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TO EVALUATE RHEOLOGICAL SYNERGISM BY COMBINING HYDROPHILIC POLYMERS AND OPTIMIZATION BY SIMPLEX MIXTURE DESIGN

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ABSTRACT: It appears that you have conducted a study on the preparation of Glipizide sustained-release tablets using different HPMC (hydroxypropyl methylcellulose) polymers of varying viscosity grades, specifically HPMCK 4M and HPMC K 15M, in different proportions. The concentration of the polymers was optimized using a simplex mixture design, with HPMC K4M, HPMC K15M and lactose as the components of the mixture. The tablets were prepared using the wet granulation method. According to your study, the prepared tablets exhibited polymeric synergism, which was confirmed through in-vitro dissolution testing. Both HPMC K4M and HPMC K15M showed a synergistic effect on the T50% drug release. However, HPMC K15M demonstrated a dominant effect compared to HPMC K4M due to its higher viscosity. It seems that the higher viscosity of HPMC K15M contributed to a more sustained drug release profile in the tablets. This finding suggests that HPMC K15M played a more significant role in controlling the release rate of Glipizide from the tablets, as compared to HPMC K4M.

INTRODUCTION: In the present work, the concept of rheological synergism was explored by combining two hydrophilic polymers, HPMC K4M and HPMC K15M, with lactose as a filler in the formulation of sustained-release tablets. The model drug used in this study was Glipizide. The aim was to optimize the composition of the formulation using a simplex mixture design in order to achieve the desired *in-vitro* drug release profile. Hydrophilic matrix systems are a type of sustained-release dosage form where the drug is uniformly dispersed within a hydrophilic polymer matrix along with a water-soluble or insoluble filler.

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The release of the drug from the matrix occurs primarily through diffusion across a swollen gel-like layer of the hydrophilic polymer and, to a lesser extent, through an erosion process. The hydrated polymeric layer forms a gel that acts as a diffusion barrier for the drug, which is in a dissolved state. Several variables need to be considered when designing hydrophilic matrix formulations.

These include the hydration rate of the polymer, the ratio of drug to polymer, the presence of other excipients, the interactions between the polymer chains and drug molecules, and the response of the gel to erosion. Rheological factors also play a role in drug release through the matrix. Previous studies have shown that using a single polymer alone, even at high concentrations, may not be sufficient to sustain drug release for an extended period of time. However, when different polymers are combined, rheological synergism can occur, resulting in a

higher net resistance to drug diffusion compared to using a single polymer alone. This synergistic effect allows for the production of smaller tablets that can achieve a more precisely tailored drug delivery effect. In this study, HPMC K4M and HPMC K15M were combined with lactose as a filler in the formulation. Glipizide was used as a model drug. The composition of the formulation was optimized using a simplex mixture design, which is a statistical experimental design method. The goal of the optimization was to achieve the desired *in-vitro* drug release profile, ensuring a sustained release of the drug over a specific period. By evaluating the rheological synergism of the polymer combination and optimizing the composition of the formulation, the researchers aimed to develop sustained-release tablets with a precise drug delivery effect. This approach allows for the development of dosage forms that can provide controlled release of the drug, improving patient compliance and therapeutic outcomes.

MATERIALS AND METHOD: Glipizide was obtained as a gift sample from Zimlaboratories limited, Nagpur. HPMC K4M, and HPMC K15M, lactose, polyvinyl pyrrolidone (PVP) K30, Talc and magnesium stearate were purchased locally.

Methods:

Preparation of Calibration Curve: Glipizide was dissolved in 0.1 M NaOH to form 1000 µg /ml solution. This was further diluted to produce final concentrations of 1, 2, 3, 4, and 5µg / ml respectively. The absorbance was measured at 276nm.

Preparation of Tablets:

Wet Granulation Method: Glipizide sustained-release matrix tablets were prepared by the wet granulation technique. All ingredients, such as Glipizide, HPMC K4M, HPMC K15M, Lactose, and polyvinyl pyrrolidone (PVP K30), were passed through 40 # mesh. The ingredients were blended for 10 minutes and granulated using PVP in isopropyl alcohol as a granulating agent. The wet mass was then passed through sieve no #16 to obtain granules. The granules were dried in an oven at 40 °C for 30 minutes. The dried granules, magnesium stearate, and talc were blended using a tumbling mixer. Tablets, each weighing 106mg, were compressed using 6mm concave punch under the Rimek Mini Press-II MT tablet punching machine.

Evaluation of Core Tablets: The tablets were evaluated for Weight variation, hardness, and content uniformity by methods described in literature [13, 14].

Weight Variation: 20 tablets were selected randomly and weighed individually, calculate the average weight.

Hardness: Five tablets were selected randomly and hardness was checked by using the (digital hardness tester). Make Orchid.

Content Uniformity: Tablets (20 no) were powdered, and a quantity equivalent to the weight of one tablet was weighed accurately. The powder was dissolved in NaOH to produce 50ml. The solution was filtered and 5.0ml of filtrate was collected and diluted to 50.0ml with NaOH. Measure the absorbance of the resulting solution at 276 nm. Calculate the content uniformity.

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies of Glipizide sustained release tablet were performed according to the dissolution test recommended by USFDA in the dissolution database [15]. Tests were performed in 900ml of phosphate buffer pH 7.4 using USP Type II apparatus paddle. The experiments were performed at 50 rpm and at 37°C±0.5°C. At specified time interval (1, 2, 3, 4, 5, 6, 7, 8 hrs.) 5ml sample were withdrawn, filtered through Whatman filter paper (0.45 µm, Millipore) and the sample volume were replaced with an equal volume of fresh dissolution medium. The sample was estimated for Glipizide dissolved by measuring the absorbance at 276 nm.

Experimental Design: A simplex mixture centroid design was used to evaluate 3 variables that are HPMCK4M, HPMCK15M and Lactose at 2 levels concentration. In order to determine their effect on 3 responses i.e., % drug release at 2nd hour, %drug release at 8th hour and T50% drug release. The layout of experimental design is shown in **Table 4.**

RESULT AND DISCUSSION:

Calibration Curve by UV Analytical Method: Calibration curve were established in phosphate buffer of 7.4 and λmax at 276nm. Beer's law was

obeyed in the concentration range 1-10µg/ml **Fig. 1.** The High value of the regression coefficient was 0.999 establishing the linearity. The regression equation for the calibration line was found to be y=0.0245x-0.0005, respectively.

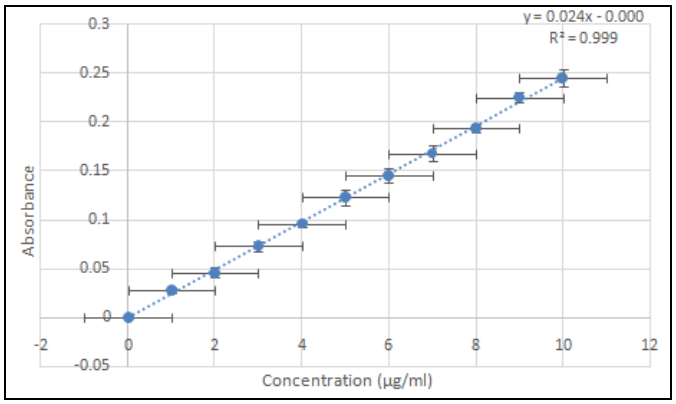

FIG. 1: CALIBRATION CURVE OF GLIPIZIDE PHOSPHATE BUFFER pH 7.4

Preliminary Study: Preliminary Batches were formulated with the single polymer i.e., using HPMC K4 M and HPMC K15M and lactose in different ratios. As per the constraints imposed for this formulation, as the concentration of polymer increases, the lactose concentration decreases because the final weight (104mg) of the sustained release matrix tablets must remain constant. *In-vitro* dissolution studies of these batches were performed, and based on the % drug release levels for the optimization batches were chosen.

TABLE 1: THE COMPOSITION OF TRIAL BATCHES

Ingredient	F1	F2	F3	F4	F5	F6
Glipizide	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
HPMC K15M	10 mg	20 mg	30 mg			
HPMCK 4M				10 mg	20 mg	30 mg
Lactose	75 mg	65 mg	55 mg	75 mg	65 mg	55 mg
Magnesium stearate	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
Talc	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg
PVP k30	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg

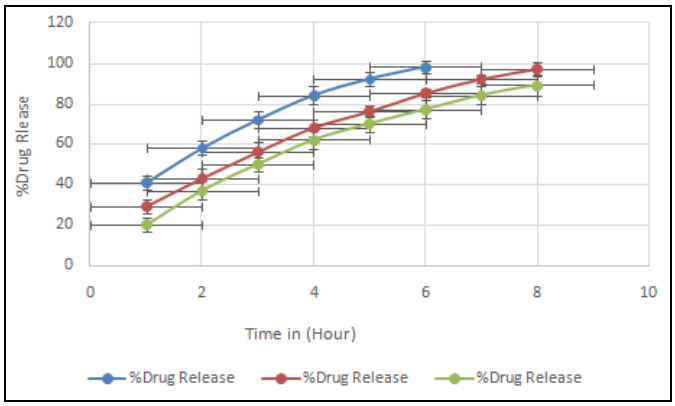

FIG. 2: % *IN-VITRO* DRUG RELEASE STUDY FROM TRAIL BATCHES F1 TO F3

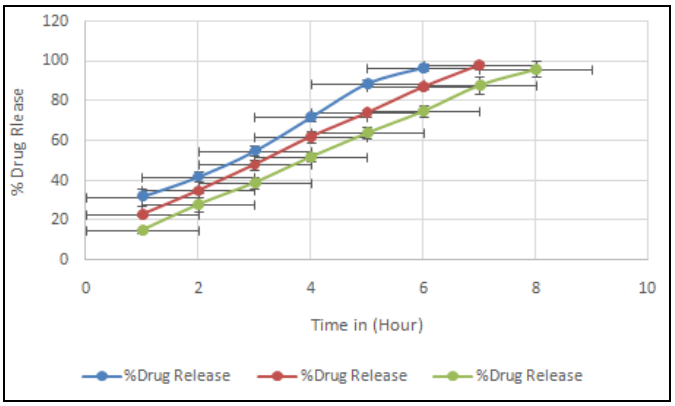

FIG. 3: % *IN-VITRO* DRUG RELEASE STUDY FROM TRAIL BATCHES F4 TO F6

Results: Based on the dissolution study results described in **Table 2**, it is evident that both polymers, HPMC k15M and HPMC k4M, are capable of prolonging drug release at low polymer contents, specifically at a 1:1 ratio. At this ratio, HPMC k15M (F1) achieves 98% drug release at the 6th hour, while HPMC k4M (F4) achieves 97% drug release at the same time point. When the concentration of HPMC k15M is increased to a 1:2 ratio (F2) and a 1:3 ratio (F3), the drug release percentages at the 8th hour decrease slightly to 97% and 89%, respectively. Similarly, for HPMC

k4M, at a 1:2 ratio (F5) and a 1:3 ratio (F6), the drug release percentages are 98% at the 7th hour and 96% at the 8th hour.

These results indicate that both polymers could prolong drug release, with variations in the release profiles depending on the polymer concentration and the specific time points evaluated.

Selection Level for Optimization: Based on the drug release result of the preliminary trial batches, levels of excipients were selected for optimization to construct a mixture design **Table 2.**

TABLE 2: SELECTION OF LEVEL FOR OPTIMIZATION

	Independent variables	Low level	High level
A Mixture	HPMC K4M	20	30
B Mixture	HPMC K15M	20	30
C Mixture	Lactose	30	40

Experimental Design: A 10 run three, factors two level simplex centroid mixture design having 1 center point and 3 replicate runs was employed to study the effect of selected independent formulation variables on dependent variables. The design layout is shown in **Table 3.**

TABLE 3: DESIGN LAYOUT

S. no.	Run	HPMC K4M(mg)	HPMC K15M(mg)	Lactose(mg)
1	1	30	20	40
2	2	25	25	40
3	3	25	30	35
4	4	30	25	35
5	5	30	25	35
6	6	25	25	40
7	7	30	30	30
8	8	25	30	35
9	9	20	30	40
10	10	26.6667	26.6667	36.6667

TABLE 4: PRECOMPRESSION EVALUATION OF THE FORMULATIONS OF OPTIMIZATION TRIAL RUNS

Batch	Angle of repose	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)
F1	27.67±0.03	0.420±0.001	0.464±0.004	9.48±0.03
F2	26.05±0.04	0.436±0.003	0.476±0.003	8.40±0.04
F3	25.35±0.04	0.447±0.002	0.492±0.002	9.1±0.01
F4	29.39±0.03	0.462±0.003	0.512±0.003	9.7±0.01
F5	25.55±0.03	0.438±0.002	0.496±0.002	11.69±0.02
F6	27.08±0.02	0.442±0.002	0.491±0.005	9.97±0.03
F7	28.46±0.03	0.465±0.004	0.515±0.003	9.7±0.03
F8	28.37±0.02	0.426±0.002	0.479±0.004	11.06±0.04
F9	26.58±0.03	0.442±0.004	0.499±0.002	11.42±0.03
F10	26.68±0.02	0.448±0.002	0.493±0.006	9.12±0.04

The angle of repose is a measure of the flowability of granular materials. A lower angle of repose suggests better flowability. In this case, the angle of repose falls within the specified range, indicating good flow properties. Carr's index is another measure of the flowability and compressibility of granular materials.

It is calculated as the difference between the tapped density and bulk density, divided by the tapped density, multiplied by 100. A lower Carr's index indicates better flow properties.

In this case, Carr's index falls within the specified range, indicating good flow properties of the granules. Additionally, the bulk density and tapped density of the granules were found to be within the range of 0.420 to 0.465 and 0.464 to 0.515, respectively.

These values indicate good compressibility of the granules. The bulk density represents the density of the granules in their loose state, while the tapped density represents the density after the granules have been tapped to eliminate air voids. The specified ranges suggest that the granules can be compressed effectively. Overall, based on the given information, it can be concluded that the granules have good flow properties and compressibility, as indicated by the angle of repose, Carr's index, bulk density, and tapped density values.

TABLE 5: POST COMPRESSION EVALUATION OF THE FORMULATIONS OF OPTIMIZATION TRIAL RUNS

Batch	Weight Variation(mg)	Hardness Kg/cm^2	Content uniformity%
F1	106±3	6.02±0.01	96±1.73
F2	105±3	8.13±0.03	96±1
F3	108±1	6.63±0.02	99±2
F4	105±2.64	7.42±0.02	95±1.73
F5	103±3	6.10±0.02	99±1.73
F6	106±2.64	8.13±0.01	99±2.64
F7	109±2	7.50±0.01	95±2.64
F8	104±1	8.82±0.02	98±1.73
F9	107±2	6.50±0.04	95±2.64
F10	106±2	7.10±0.04	102±1

Based on the post-compression study of the tablets, several parameters were evaluated, including weight variation, hardness, and content uniformity. The results obtained for these parameters were found to be within the limits specified by the Indian Pharmacopeia. Weight variation measures the uniformity of weight among individual tablets in a batch. In this case, the weight of the tablets varied between 103 to 107 mg, which falls within the limit of ±7.5%. This indicates that the tablets meet the requirement for weight uniformity. Hardness is a measure of the tablet's mechanical strength or resistance to breakage. The hardness values obtained for the tablets were in the range of 6.02 to 8.13 kg/cm^2. Although the specific hardness requirements may vary depending on the formulation and intended use of the tablets, these values generally indicate acceptable tablet hardness. Content uniformity refers to the consistency of the active ingredient's distribution within the tablets. The content uniformity was found to be between 95% and 102% within the Indian Pharmacopeial limit of 85% to 115%. This suggests that the tablets have a uniform distribution of the active ingredient, ensuring consistent dosing.

***In-vitro* Drug Release Studies (n=3):**

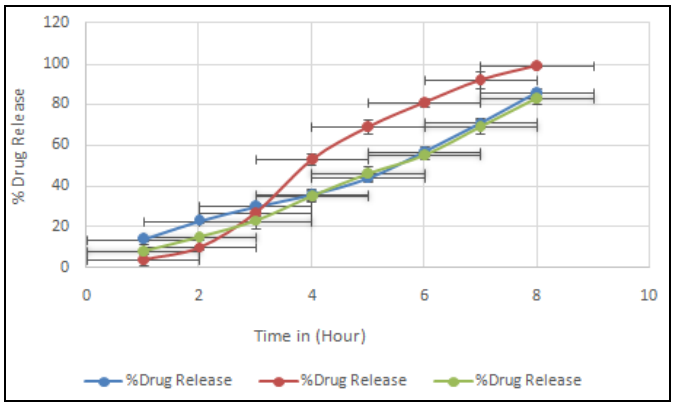

FIG. 4: % RELEASE *IN-VITRO* STUDIES OF EXPERIMENTAL DESIGN RUNS F1 TO F3 BATCHES

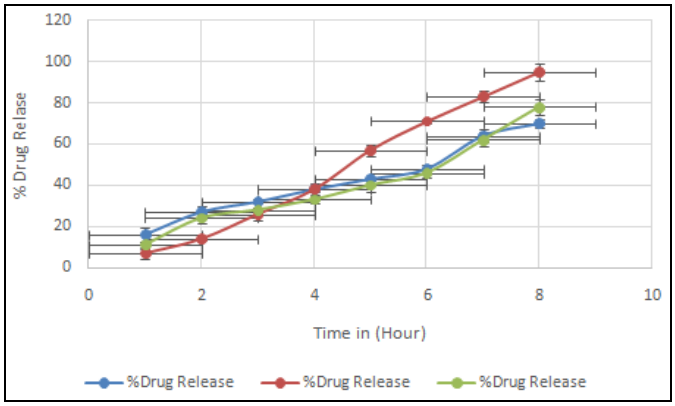

FIG. 5: % RELEASE *IN-VITRO* STUDIES OF EXPERIMENTAL DESIGN RUNS F4 TO F6 BATCHES

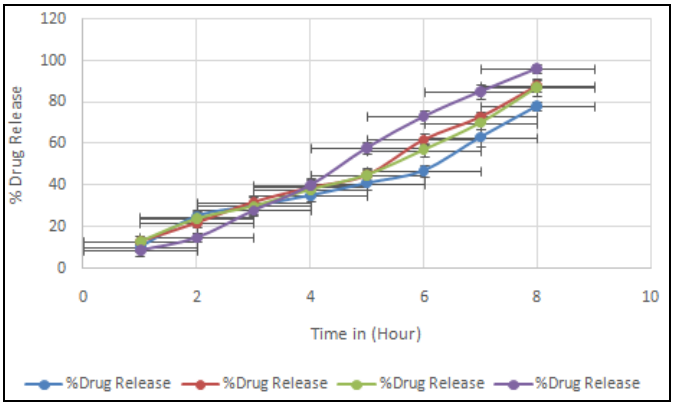

FIG. 6: %RELEASE *IN-VITRO* STUDIES OF EXPERIMENTAL DESIGN RUNS F7 TO F10 BATCHES

Statistical Analysis: Statistical analysis was done by using Design of Expert Software (version 12), The ANOVA shows that lack of fit for the suggested model is non-significant, i.e. the quadratic model selected fits to data. lower P value suggested that the null hypothesis was rejected and the research hypothesis was accepted. Higher F value and lower P suggest that factors HPMC K4M, HPMCK15M and Lactose have significant effect on the drug release response.

TABLE 6: STATISTICAL ANALYSIS OF DEPENDENT VARIABLES

Sr. no.	Outcomes Models	% drug release at 2nd Hour Quadratic	T 50% Quadratic	% drug release at 8th hour Quadratic
1.	R^2 value	0.9951	0.9460	0.9308
2.	F-value	161.81	6135.76	520.39
3.	P-value	0.0001	0.0001	0.0001

The equation for the % drug release at 2nd hour is as follows.

% drug release at 2nd Hour = -28.00 A +18.00 B +20.00 C + 80.00 AB + 56.00 AC + 32.00 BC----------Equation No.1

Where, A = HPMC K4M, B = HPMC K15M, C = Lactose

% Drug Release at 2nd Hour: The negative sign of A in Equation No.1 indicates that an increase in the concentration of HPMC K4M will lead to retardation of drug release at the 2nd hour. On the other hand, HPMC K15M (B) and lactose (C) increase the drug release at the 2nd hour. When the concentration of HPMC K15M (B) increases, the 2nd hour % Drug Release decreases. This suggests that HPMC K15M has a retarding effect on drug release at the 2nd hour. The interaction between A and B (HPMC K4M and HPMC K15M) shows a more dominant synergistic effect compared to the interactions between A and C (HPMC K4M and lactose) or B and C (HPMC K15M and lactose). Based on **Fig. 2**, it can be observed that HPMC K4M provides better drug release retardation in the first few hours (1-3 hours) because it is a low-viscosity polymer that swells faster than the high-viscosity HPMC K15M. On the other hand, HPMC K15M, being a higher viscosity polymer, provides better release retardation in the final stages of drug release. Lactose, being a water-soluble diluent, helps to facilitate the penetration of more water into the matrix. This increased swelling of the polymer leads to erosion of the polymer matrix, which is observed in F1 and F4 batches.

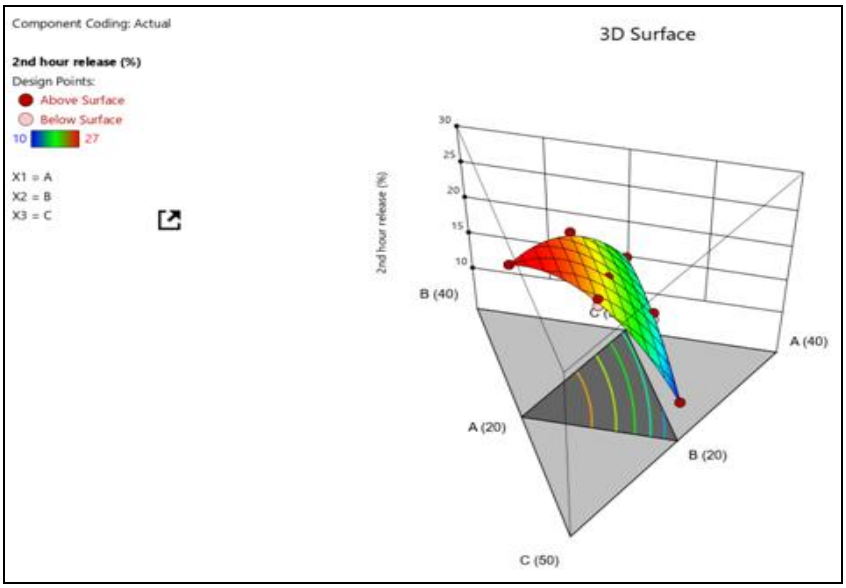

FIG. 7: RESPONSE SURFACE PLOT FOR DRUG RELEASE AT 2ND HOUR

T50% Drug Release: The equation for the time for T50% release is as follows.

T50% = +1.05 A + 9.65 B + 7.05 C + 2.58 AB – 3.02 AC – 5.42 BC ----------Equation No.2

Where, A = HPMC K4M, B = HPMC K15M, C = Lactose.

This model suggests an increase in concentration of HPMC K15M: As the concentration of HPMC K15M increases, the time required for 50% drug release also increases. This suggests that higher concentrations of HPMC K15M slow down the drug release process.

Effect of Lactose (C Lactose): Increasing the concentration of lactose has a positive effect on T50% drug release. This means that as the concentration of lactose increases, the time required for 50% drug release increases.

Interaction between Factors A and B: The interaction between factors A and B (which are not explicitly defined in your statement) shows a synergistic effect on T50% drug release. This suggests that the combined effect of these factors is greater than the sum of their individual effects.

Comparison between HPMC K15M and HPMC K4M: HPMC K15M (factor B) has a stronger effect compared to HPMC K4M (factor A) on T50% drug release. This is attributed to the higher viscosity of HPMC K15M compared to HPMC K4M. The response surface plot shows the mapping of these effects and interactions **Fig. 3.**

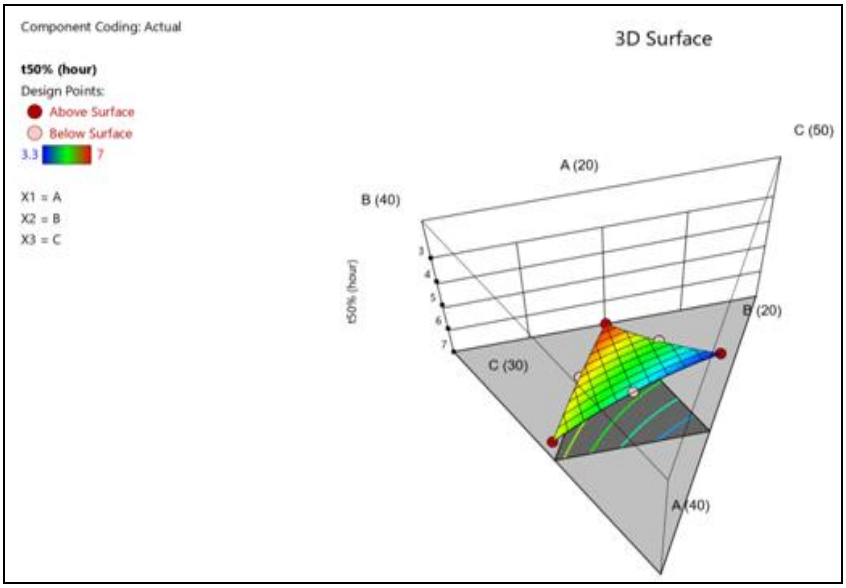

FIG. 8: RESPONSE SURFACE PLOT FOR T50%

% Drug Release at 8th Hour: The equation for the % drug release at 8th hour is as follows.

%Drug release at 8thHour = +115.52 A +33.52 B +69.52 C + 33.78 AB + 25.78 AC + 73.78 BC ----------Equation No.3

Where, A = HPMC K4M, B = HPMC K15M, C = Lactose.

According to the model, all factors show a positive effect on drug release, with factor A having the most dominant effect compared to the other factors.

Furthermore, all interactions between the factors demonstrate a synergistic effect, meaning that the combined effect of the factors is greater than the sum of their individual effects. However, the BC interaction appears to have the most dominant effect on the 8th Hour %Drug Release C.

Specifically, increasing the concentration of lactose (factor B) leads to an increase in the 8th Hour %Drug Release C. This effect is attributed to lactose's ability to attract more water inside the matrix, which potentially enhances drug release. Similarly, increasing the concentration of HPMC K15M (factor C) also increases the 8th Hour %Drug Release C.

This indicates that HPMC K15M plays a role in enhancing drug release at the 8th hour. The responses are depicted in **Fig. 4.**

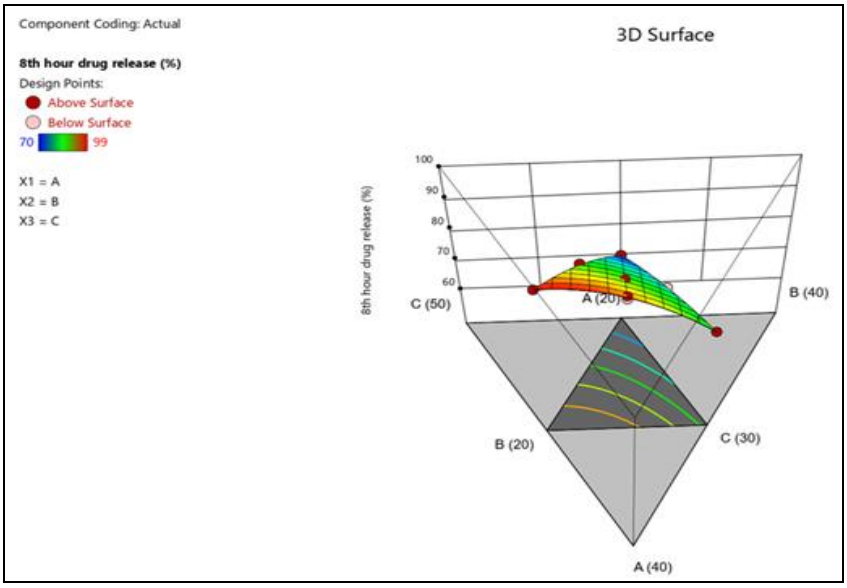

FIG. 9: RESPONSE SURFACE PLOT FOR EFFECT OF VARIABLES ON DRUG RELEASE AT 8TH HOUR

Search for Optimized Formulation: Based on the given solutions and their desirability value suggested by Design of Expert Software, we selected the optimized formulation. The desirability value of the optimized formulation was found to be 1 and it is the most favourable (desirability of 1 is a rare case).

Validation of Optimized Batch: The optimized solutions were formulated and evaluated for drug release. The composition in **Table 9** and predicted / observed responses are presented in **Table 11.**

TABLE 7: THE COMPOSITION OF THE OPTIMIZED BATCH

Ingredient	Quantity (mg)
Glipizide	10
HPMC K4M	30
HPMC K15M	25
Lactose	35
Talc	1
Magnesium Stearate	1
PVP K30	3
Total	105mg

***In-vitro* Drug Release Studies of Optimized Batch (n=3):**

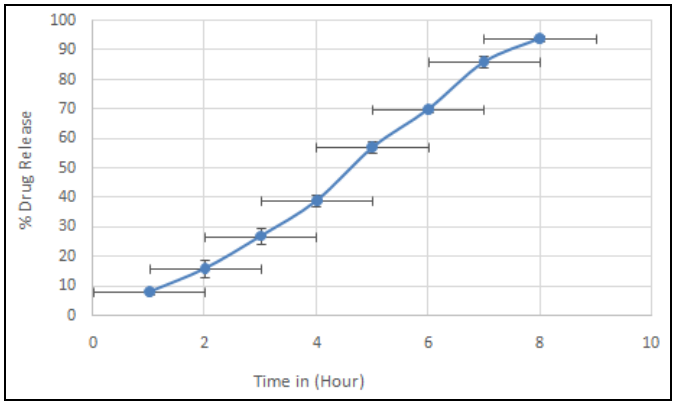

FIG. 10: % DRUG RELEASE OF OPTIMIZED BATCH

TABLE 8: VALIDATION OF OPTIMIZED BATCH

Response Variable	Experimental Value	Predicted Value	Percentage prediction
2nd hour %drug release	16	14.5	2.5
T50 % drug release in h	4.3	4.3	0
8thhour % drug release	94	95	1

CONCLUSION: The above research study is related to drug release and the use of polymers. Rheological synergisms were evaluated, and the percentage of drug release was used to confirm the

results. The formulation that involved polymers with synergistic interactions was able to sustain the drug release for 8 to 10 hours. Among the polymers used, HPMC K15 M played a major role in sustaining the drug release during the later hours. On the other hand, HPMC K4 M prevented burst release at the initial stage of the drug release profile. These findings suggest that the combination of these polymers can provide a controlled and sustained release of the drug over an extended period. To achieve high accuracy in the study, the researchers utilized Response Surface Methodology (RSM). RSM is a statistical technique that allows for the optimization of complex systems by exploring the relationship between multiple variables. In this case, it helped in determining the optimal formulation for drug delivery systems.

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CONFLICTS OF INTEREST: Authors have no conflict of interest.

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