or other polar solvents.eg polyethylene vinyl acetate, poly dimethyl isiloxane, polyether urethane.
3. **Hydrogels-** A hydrogel is a crosslinked hydrophilic polymer that does not dissolve in water. They are highly absorbent yet maintain well defined structures.
4. **Biodegradable polymers-** Biodegradable polymers are a special class of polymers that breaks down after their intended purpose by bacterial decomposition process to result in natural byproducts.
5. **Mucoadhesive polymers-** Mucoadhesive polymers are water-soluble and water-insoluble polymers.

In the present work, Sustained release matrix tablets of Meclizine HCl were prepared by direct compression technique. Trial batches were prepared. Optimization was carried out by 3^2 Factorial design Using Design- Expert software version 11. Preformulation parameters such as bulk density, tapped density were studied. After that post compression parameters such as Friability, Hardness, are Thickness were performed. Invitro dissolution study and swelling index for optimized Formulations F1-F9 was carried out. The in-vitro drug release data of all formulations were analyzed for determining the kinetics of drug release.

MATERIALS

Meclizine HCl was obtained as a gift sample from Harika Lab, Sangareddy. Other chemicals such as HPMC K4M, and Carbopol 934 were purchased from MSN Labs Limited, Hyderabad. Microcrystalline cellulose and talc were purchased from Loba chemicals Mumbai.

METHODS

Preparation of sustained release matrix tablets

Matrix tablets of meclizine HCl were prepared by direct compression technique. Ingredients except glidant and lubricant were individually screened. The required quantity of drug, polymer, and diluent were weighed and mixed in a polybag. The obtained blend was lubricated with talc and magnesium stearate. The resultant mixture was directly compressed into tablet by using 6 mm Punch. with the help of tablet punching machine. (RIMEK MINI PRESSII MT)[4]

Formulation of trial batches

Formulation of trial batches was done and *in-vitro* drug release study was performed.

Ingredients	**Trial batches**		
	T1	T2	T3
Meclizine HCl	40	40	40
HPMC K4M	40	-	-
Carbopol 934	-	40	20
MCC	20	20	20
Talc	2	2	2
Total(mg)	102 mg	102mg	102mg

In vitro dissolution studies of trial batches

The USP type II paddle apparatus was used to study the drug release from the tablet. The dissolution medium consisted of 900 ml of 0.1 N HCL for 2 h and 900 ml of phosphate buffer pH 6.8 for the next 6 h. Test was performed at 37 ± 0.5˚C with a rotation speed of 50 rpm. Samples were withdrawn after 1h,2h, 4h, and 8h and replaced with fresh medium to maintain sink conditions.

The percentage of drug release at the 2nd hour of T1 to T3 formulations was in the range of 8.18, 33.65, and 21.56 % respectively. The T3 Formulation releases 20% of the drug in the 2nd hour. So, the T3 formulation was able to give sustained release.

Factorial Design[25][26]

For optimizing the formulation tablets 3^2 full factorial design was used. The concentrations of HPMC K4M and Carbopol 934 were chosen as independent variables with levels coded as -1, 0, and +1, while drug release at 8^{th} h and swelling index were chosen as the dependent variables. Design-Expert software version 11 was used to optimize the formulation. The optimized formulation was later again tested for the drug release and swelling index. Batches prepared for optimization are given in table 3. The layout of the experimental design is given in table 4. Two factors were evaluated each at three levels and experimental trials was performed at all possible nine combinations as shown in table 3.

Table 2: 3^2 full factorial design for optimization of meclizine HCL tablets

Sr no	Factors				Response
1	HPMC K4M	-1	0	1	% drug release at 8h
2	Carbopol 934	-1	0	1	% swelling index

Formulation of Factorial batches (F1 – F9)

Nine batches F1-F9 of Meclizine HCl were prepared to vary the compositions of the polymers used as shown in Table 4.

TABLE 3: OPTIMIZATION OF MECLIZINE HCL MATRIX TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Meclizine HCl	25	25	25	25	25	25	25	25	25
HPMC K_4M	45	60	30	45	30	30	60	45	60
Carbopol 930	60	60	60	30	30	45	30	45	45
Microcrystalline cellulose	25	10	40	55	70	55	40	40	25
Talc	5	5	5	5	5	5	5	5	5
Average weight (mg)	160	160	160	160	160	160	160	160	160

Pre-compression Studies [3][5]

All formulation blends were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hauser's ratio The two most important attributes of the direct compression formula are good flow and good compressibility.

Angle of Repose :[3]

For determination of the angle of repose (θ), the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above the hard surface. The drug or the blend was poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using the following equation.

$$\text{Tan}\ (\theta) = h / r \ ^{(8)}$$

Where θ = Angle of repose, h = Height of Stack, r = Radius of the pile

Bulk Density [17]

It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the initial weight was noted. This initial volume was called the bulk volume. From this, the bulk density was calculated according to the formula mentioned below.

$$\text{Bulk density} = M / V_0 \ ^{(17)}$$

Where M=mass of powder, V_0 = Bulk volume of powder

Tapped Density [17]

Weighed powder sample was transferred to a graduated cylinder and the cylinder was placed On the tap density apparatus, which was operated for fixed number of taps . The tapped density was determined by the following formula

$$\text{Tapped density} = M / Vr^{(17)}$$

Where M=Mass of powder Vr= final(Tapped) Volume of Powder

Compressibility Index and Hausner Ratio

Measure the unsettled apparent volume, (V_0) and the final tapped volume, (Vf) of the powder after tapping the material until no further volume changes occur .it is given by

$$\textbf{Compressibility Index} = \frac{1-\text{Bulk density}}{\text{Tapped density}} \times 100 \ ^{(16)}$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad ..(16)$$

Post-compression Parameters[5]

Hardness, Friability, and Thickness

For each formulation, the hardness of six tablets was measured using the Monsanto hardness tester and the mean value and standard deviation was calculated. Friability of the prepared formulations was determined by using Roche Friabilator (Lab India). Pre-weighed sample of tablets was placed in the friability tester, which was then operated for 100 revolutions. Tablets were dedusted and reweighed. The friability of the tablets was calculated using the formula mentioned below,

$$\text{The \% friability} = \frac{W1 - W2}{W1} \times 100$$

W_1= Weight of tablets before test W_2=Weight of the tablets after the test

The thickness of the tablet was determined using a Vernier caliper. Six tablets from each batch of formulation were used and the mean thickness value and standard deviation were calculated for each formulation.

***Invitro* Dissolution Test**

The USP type II paddle apparatus was used to study the drug release from the tablet. The dissolution medium consists of 900 ml of 0.1 N HCL for 2 h and 900 ml of phosphate buffer 6.8 for the next 6 h. The test was performed at 37 ± 0.5 °C with a rotation speed of 50 rpm. Samples were withdrawn after 1h,2h,4h, and 8h and replaced with fresh medium to maintain sink conditions The samples were filtered with appropriate dilutions with phosphate buffer pH 6.8 and were analyzed spectrophotometrically by using UV – Visible spectrophotometer V730 at 238 nm.

Release kinetics of drug release profile :[8]

The *invitro* drug release data of all formulations were analyzed with the help of DD solver software. For determining the kinetics of drug release. The obtained data were fitted to zero-order kinetics, first-order kinetics, and the Higuchi model.

Swelling Index:

Initially, all tablets were weighed. Then the tablet was placed in 50 ml of 0.1 N HCL for 2 h. After a specific interval tablets were withdrawn and placed on tissue paper to remove excess of buffer. Same procedure was repeated For the next 6 h with a change in medium i.e with Phosphate buffer pH 6.8. Initial weight(M_0) and final weight(M_t)of the tablet was calculated the swelling index was calculated with the formula.

Swelling Index(SI)[27]=

$$SI=\frac{(Mt-M0)}{M0} X\ 100^{(27)}$$

Where, Mt = weight of tablet at the time (t) and Mo = weight of tablet at time= 0

RESULTS AND DISCUSSION

Pre-compression Parameters

Table 4: Pre compression parameters of Meclizine HCL Tablets

Formulation	Bulk density Mean ±SD	Tapped density Mean ±SD	Carr's index Mean ±SD	Hausner'sratio Mean ±SD	Angle of repose Mean ±SD
F1	0.43 ±0.11	0.70±0.09	33.37±0.09	1.62±0.05	40˚27±0.11
F2	0.41±0.13	0.60±0.08	31.34±0.06	1.48±0.06	44˚47 ±0.14
F3	0.37±0.35	0.5±0.06	34.66±0.06	1.55±0.08	39˚32±0.15
F4	0.40±0.37	0.55±0.04	24.44±0.05	1.31±0.09	36˚43±0.15
F5	0.37±0.35	0.45±0.09	36.76±0.08	1.31±0.05	29˚32±0.15
F6	0.39±0.43	0.49±0.11	32.78±0.09	1.26±0.05	38˚32 ± 0.15
F7	0.41±0.37	0.52±0.06	28.66±0.06	1.38±0.06	31˚73±0.15
F8	0.37±0.38	0.49±0.08	35.66±0.08	1.25±0.04	32˚54±0.15
F9	0.38±0.66	0.50±0.05	34.28±0.02	1.3±0.03	36˚53± 0.15

Mean n=3

Results of Pre-compressional parameters performed on the blend of batch F1 – F9 are reported in Table 6 . The angle of repose for F1, and F2 batches was > 40 indicating the flow was very poor and the angle of repose < 40 indicating that the flow was good.

Post-compression Parameters

Post compression parameters of tablet were evaluated, and all the results were found to be within the Indian Pharmacopeial standards these are mentioned in following Table 7.

Table 5: Post compression parameters of Meclizine HCL Tablets

Formulation	Thickness(mm) Mean ±SD	Hardness(kg) Mean ±SD	Friability(%) Mean ±SD
F1	5.2±0.17	5.79±0.50	0.19±0.35
F2	4.9±0.18	5.83±0.53	0.22±0.34
F3	5.1±0.15	5.8±0.42	0.26±0.05
F4	5.3±0.15	5.98±0.46	0.25±0.06
F5	5.4±0.15	5.76±0.52	0.21±0.05
F6	5.0±0.14	5.70±0.49	0.17±0.045
F7	5.2±0.09	5.52±0.49	0.18±0.061
F8	5.3±0.08	5.50±0.55	0.10±0.05
F9	5.3±0.07	5.66±0.35	0.14±0.04

n=3

Tablets hardness was in the range of 5.50±0.55 to 5.98±0.46 kg/cm^2 . For all the prepared formulations friability percentage was less than 1% and results obtained were in acceptable limit.

***In vitro* Dissolution Studies**

The formulations of Meclizine HCL were subjected to in-vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium was 900 ml of standard buffer pH 1.2 for the first 2 hours, followed by pH 6.8 for the rest of the time. Release of meclizine HCl from the various formulations of sustained release tablets varied according to the ratio and degree of the different polymers.

Table 6: *In-vitro* drug release study

Time	F1 Mean ±SD	F2 Mean ±SD	F3 Mean ±SD	F4 Mean ±SD	F5 Mean ±SD	F6 Mean ±SD	F7 Mean ±SD	F8 Mean ±SD	F9 Mean ±SD
1	11±0.34	9.84±0.33	12.95±0.57	10.02±0.51	10.52±0.5	10.72±0.50	8.20±0.45	10.73±0.50	11.23±0.41
2	17.22±0.37	18.69±0.35	23.29±0.44	24.42±0.56	28.45±0.49	36.42±0.5	17.23±0.23	23.47±0.42	26.44±0.39
4	42.54±0.41	33.35±0.43	34.54±0.28	44.24±0.49	44.61±0.45	54.28±0.46	31.31±0.45	36.42±0.59	39.22±0.5
6	66.50±0.45	56.39±0.35	64.20±0.50	58.48±0.5	63.86±0.55	65.44±0.4	42.20±0.50	56.52±0.37	54.32±0.44
8	80.44±0.44	71.32±0.44	92.53±0.51	76.45±0.6	83.80±0.55	89.47±0.48	57.02±0.46	78.00±0.76	66.00±0.25

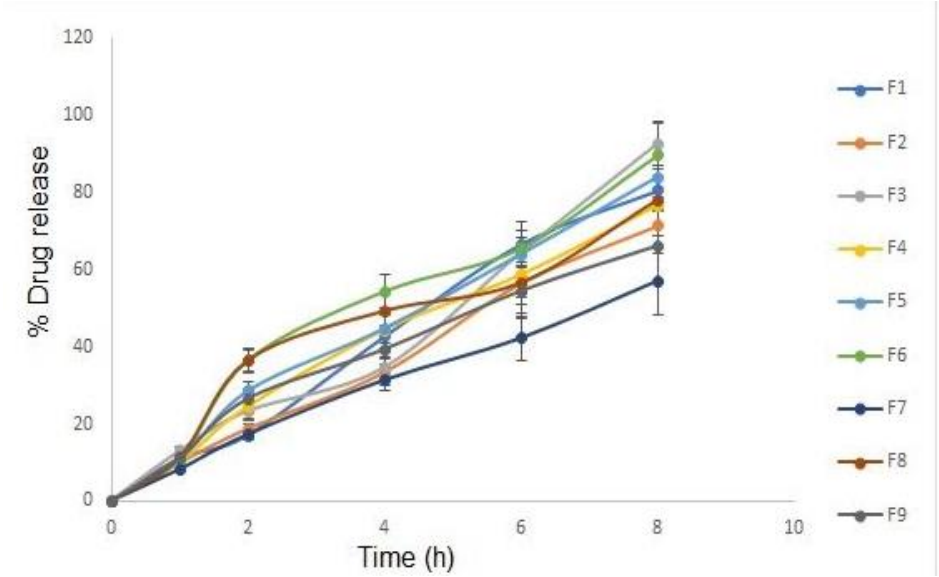

Fig 1: *In-vitro* drug release studyof formulations F1-F9

The % drug release of the optimized batches F1 to F9 is given in Figure 1. The study shows that during 8 hours of study. Polymer concentration in each formulation sustains the drug release. In F1 to F9 formulation. The F7 that is (60:30) (HPMC K4 M and carbopol934) formulation gives the more sustained release as compared to other formulations shown in table 8. The release rate of Meclizine HCl from the tablets decreases as the concentration of HPMC K4M increases. Because HPMC K4M swells faster and forms the gel which helps to retard the drug release. This helps to give sustained release of the drug over a longer period.

Table 7: Release kinetics of drug release profile:

Batch code of formulation	Zero order	First order	Higuchi model	Hixon-Crowell model	Korsmeyer peppas model		Best fit model	Drug
	R^2	R^2	R^2	R^2	R^2	n		
F1	0.9912	0.9922	0.8660	0.9750	0.9923	0.997	Korsmeyer peppas model	Non-fickian diffusion
F2	0.9951	0.9588	0.8730	0.9819	0.9963	0.998	Korsmeyer peppas model	Non-fickian diffusion
F3	0.9693	0.9919	0.8305	0.9297	0.9850	1.140	Korsmeyer peppas model	Non-fickian diffusion
F4	0.9682	0.9750	0.9148	0.9949	0.9965	0.858	Korsmeyer peppas model	Non-fickian diffusion
F5	0.9890	0.9732	0.9095	0.9871	0.9953	0.875	Korsmeyer peppas model	Non-fickian diffusion
F6	0.9536	0.9688	0.9255	0.9768	0.9786	0.770	Korsmeyer peppas model	Non-fickian diffusion
F7	0.9683	0.9738	0.9092	0.9969	0.9981	0.885	Korsmeyer peppas model	Non-fickian diffusion
F8	0.9721	0.9620	0.8850	0.9781	0.9944	0.961	Korsmeyer peppas model	Non-fickian diffusion
F9	0.9730	0.9630	0.9485	0.9981	0.9947	0.745	Korsmeyer peppas model	Non-fickian diffusion

From the Correlation coefficient values, the first order was the best fitting model for the Meclizine HCl release. Higher R^2 values were obtained for the entire release process showed that the first order release was the best fit model. The R^2 values for the zero-order release were in the range of 0. 8721 – 0. 9951 for the first-order release it was 0.9588 –0.9922, Higuchi plot it was 0.8305 – 0.9485. To confirm the drug release mechanism the data were fitted into Korsmeyer's model and all the formulations showed good linearity (R^2 = 0.9786 – 0.9981) with diffusional Co-efficient (n) values ranging from 0.745 – 1.14 indicating that diffusion was the mechanism of drug release.

Swelling index

Swelling index was calculated with formula. The results were plotted in table below:

Table 8 % swelling index

Formulation	1h	2h	4h	6h	8h
F1	72±0.27	91±0.14	108±0.84	122±0.64	137±0.65
F2	75±0.48	102±0.12	128±0.28	152±0.86	166±0.33
F3	48±0.54	65±0.18	88±0.33	108±0.43	128±0.28
F4	74±0.36	95±0.43	110±0.43	139±0.05	160±0.75
F5	71±0.85	92±0.65	102±0.75	121±0.69	142±0.23
F6	80±0.44	87±0.75	103±0.65	122±0.76	136±0.44
F7	58±0.76	98±0.76	123±0.32	158±0.06	189±0.59
F8	50±0.6	78±0.65	92±0.55	114±0.57	144±0.34
F9	56±0.66	105±0.09	120±0.52	148±0.88	178±0.20

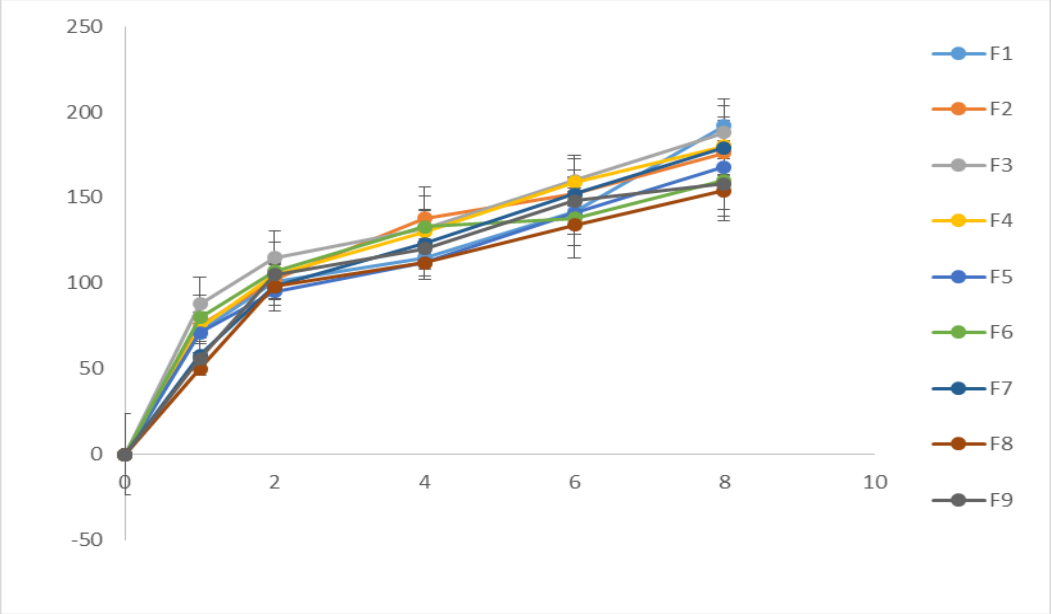

Fig 2. % swelling index of formulations F1-F9

The % swelling index of the optimized batches F1 to F9 is given in Fig.2 In F1 to F9 formulation. The swelling index of Meclizine HCl from the tablets increases as the concentration of HPMC K4 M increases. and swelling index increases as the concentration of Carbopol 934 decreases. As a result formulation F7 shows the highest swelling index (189

%). The swelling index ranges from 128 % to 189 %.depending on the concentration of polymers.

Experimental Design

For optimization of the co-crystal tablet formula, a 3^2 full factorial design was constructed. The design consists of 9 experimental runs to evaluate the significance of the concentration of HPMC K4 M and Carbopol 934 on drug release and swelling index. Quantitative effects of the independent variable in the obtained equation are mean results obtained by changing one factor from its low to high value while keeping another factor constant.

The results are visualized with the help of 3D response Surface Graphs.

Table 9: Experimental run &responses for optimization

	Factor 1	Factor 2	Response 1	Response 2
RUNS	Carbopol 934	HPMC K4M	% drug release	% swelling index
1	60	45	80.44±0.44	137±0.65
2	60	60	71.32±0.45	166±0.33
3	60	30	92.44±0.51	128±0.28
4	30	45	76.45±0.6	160±0.75
5	30	30	83.80±0.48	142±0.23
6	45	30	89.47± 0.44	136±0.44
7	30	60	57.04±0.46	189±0.59
8	30	45	78.00± 0.76	144±0.34
9	45	60	66.00± 0.25	178±0.20

Analysis of optimization data

The formulations prepared as per the experimental design were evaluated and the analysis of experimental results was done by using Stat-Ease Design Expert. The ANOVA, P-value, and Model F-value were obtained. The drug release values between experimental batches varied between 8.20±0.45 to 92.44±0.51. The swelling index varied between 50 to 189 %. The response surface graph shows the inverse effect of HPMC K4M on drug release. While HPMC K4M has direct effect on Swelling Index. And Carbopol 934 has direct effect on drug release. Thus the formulation batch giving % drug release was chosen as the optimized batch

based on the desirability function. The optimized formula was subjected to verification and no significant difference was seen between the theoretical and actual values.

$$\text{Swelling index}== +153.33 + 21.17 * A - 10.00 * B - 2.25 * A * B$$

$$\text{Drug release} = +76.89 - 11.67 * A + 4.50 * B + 1.25 * A * B$$

The two-factor interaction model was found to be significant with p values If the p-value is less than or equal to the significance level, you can conclude that there is a statistically significant association between the response variable and the term. A higher the value of R^2 indicates better fit of model to data. Adequate precision denotes signal-to-noise ratio. It compares the range of the predicted values at the design points to the average prediction error. Ratios greater than 4 indicate adequate model discrimination.

Table 10: ANOVA output for optimization of Meclizine HCl

Sir no	Outcomes	Drug release	Swelling index
1	Models	2FI	2FI
2	R^2 Value	0.9772	0.9426
3	F – Value	22.88	27.35
4	P – Value	0.0021	0.0016

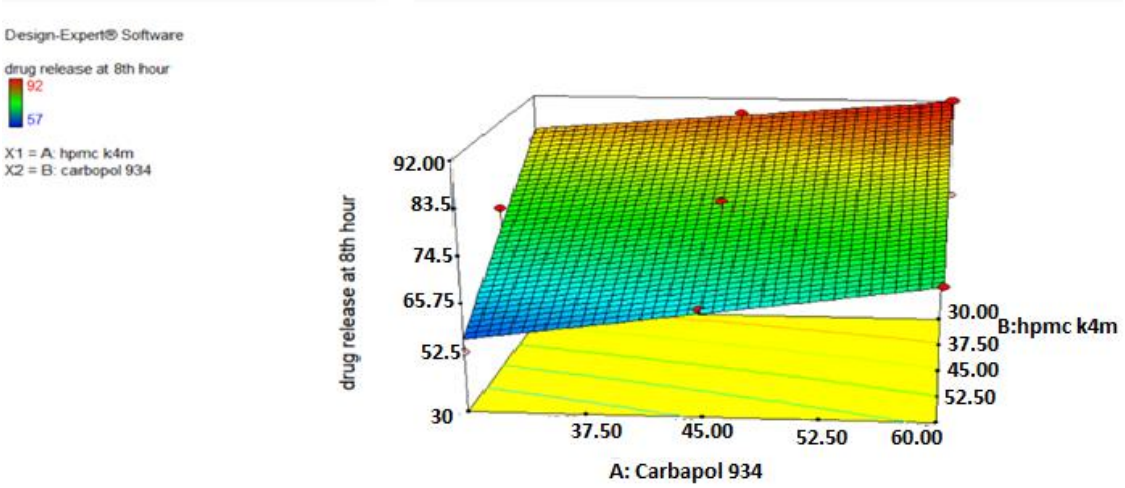

Fig 3: Response surface plot (3D) showing the effect of Carbopol 934 and Him K4M on % drug release

The 3D graph shows that, the drug release from the matrix tablet decreases as the concentration of HPMC K4Mincreases. It is due to the faster swelling of the HPMC K4M.

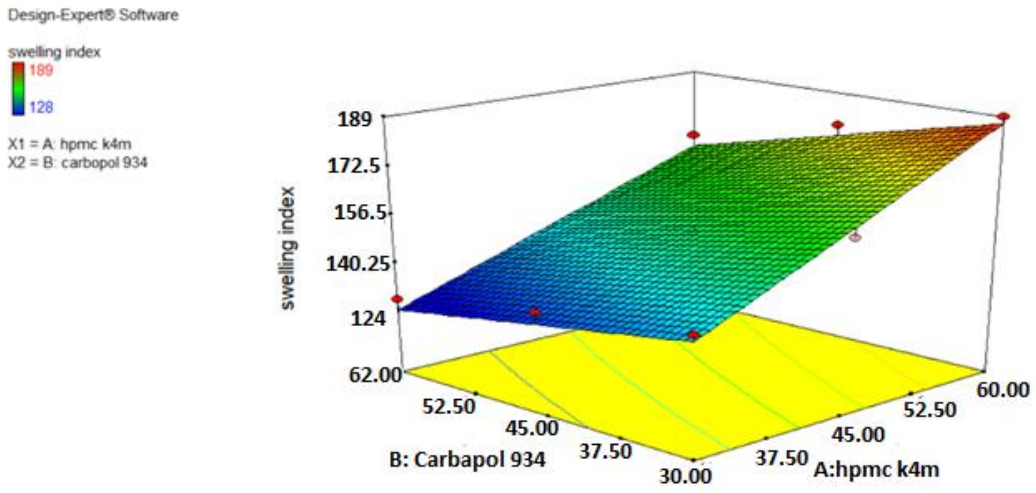

Fig 4: Response surface plot (3D) showing the effect of Carbopol 934 and HPMC K4M on % Swelling index

CONCLUSION

Sustained release dosage forms are intended to provide a therapeutic effect for an extended period. Meclizine HCL is an antihistamine used to treat vomiting nausea Dizziness and motion sickness. The present research is directed towards the development of formulation and evaluation of sustained release matrix tablets of Meclizine HCl to improve the bioavailability of the Meclizine HCl**.** HPMC K4 M and Carbopol 934 polymers were used for formulating a sustained release dosage form. The HPMC K4 M is a hydrophilic polymer with good drug holding capacity due to the formation of a gel, which delays drug release and gives sustained release over a longer period of time. The higher concentration of the HPMC K4 M in the matrix tablet can retard the drug release which gives the sustained release for a longer period. Selected polymers and their concentrations are also capable of sustaining the drug release of Meclizine HCl The In- vitro dissolution study of the Meclizine HCl matrix tablet also shows that the HPMC K4 M and Carpool 934 were able to give sustained release over a longer period of time.

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