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Design of Experiment Assisted Formulation and Development of Multiparticulate Systems Based Sustained Release Tablets of Glibenclamide

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Abstract:
Background: Tablets or capsules being the conventional dosage forms can be modified for providing the desired therapeutic effect to the patients. The network of matrix in the tablet allows the drug release to be slowed down considerably.
Objective: The prime objective of the study was to formulate sustained release Glibenclamide matrix tablets by compressing pellets prepared using wax material and pore-forming agent.
Methods: Tablets were formulated by compressing optimized pellets. Pellets were prepared using hot melt extrusion method and optimized using 32 full factorial design. The independent variables were the amount of wax material (cetostearyl alcohol) (X1) and pore-forming agent (HPMC K 100M) (X2) while the dependent variables selected were entrapment efficiency, aspect ratio, Q2, Q12 and Q20. Prepared optimized pellets were mixed with suitable excipients and compressed as a matrix tablet and characterized for quality parameters and drug release kinetics.
Results: All the formulations (pellets) showed retarded drug release as the concentration of the polymer was increased. Optimized formulation of pellets showed about 95 % drug release within 24 hr. The results of release kinetics studies of the optimized formulation suggested that formulation followed Korsmeyer-Peppas release model suggesting the diffusion dominant release mechanism while all the other parameters were in accordance with pharmacopoeial limits.
Conclusion: A 32 full factorial design was successfully employed to optimize pellets with desired characteristics. Optimized pellets were successfully compressed in the form of a sustained release matrix tablet of Glibenclamide.

Keywords: Glibenclamide, Pellets,Cetostearyl alcohol, HPMC K100M, Hot melt extrusion.

1. Introduction

Tablets being the conventional dosage forms can be modified for providing the desired therapeutic effect to the patients.The network of matrix in the tablet allows the drug

release to be slowed down considerably. Thus, the drug delivery to the body is slow and can be controlled relatively.This mechanism allows the plasma drug levels to remain within the therapeutic window, as slow drug presentation and excretion mechanism compensate the accumulation of dose. Moreover, the duration of action is prolonged due to the sustained release of the medicament. A tablet dosage form, with reduced frequency of administration, results in better patient compliance. Oral sustained release delivery systems are designed to achieve a therapeutically effective concentration of drug in systemic circulation over an extended period of time.Therapeutic benefits of designing SR dosage form include low cost, simple processing, improved efficacy, reduced adverse effects, flexibility in terms of the range of release profiles attainable, increased patient compliance and convenience.

Many innovative methods have been developed for obtaining modified drug release. From the practical viewpoint, the least complicated approach for developing a modified release dosage form is the formulation of a hydrophilic matrix tablet (Ponchel and Irache 1998). It has been observed that the hydrophilic matrices are a complex interaction between swelling, diffusion and erosion mechanism, which is responsible for the release of drug. The hydrophilic gel-forming matrix tablets are widely used for oral extended-release dosage forms due to their cost-effectiveness, simplicity, and reduction of systemic toxicity, risk and dose dumping(Furlanetto, Cirri et al. 2006).

Extensive work is being taken up not only to develop newer more specific molecules for Type-2 diabetes but also develop proper delivery system to maintain the activity of the drug over a prolong period of time so the proper compliance of taking the drugs regularly. The principal aim of the investigation undertaken is to develop a Multi-Particulate Drug Delivery System for non-insulin dependent diabetes mellitus drug. This type of diabetes is rising exponentially even in developing country like India due to fast life style with concomitant stressful living condition. It is expected that within coming 5 years fifty million Indian of both sexes and different age group including children will suffer from this destructive diseases, keeping above view the investigation has undertaken as the topic of national importance.

As the objective of the investigation desires most important FDA approved type 2 diabetes second generation sulfonylurea drugs, for clinical use of oral non-insulin dependent diabetes mellitus, namely Glibenclamide. Glibenclamide is a potent sulphonyl urea class which uses an oral hypoglycemic agent. It stimulates insulin release from the beta cells of the pancreas that leads to hypoglycemia. Glibenclamide increases insulin level by reducing the hepatic clearance of the hormone(Wei and Löbenberg 2006). Glibenclamide belongs to class II (*i.e*. drugs with low solubility and high permeability) according to the biopharmaceutical classification system(Dressman, Amidon et al. 1998). It is practically insoluble in water and consequently, its dissolution has been considered to be the rate-limiting step for absorption. Being weak acid with a pKa 5.3, it shows pH dependent solubility and its absorption is expected to be better from the upper part of the gastrointestinal tract (GIT). The drug in oral conventional dosage form has the dosage regime of three times a day due to having short elimination half-life of 4-5 hour. Plasma half-life of Glibenclamide is about 2 to 4 hrs. Thus, the development of controlled release dosage forms is to be designed considering the above factors(Luzi and Pozza 1997).

2. MATERIALS AND METHODS

2.1. Chemicals

Glibenclamide was supplied as gift samples by Cipla Pvt.Ltd.Vikhroli, Mumbai. Bees wax, carnauba wax, cetostearyl alcohol and HPMCwere purchased from Research-lab fine chem.

Industries,Mumbai, India. Dicalcium phosphate, talc, magnesium stearate, and other chemicals were of analytical grade and were obtained from Loba Chemicals Pvt.Ltd. Mumbai, India.

3. METHODOLOGY

Formulation of Glibenclamide Sustained Release Tablets

Formulation of tablets was carried out in two steps. Initially the pellets were prepared and optimized using 3^2 full factorial design using hot melt extrusion method using polymers (cetostearyl alcohol and HPMCK100M) and in the other step, prepared pellets were compressed in the form of a matrix tablet.

Preparation of Pellets using hot melt extrusion method(Young, Koleng et al. 2002)

The polymers and drugs were sifted using a sieve (USP #30 screen size) and dried in an oven at 40°C to remove any residual moisture present. The materials were blended using a twin shell V-blender (GlobePharma, Maxiblend®) at 25 rpm for 15 min at 120°C. Experiments were performed using a 6-mm counter-rotating mini extruder (Haake Minilab, Thermo Electron, Germany), and there after formulations were finally extruded using the pilot scale 16-mm co-rotating twin screw extruder Formulation compositions of experiments on the 16-mm extruder are listed in Table 1. Initial extrudates obtained during the extrusion process were discarded until the extruder had attained a steady state, and then extrudates collected were cooled at ambient temperature and pelletized.

Preparation of sustained release matrix tablet of Optimized pellets(Gryczke, Schminke et al. 2011)

Optimized pellets and all other excipients were passed through sieve # 20 separately and mixed homogeneously by triturating up to 15 min. Finally, this mixture was compressed on an 8-station rotary tablet machine using an 8 mm concave punches and an average weight of 250 mg. Composition of prepared batches is shown in Table 2.

Optimization of pellets by 3*2 Full Factorial Design(Barot, Parejiya et al. 2012)

A 3^2 full factorial design was constructed to study the influence of the effect of independent variable. Total 9 experiments were conducted. The factorial design was applied to find out the optimized formulation containing cetostearyl alcohol and HPMC. Magnesium stearate and Talc were used in each formulation for the purpose of lubrication. Dicalcium phosphate was used as diluents. The polymers were added in the formulation as specified in the factorial design. In the present study, concentration of cetostearyl alcohol (X1) and HPMC(X2) were considered as independent variables while entrapment efficiency(Y1), aspect ratio(Y2), Q2(Y3), Q12(Y4) and Q20 (Y5) were considered as dependent variables. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials are performed in all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response. Polynomial equation generated by this design is as follows:

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b1 to b2 are the regression coefficients. The response values are subjected to MLRA (Multiple linear regression analysis) to find out the relationship between the factors used and response values obtained. After application of full factorial design and with the help of produced polynomial terms, amount of formulation variable was optimized.

Optimization of formulation

The computation for optimized formulation was carried using design expert software (Design Expert®, Stat Ease, Version 12.0.1). The optimized formulation was obtained by applying constraints (goals) on the dependent variables. The models were evaluated in terms of statistically significant coefficients and R^2 values. Both numerical and graphical methods were applied to find the optimum conditions and an overlay plot was generated.

Validation of design using checkpoint batch

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses.Values of independent variables were taken at 3 points and the theoretical values of entrapment efficiency, aspect ratio, % CDR at 2 hr, % CDR at 12 hr and % CDR at 20 hr were calculated by substituting the values in the polynomial equation.

Table 1. Experimental matrix for 3^2 full factorial design(Coded and Actual Values)

Sr No.	**Batch no**	**Concentrationof cetostearylalcohol(X_1)**		**Concentration of HPMC K-100M(X_2)**	
		CODED VALUE	ACTUAL VALUE	CODED VALUE	ACTUAL VALUE
1	F1	-1	10%	-1	5%
2	F2	-1	10%	0	10%
3	F3	-1	10%	1	15%
4	F4	0	15%	-1	5%
5	F5	0	15%	0	10%
6	F6	0	15%	1	15%
7	F7	1	20%	-1	5%
8	F8	1	20%	0	10%
9	F9	1	20%	1	15%

Table 2. Composition of Glibenclamide sustained release factorial design batches

Sr. No	**Ingredients (mg/Tablet)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Glibenclamide pellets	Equivalent to 40mg								
4	Dicalcium Phosphate (mg)	Equivalent to 250 mg								
5	Magnesium Stearate (mg)	1	1	1	1	1	1	1	1	1
6	Talc(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Total Wt.(mg)	250	250	250	250	250	250	250	250	250

Characterization of pellets(Puah, Yap et al. 2014):

Entrapment efficiency

Drug entrapment efficiency represents the proportion of the amount of drug, which has been incorporated into the pellets. To check the entrapment efficiency, specific amount of crushed pellets were suspended in 100 ml of pH 6.8 phosphate buffer with constant agitation at room temperature for 24 h. Then, the solution was filtered through Whatman

filter, drug content was determined UV spectrophotometrically (Shimadzu 1800), at the λ_{max} using 6.8pH phosphate buffer as blank. The entrapment efficiency was calculated by using the given equation.

% Entrapment Ef1iciency = AQ/TQ * 100

AQ = the actual quantity of drug present in pellets

TQ = the theoretical quantity of drug present in the pellets

Aspect ratio (AR)

It was investigated by optical microscopic image analysis by randomly selected pellets. The microscope was fitted with ocular and stage micrometers. Aspect ratio of formulation was calculated from following equation

$AR = d_{max}/d_{min}$

d_{max} and d_{min} are Feret diameter measured by image analysis software.

Characterization of sustained release matrix tablet(Amighi, Timmermans et al. 1998):

Weight variation

Uniformity of weight as described in the United States Pharmacopeia (USP) was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded.

Thickness

The thickness of three tablets was measured using vernier callipers. The extent to which the thickness of each tablet deviated from ±5% of the standard value was determined.

Hardness

The hardness of the tablet was determined by Monsanto hardness tester. Tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded.

Friability

Friability of tablets was performed in a Roche friabilator. Five tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed.

$\%\ Friability = (Wt_{initial} - Wt_{Final}) / Wt_{initial} * 100$

Drug Content

Ten tablets containing Glibenclamide were selected and the average weight was calculated. The tablets were then powdered and 10 mg of Glibenclamide equivalent powder was taken in a volumetric flask and 0.1 N HCl was added to dissolve the powder and made up to the volume with 0.1 N HCl passed through Whatman filter. Serial dilutions were made and absorbance of the solution was measured using aUV-Visible spectrophotometer (Shimadzu 1800) at wavelength maxima(Ahad, Kumar et al. 2010).

In vitro Drug Release Studies

Glibenclamide release studies were performed on USP,Type II apparatus at a 100 rpm and 37°C in 900 ml of 0.1N HCl for 2 hours followed by phosphate buffer (pH 6.8) for the rest of period. The paddle was adjusted at 100 RPM and the temperature of 37±1 °C was maintained throughout the experiment. Withdrawn not less than 5 ml of the dissolution medium at 0, 1, 2, 4, 8, 12, 18, 20, 24 h time interval up to 24 h and were replaced with the same volume of fresh dissolution media after each withdrawal to maintain sink condition. Filtered each sample through a membrane filter with a pore size of not more than 0.45mm. The samples were analysed after appropriate dilution by UV spectrophotometer at λ max against a blank reagent(Essa, Elkotb et al. 2015).

Kinetic Analysis of Dissolution drug release Data

Drug release kinetics is assumed to reflect the order and different release mechanisms of different types of controlled release formulations. In order to propose a possible release mechanism, drug release from different sustained release formulation combinations were fitted to zero order, first order, Korsmeyer-Peppas and Higuchi equations. Zero order, firstorder, Higuchi's and Korsmeyer-Peppas are given as follows(Ahad, Kumar et al. 2010).

$$Qt = Q_0 + K_0 t$$

$$\text{Log } Qt = \log Q_0 - K_t t$$

$$Q = KHt^{1/2}$$

$$F = Mt/M = Kmt_n$$

Where, Qt is the amount of drug released at time t, Q0 is the initial amount of the drug in the formulation. K0, Kt, KH and Km are the release rate constants for zero order, first order, Higuchi model and Korsmeyer-Peppas model, respectively.Mt/M is the amount of drug released in time t and n is the diffusion coefficient.

The criteria for the selection of most suitable model were the value of regression coefficient (R2) nearer to 1, Model Selection Criteria (MSC) and Akaike Information Criteria (AIC) (Jadav, Teraiya et al. 2012).

Stability Studies

Stability studies of the optimized formulation were carried out to determine the effect of the presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminium foil and subjected to elevated temperature and humidity conditions of 40±2 °C/75±5 % RH for a time period of three months and evaluated for their physical appearance, hardness, drug content and *invitro* drug release studies at specified intervals of studies.

4. RESULTS AND DISCUSSION

Preparation of Pellets (Factorial Batches)

Factorial batches for pellets were prepared using the experimental matrix shown in the Table 1 and the results of all factorial batches are shown in Table 3. Results of factorial batches were evaluated by the Design Expert®(V 12.0.1, Stat ease, Philadelphia, USA) software and the relationship between independent and dependent variables were established.

Table 3. Results of prepared factorial batches

Run	Entrapment Efficiency	Aspect Ratio	Q2	Q12	Q20

F1	85.22±2.59	1.88	15.23±1.18	59.85±2.58	88.56±1.36
F2	58.89±1.26	1.18	27.89±0.98	73.59±1.59	98.56±1.48
F3	66.23±1.38	1.61	18.59±1.18	54.89±1.68	84.56±1.28
F4	84.99±1.85	1.59	21.25±1.19	52.29±1.44	81.25±1.68
F5	81.56±1.08	1.34	22.59±1.24	57.89±1.38	87.59±1.53
F6	64.23±1.14	1.28	27.58±1.38	64.89±1.23	90.12±1.48
F7	80.15±1.25	1.78	17.23±1.68	54.25±0.98	82.31±1.28
F8	78.89±1.35	1.36	21.08±1.58	51.23±1.25	78.56±1.68
F9	68.79±1.38	1.48	24.89±1.48	56.89±1.38	87.01±1.59

Optimization of Pellets

Preliminary investigations of the process parameters revealed that independent variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) highly influenced dependent variables.

Effect of Polymers on Entrapment Efficiency

Mathematical relationships generated for the studied response variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) for entrapment efficiency (Y1) is as follows:

Entrapment Efficiency = 74.3278 + 4.93167 * Wax material + -9.19833 * Pore forming agent

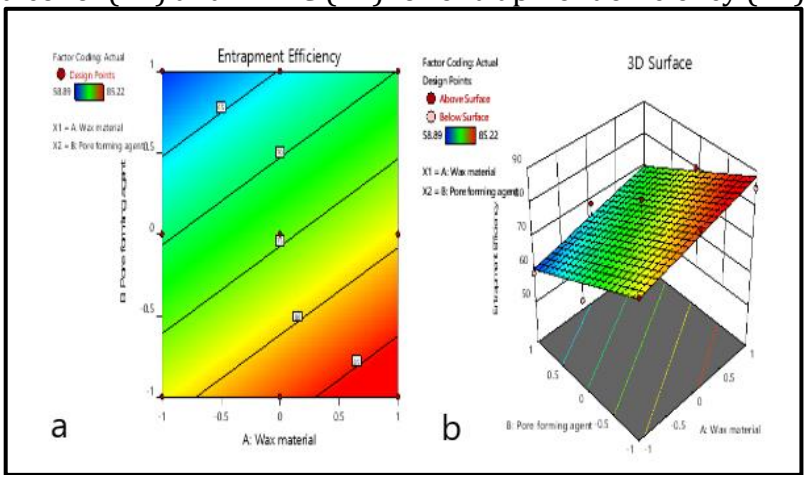
Table 4. Analysis of ANOVA response surface model for Y1

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	653.58	2	326.79	16.03	0.0039	significant
A-Wax material	145.93	1	145.93	7.16	0.0367	
B-Pore forming agent	507.66	1	507.66	24.91	0.0025	
Residual	122.29	6	20.38			
Cor Total	775.87	8				

SS-sum of squares, Df-degrees of freedom, MS-mean of squares, F-Fischer's ratio.

The change in entrapment efficiency as a function of X1 and X2 is depicted in the form of contour plot and response surface plot fig 1 (a), (b) based on full factorial design.

Fig 1 (a)Contour plotand (b)3-D Response surface graph showing the effect of Cetostearyl alcohol (X1) and HPMC (X2) for entrapment efficiency (Y1)



Effect of Polymers on Aspect Ratio

Mathematical relationships generated for the studied response variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) for aspect ratio (Y2) is as follows:

Aspect Ratio= 0.785556 + -0.1281667 * Wax material + 0.056333 * Pore forming agent

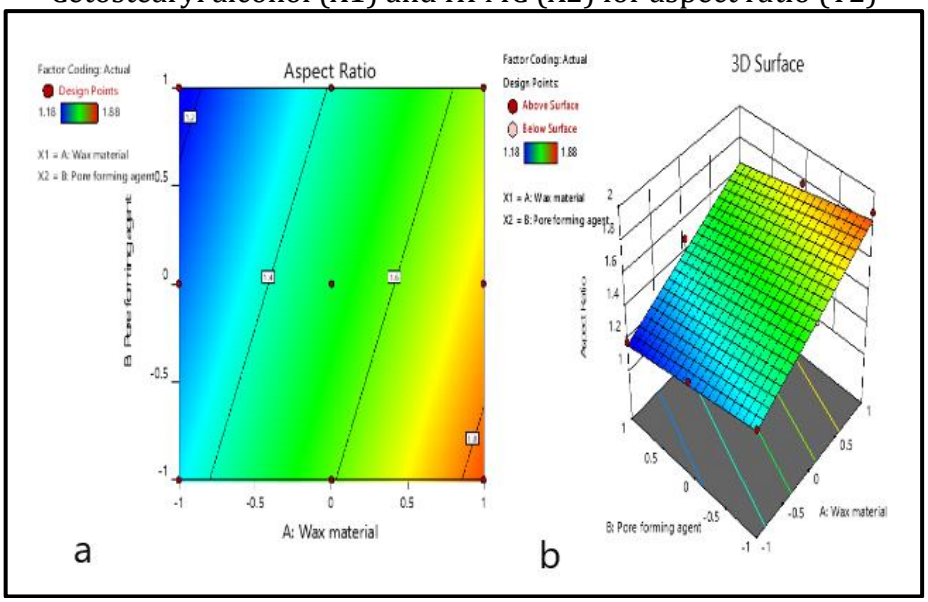
Table 5 shows the results of ANOVA, which was performed to identify in significant factors. All the coefficients were found to be significant at P is less than 0.05 as the model is linear

Table 5. Analysis of ANOVA response surface model for Y2

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.4027	2	0.2013	32.90	0.0006	significant
A-Wax material	0.3504	1	0.3504	57.26	0.0003	
B-Pore forming agent	0.0523	1	0.0523	8.54	0.0265	
Residual	0.0367	6	0.0061			
Cor Total	0.4394	8				

The change in aspect ratio as a function of X1 and X2 is depicted in the form of response surface plot fig 2 (a), (b) based on full factorial design.

Fig 2 (a)Contour curve and Fig 2 (b)3-D Response surface graph showing the effect of Cetostearyl alcohol (X1) and HPMC (X2) for aspect ratio (Y2)



Effect of Polymers on % CDR at 2 Hr (Q2)

Mathematical relationships generated for the studied response variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) for % CDR at 2 h (Y3) is as follows:

Q2= 21.8144 + -4.25 * Wax material + 2.30167 * Pore forming agent

Higher values of correlation coefficients for % CDR at 2 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries, i.e. positive or negative. Software revealed that coefficient b1 and b2 is negative. This indicates that on decreasing X1 and X2, % CDR increases.

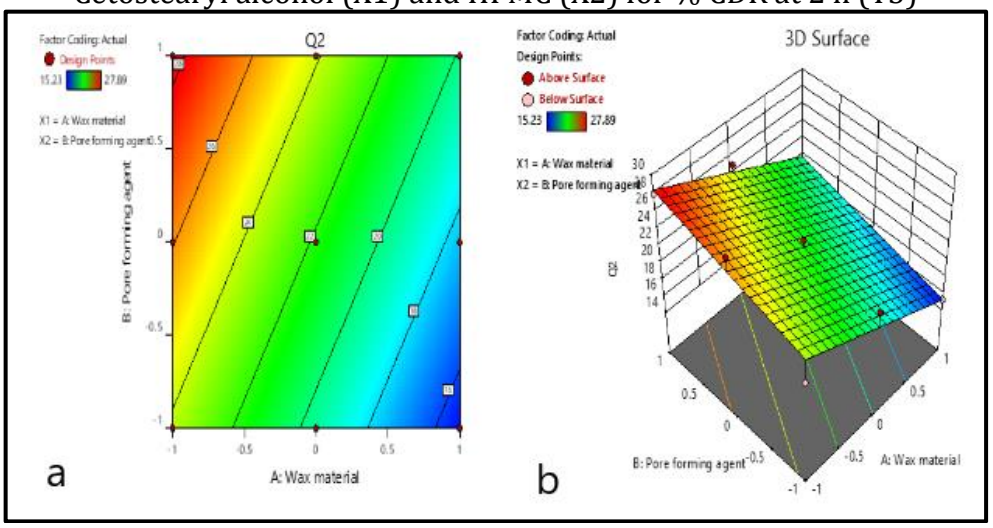
Table 6 shows the results of ANOVA, which was performed to identify insignificant factors. All the coefficients were found to be significant at P is less than 0.05 as the model is linear.

Table 6. Analysis of ANOVA response surface model for Y3

Source	Sum of Square	df	Mean Square	F-Value	P-Value	
Model	**140.16**	**2**	**70.08**	**26.82**	**0.0010**	**Significant**
Wax material	108.37	1	108.37	41.47	0.0007	
Pore forming agent	31.79	1	31.79	12.16	0.0130	
Residual	15.68	6	2.61			
Cor total	155.84	8		-	-	

The change in % CDR at 2 hr as a function of X1 and X2 is depicted in the form of response surface plot fig 3 (a), (b) based on full factorial design.

Fig 3 (a)Contour curve and Fig 3 (b)3-D Response surface graph showing the effect of Cetostearyl alcohol (X1) and HPMC (X2) for % CDR at 2 h (Y3)



Effect of Polymers on % CDRat 12 Hr (Q12)

Mathematical relationships generated for the studied response variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) for %CDR at 12 h (Q12) is as follows:

Q12= 58.4189 + -3.45333 * Wax material + 3.66667 * Pore forming agent + -6.83 * Wax material * Pore forming agent

Sequential sum of squares for the two-factor interaction terms AB. The F- value tests the significance of adding interaction terms to the linear model. A small p-value (prob> F) indicates that adding interaction terms has improved the model(Table 7).

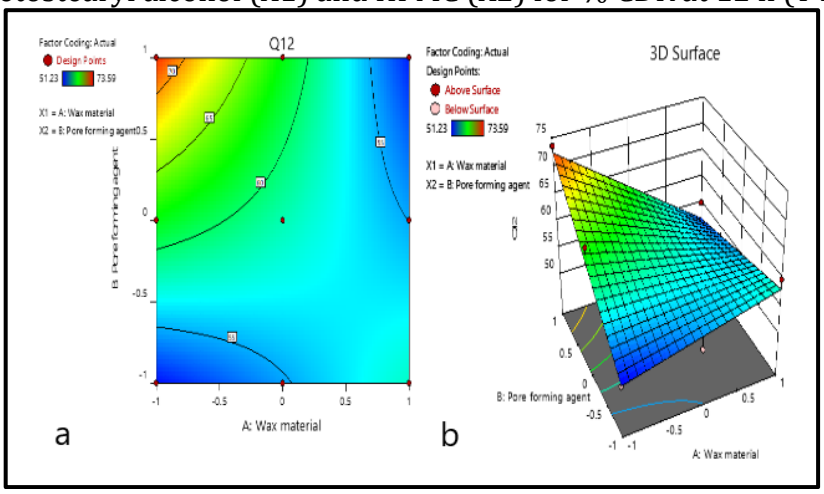
Table 7. Analysis of ANOVA response surface model for Y4 (Response Q12)

Source	Sum of Square	df	Mean Square	F-Value	P-Value	
Model	**338.82**	**3**	**112.94**	**9.91**	**0.0152**	**significant**

Wax material	71.55	1	71.55	6.28	0.0541	
Pore forming agent	80.67	1	80.67	7.08	0.0448	
AB	186.60	1	186.60	16.38	0.0099	
Residual	56.96	5	11.39			
Cor total	395.78	8				

The change in % CDR at 12 h as a function of X1 and X2 is depicted in the form of response surface plot fig.4 (a) and (b) based on full factorial design.

Fig 4 (a)Contour curve and Fig 4 (b)3-D Response surface graph showing the effect of Cetostearyl alcohol (X1) and HPMC (X2) for % CDR at 12 h (Y4)



Effect of Polymers on % CDR at 20 Hr (Q20)

Mathematical relationships generated for the studied response variables concentration of cetostearyl alcohol (X1) and concentration of HPMC (X2) for %CDR at20 h (Q20) is as follows:

Q20 = 86.5022 + -1.96833 * Wax material + 3.62667 * Pore forming agent + -6 * Wax material * Pore forming agent

Sequential sum of squares for the two-factor interaction terms AB. The F- value tests the significance of adding interaction terms to the linear model (Table 8). A small p-value (prob> F) indicates that adding interaction terms has improved the model.

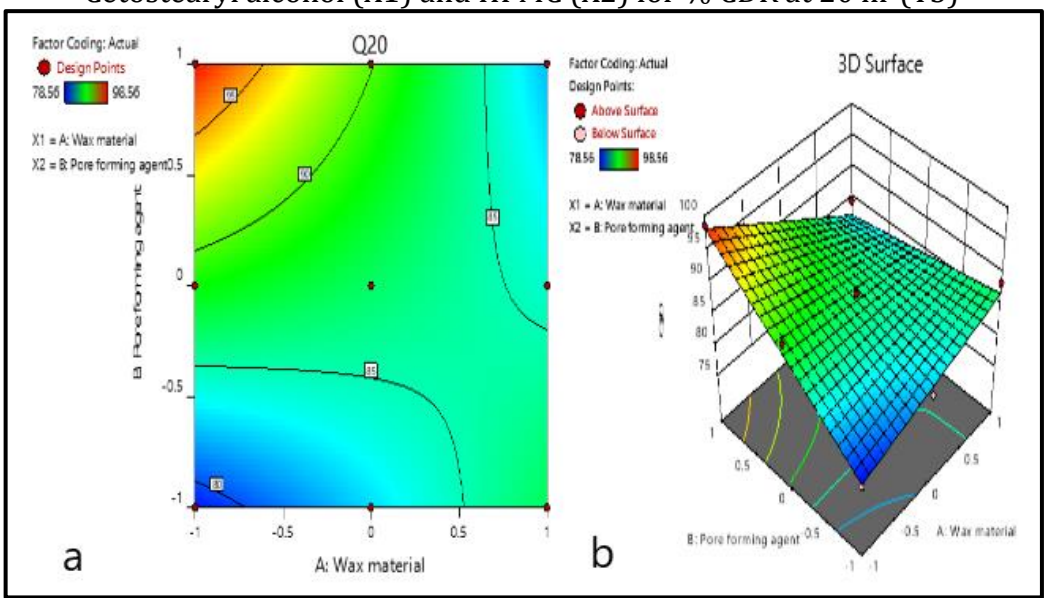
Table 8. Analysis of ANOVA response surface quadratic model for Y2 (Response Q20)

Source	**Sum of Square**	**df**	**Mean Square**	**F-Value**	**P-Value**	
Model	**246.16**	**3**	**82.05**	**13.67**	**0.0076**	**significant**
Wax material	23.25	1	23.25	3.87	0.1062	
Pore forming agent	78.92	1	78.92	13.15	0.0151	
AB	144.00	1	144.00	24.00	0.0045	
Residual	30.00	5	6.00			

Cor total	276.17	8				

The change in % CDR at 20 hr as a function of X1 and X2 is depicted in the form of response surface plot fig 5 (a), (b) based on full factorial design.

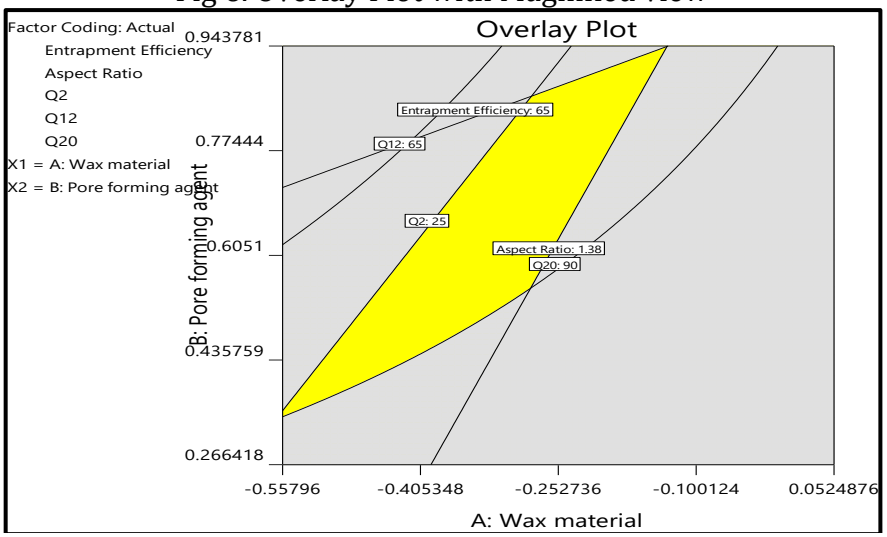
Fig 5 (a)Contour curve and Fig 5 (b)3-D Response surface graph showing the effect of Cetostearyl alcohol (X1) and HPMC (X2) for % CDR at 20 hr (Y5)



Optimization of formulation

The overlay plot of responses, generates an optimized area as per desired criteria as shown in Fig.6. After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria that the said formulation released around 25 % of the drug in 2 h and 65 % in 12 h, however, the drug completely got released, i.e. 90 % in 20 h, entrapment efficiency was 65 % and aspect ratio was 1.38. Yellow region in the overlay plot shows optimization region (Figure 6)

Fig 6. Overlay Plot with Magnified view



Checkpoint analysis

Three checkpoint batches were prepared and evaluated for entrapment efficiency, aspect

ratio, %CDR at 2 hr, %CDR at 12 hr and % CDR at 20 h. When measured values were compared with predicted values, the differences were found to be insignificant (Table 8). Thus, it can be concluded that the obtained mathematical equation is valid for predicted values (Mehta, Parejiya et al. 2016).

Table 9. Checkpoint batches composition with predicted and measured value

No.		Entrapment Efficiency	Aspect Ratio	Q2	Q12	Q20
CPP 1	Predicted value	73.46	1.13	22.80	59.07	90.78
	Observed value	73.56	1.1342	22.97	59.75	89.92
CPP 2	Predicted value	70.08	1.13	23.77	61.16	92.72
	Observed value	70	1.1318	23.15	61.23	92.03
CPP 3	Predicted value	71.98	1.14	22.53	59.48	91.48
	Observed value	72.02	1.1449	22.08	59.98	91.25

Characterization of Tablets

The physical appearance thickness, hardness, friability, weight variationand drug content of the tablets formulated were found to be within range as per pharmacopoeial standards. The value of thickness was ranged from 3.24 mm to 3.28 mm. The mean values of hardness ranged from 4.92 to 5.79 kg/cm2. The values of average weight for all the formulations passed test of weight variation. Friability was less than 1% for all batches, so formulations had good compactness and mechanical strength to handle and for transport. % Entrapment efficiency of pellets was in range of 58.89 to 85.22; which is acceptable for all the formulations. Aspect ratio of pellets was found to be in the range of 1.28 to 1.89 for all the formulations. Good uniformity in drug content was found among different batches of the tablets and the percent of drug content was 98-100 % as shown in Table10. Thus, all the evaluated physical parameters were found to be practically within limits.

Table 10. Evaluation parameters of Tablets

Formulation	Thickness # (mm) ± SD	Weight variation* (mg) ± SD	Hardness (kg/cm^2)$ ± SD	Friability $ (%) ± SD	Drug Content Uniformity @ (%) ± SD
F1	3.27±0.04	Passes	4.92±0.072	0.28 ± 0.01	99.38±0.11
F2	3.26± 0.015	Passes	5.48±0.03	0.34± 0.022	98.28±0.74
F3	3.24± 0.02	Passes	5.79±0.062	0.72± 0.016	99.57±0.89
F4	3.26± 0.056	Passes	5.11±0.023	0.68± 0.019	99.16±0.49

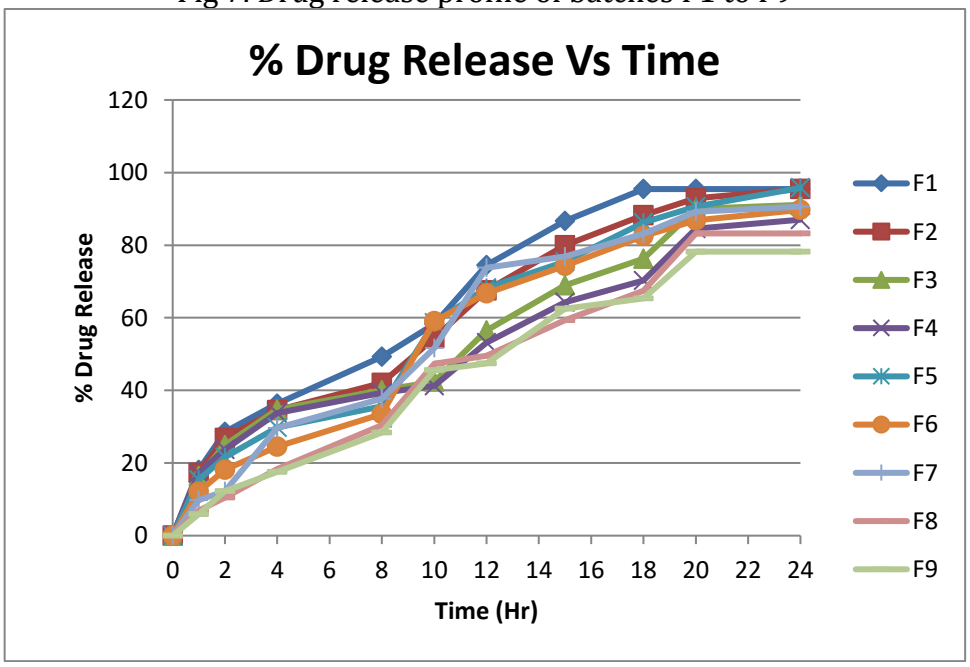
F5	3.28 ± 0.071	Passes	4.99 ± 0.12	0.25± 0.021	98.22±0.55
F6	3.25± 0.06	Passes	5.31±0.053	0.39± 0.043	99.77±0.37
F7	3.25± 0.025	Passes	5.68±0.077	0.41± 0.051	98.88±0.65
F8	3.27± 0.011	Passes	5.58±0.095	0.59± 0.062	99.39±0.74
F9	3.28 ± 0.017	Passes	5.42±0.082	0.71± 0.077	99.63±0.36

*n = 20, # = 3, $ = 5 and @ = 10. (mean±SD)

***In vitro* Drug Release Studies**

The studies of the formulation Batches from F1-F9 were carried out to know the *in-vitro* drug release pattern. It was observed that the drug release increased with the increase in the concentration of the polymers. The % CDR was found tobe in the range of 78.23% to 95.8% for matrix tablets. The value of release after 2 hrs varied between 17.45%and 29.81%; release after 12 hrs found between 49.54% and 73.78 % and release after 20hrs found between 94.19%and 101.76%. Cetostearyl alcohol was used as a release retarding polymer because it is hydrophobic in nature and could be useful in controlling the release in delivery system. At a high level of cetostearyl alcohol, the release at the end of 24hrs decreasing; but HPMC K 100 is high viscosity building and pore forming polymer to facilitate the release from tablet formulation. The rate of drug release tends to decrease with an increase in polymer concentration (cetostearyl alcohol + HPMC). The viscosity of the gel layer around the tablet increases with an increase in HPMC K 100 concentration thus limiting the release of drug after a concentration. The gel formed during the penetration of dissolution media into the matrix structure, consists of a closely packed swollen particle. The release profiles of the three factorial design formulations (F1 to F9) are shown inFig. 7.

Fig 7. Drug release profile of batches F1 to F9



Kinetic Release of Dissolution Data with DifferentModels

The results of kinetics treatment applied to dissolution profiles of the tablet of each batch are shown in Table 11.The curve fitting result of the release rate profiles of the formulation gave an idea on the release rate and mechanism of drug release. Here, in this study, Batches F1, F2, F5, F8 and F9 followed Korsmeyer Peppas model; Batch F8 followed zero-order model; Batches F1 followed the Higuchi model. Fitting of the release data to Korsmeyer Peppas model indicated that the diffusion coefficient for all the batches F1 to F9 were found to be between 0.45-0.89 indicating anomalous transport (Non-fickian diffusion) mechanism. The optimized batch showed higher values of correlation coefficient with Korsmeyer Peppas model suggesting that the primary drug release mechanism is diffusion controlled. As the combination of polymer include wax material and hydrophilic polymer it is apparent that the drug release will be diffusion controlled. However, the n value for optimized batch is 0.58 suggesting that it follows non fickian diffusion mechanism of drug release (Caccavo, Lamberti et al. 2017).

Table 11. Kinetic release of dissolution data of formulation batches

			First order	**Higuchi**	**Hixson-Crowell**	**Korsmeyer Peppas**		**Best Fit model**		
		R^2	**R^2**	**R^2**	**R^2**	**R^2**	**N**			**R^2**
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**OB**
Zero order										
k0	5.021	4.766	4.326	4.085	4.673	4.476	4.566	3.872	3.726	4.346
Rsqr_adj	0.834	0.8788	0.8936	0.8806	0.9115	0.9126	0.9143	0.9733	0.9641	0.8998
AIC	85.2559	80.9272	77.5287	77.1947	77.858	77.3681	77.997	62.4332	64.7196	77.6781
MSC	1.2736	1.6067	1.7464	1.6132	1.9597	1.9951	2.0296	3.2323	2.9296	1.9451
First order										
k1	0.114	0.098	0.079	0.072	0.093	0.085	0.089	0.063	0.06	0.0879
Rsqr_adj	0.9611	0.9554	0.9323	0.9316	0.9588	0.9669	0.9679	0.9693	0.9748	0.9587
AIC	69.2895	69.9199	72.5562	71.0675	69.4504	66.6866	67.194	63.9737	60.8138	67.0158
MSC	2.725	2.6073	2.1985	2.1702	2.724	2.9661	3.0117	3.0923	3.2847	3.0155
Higuchi										
kH	20.596	19.442	17.575	16.631	18.954	18.123	18.468	15.454	14.908	18.569
Rsqr_adj	0.9726	0.9692	0.9505	0.9559	0.9535	0.9403	0.9342	0.9107	0.9149	0.9389
AIC	65.4558	65.8762	69.1145	66.2249	70.776	73.1718	75.0835	75.722	74.1985	74.5698
MSC	3.0736	2.975	2.5114	2.6104	2.6035	2.3766	2.2945	2.0242	2.0679	2.2894

Korsmeyer-Peppas										
kKP	17.604	14.748	12.194	12.337	12.259	11.089	10.964	6.236	6.495	12.085
N	0.558	0.603	0.635	0.611	0.661	0.682	0.693	0.833	0.806	0.672
Rsqr_adj	0.9741	0.9781	0.9637	0.9643	0.9753	0.9672	0.9644	0.9836	0.9792	0.9788
AIC	65.6591	62.9597	66.5433	64.7602	64.6642	67.435	69.1862	57.8884	59.5308	68.2385
MSC	3.0551	3.2401	2.7451	2.7436	3.1591	2.8981	2.8306	3.6455	3.4013	2.7981

Accelerated Stability Study

The % drug content, entrapment efficiency, aspect ratio before and after storage was found to be nearly similar. The dissolution profiles before and after storage were nearly overlapped. The stability studies of the optimized formulation shown no significant changes in the physical parameters, % drug content and % drug release in 24 hr. The results of stability study are mentioned in Table 12.

Table 12. Results of Stability study for optimized batch

Sr. No.	Month	Entrapment efficiency	Drug Content (%)	% CDR
1	0	91.99±0.33	99.45± 0.02	96.56 ± 0.29
2	1	90.02±0.18	99.15 ± 0.01	95.28 ± 0.41
3	2	90.81±0.94	98.11 ± 0.03	93.90 ± 0.57
4	3	89.91±0.75	98.90 ± 0.01	94.01± 0.47

CONCLUSION

The matrix types of tablets are potential to be an effective sustained release drug delivery system over a prolong period of time. The type and level of polymer used are important factors that may affect the drug release and also their physicochemical properties of hot melt sustained release matrix tablets. 3^2 full factorial design was applied to achieve controlled drug release up to 24 h.The optimized formulation consisted of 12.5% of cetostearyl alcohol and 13.56% of HPMCK 100M gave sustained drug release for 24 h when compared to other formulations. The drug release kinetics follows korsemeyer-peppas. So, the mechanism was found to be non fickian and shows continuous and uniform drug release for an extended period of time, an attribute highly desirable for any sustained release formulation. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable upto 3 months.

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