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Formulation and optimization of Metformin hydrochloride matrix tablets using natural polysaccharide blend for sustained release drug delivery: a factorial design optimization approach

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ABSTRACT

The aim of this investigation was to develop and optimize Metformin HCl matrix tablets for sustained release application by response surface methodology based on two factor-three response factorial design. The effects of the amounts of polysaccharide from tamarind and polysaccharide from jackfruit in Metformin HCl matrix tablets on the properties of Metformin HCl sustained release matrix tablets drug release was analyzed and optimized. The observed responses were coincided well with the predicted values by the experimental design. The optimized Metformin HCl matrix tablets showed prolonged sustained release of Metformin HCl over 6 hours. These matrix tablets followed the first-order model with anomalous (non-Fickian) diffusion mechanism.

Keywords: Metformin, Matrix tablet, Sustained Release, Factorial, Design of experiment, Jackfruit, Tamarind, Polysaccharide

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INTRODUCTION

Matrix tablets establishes itself as potential drug delivery system due to its simplicity, cost effectiveness, reduced risk of systemic toxicity, and minimal chance of dose dumping[1,2.] With the advent of this matrix system complexicity of production including coating and pelleatization during manufacturing are sufficiently reduced and also the drug release is controlled from the dosage form by the type and proportion of polymer used in the preparations. Both the synthetic and natural polymers have been used in the preparation of matrix tablet. Matrix tablets have been prepared regardless the drug solubility. Over the years, the use of polymer combinations as blends to prolong the drug release rate has become more popular, which may allow formulators to develop sustained release dosage forms that may show performance improvements over the individual polymer components. In the development of any pharmaceutical formulation like matrix tablet for sustained release ability, an important issue is to design a formulation with optimized quality in a short time period and minimum number of trials. The response surface methodology has been commonly used for designing and optimization of different pharmaceutical formulations, which requires minimum experimentation. Thus, it is less time-consuming and cost-effective than the conventional methods of formulating dosage forms. Based on the design of experiments, response surface methodology encompasses the generation of polynomial equations and of the response over the experimental domain to determine the optimum formulation(s). A computer-aided optimization technique using factorial design was employed to investigate the effect of the amounts of various natural polymers, in polymer-blend used as two independent process variables (factors), on the properties of metformin HCl sustained release matrix tablets. Coming from renewable sources, polysaccharides also have frequently economical advantage over synthetic polymers.[3] Exploiting the use of this naturally occurring dietary polysaccharides for drug carrier means that issues of safety, toxicity and availability are simplified[4] Apart from this natural polysaccharides have been reported to have binder potential for tablet formulation.[5] Tamarind and jackfruits are also common components of Indian diet .The fruits have been used medicinally in the treatment of several disorders.[6,7] The purpose of the present study was to formulate sustained release matrix tablets using the blend of extracted polysaccharides. Metformin was used as model drug as it is absorbed throughout the gastrointestinal tract. The tablets were tested for its efficacy by performing *in vitro* dissolution test.

MATERIAL AND METHODS

Materials

Fresh young Jackfruits and Tamarind were bought from local market of Khandowa (Madhya Pradesh) for the extraction of the polysaccharide. Metformin was received as a gift sample from Yarrow Chem. Products, Mumbai. Lactose monohydrate, Magnesium stearate and other excipients used to prepare the tablets were of standard pharmaceutical grade and all other chemical reagents used were of analytical grade.

Extraction and evaluation of polysaccharide

The natural polysaccharides from the respective natural source (Tamarind pulp & Jackfruit pulp) were extracted following the method described elsewhere[8]. In this method, 250 gm natural material obtained from the source were soaked in double distilled water and boiled for 5 hrs in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight so that most of the undisclosed portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 minutes. The supernatant was concentrated at 60°C on a water bath until the volume reduced to one third of its original volume. Solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50°C under vacuum. The dried material was powdered and kept in desiccators. The extracted polysaccharides were evaluated for the following parameters:

Colour:

After complete extraction and drying the polysaccharide was evaluated for colour by visualization.

pH:

A 1%w/v solution of the polysaccharide was prepared and its pH was measured in digital pH meter.[9]

Viscosity:

The viscosity of 1% w/v solution of the polysaccharides was measured in Ostwald viscometer.

Biodegradability:

The *in vitro* biodegradation studies of the polysaccharides were carried out by viscosity measurement by using 1% w/v dispersion of the polysaccharides after incubation at 37°C for 24 hrs[10].

Preparation of Matrix Tablets

Tablets containing Metformin HCl were prepared by wet granulation technique using the formula given in the table 1 and lactose as filler. Different tablets formulations were prepared by

wet granulation method. All the powders were passed though #60 sieve. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules. Metformin HCl controlled release tablets were prepared with natural polysaccharide and other additives. Metformin HCl and, lactose were mixed together, and granulate it with the natural polysaccharide solution until a wet mass was obtained. Then the coherent mass was passed through #16 and the granules were dried at 40 + 2 °C for 2 hours. Dried granules were passed through #20 and lubricated it with magnesium stearate and talc was added to the granules. Then the lubricated granules were compressed into tablets using tablet punching machine. The compressed tablets were dedusted and evaluated for various tablet properties.

Table 1: The formulation chart for all proposed trial formulations of Metformin HCL matrix tablets.

Formulation codes	Drug (mg)	Tamarind Pulp Polysaccharide (mg)(*A*)	Jackfruit Seed Polysaccharide (mg)(*B*)	Lactose monohydrate (mg)	Talc (mg)	Mg-stearate (mg)	Total
F-1	500	40 (+1)	26(+1)	64.4	6.4	3.2	640
F-2	500	40(+1)	19(0)	71.4	6.4	3.2	640
F-3	500	26 (0)	12(-1)	92.4	6.4	3.2	640
F-4	500	26(0)	19(0)	85.4	6.4	3.2	640
F-5	500	26(0)	26(+1)	78.4	6.4	3.2	640
F-6	500	12(-1)	19(0)	99.4	6.4	3.2	640
F-7	500	12(-1)	12(-1)	106.4	6.4	3.2	640
F-8	500	40(+1)	12(-1)	78.4	6.4	3.2	640
F-9	500	12 (-1)	26(+1)	92.4	6.4	3.2	640

*(+1): higher value and (−1): lower value and (0): mid value

Drug and excipients compatibility study

The compatibility between drug and the polysaccharides was investigated using IR spectrophotometer (Shimadzu FTIR 8400S,USA) according to potassium bromide pellet method.[11]

Experimental Design

Two-factor and three-level response surface factorial design was employed for the optimization of Metformin HCl matrix tablet. The amount of natural polymers in polymer-blend, namely, amount of Tamarind Pulp Polysaccharide (*A*) and Jackfruit Seed Polysaccharide (*B*) as the prime selected independent variables (factors), which were varied at three levels (-1,0,+1). Different trial formulations of Metformin HCl matrix tablets were prepared according to the trial proposal of response surface factorial design. The formulation chart for all proposed trial formulations is

presented in Table 2. The time in hours at 20 %, 50% and 80 % cumulative drug release ($T_{20\%}$, $T_{50\%}$ & $T_{80\%}$) was investigated as dependent variable (responses). Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA) was used for generation and evaluation of the statistical experimental design. The matrix of the design including investigated factors and responses is shown in Table 2**.** For optimization, the effects of independent variables upon the responses were modeled using the following quadratic equations involving independent variables and their interactions for various measured responses, studied in this investigation. For optimization, effects of various independent variables upon measured responses were modeled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by response surface factorial design is as follows:

$T_{20\%} = b_0 + b_1 * A + b_2 * B - b_3 * A * B - b_4 * A^2 + b_5 * B^2$

$T_{50\%} = b_0 + b_1 * A + b_2 * B - b_3 * A * B - b_4 * A\text{^}2 + b_5 * B\text{^}2$

$T_{80\%} = b_0 + b_1 * A + b_2 * B - b_3 * A * B - b_4 * A\text{^}2 + b_5 * B\text{^}2$

Determination of Drug Content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 233 nm after suitable dilution using a UV- Vis double beam spectrophotometer Shimadzu 1800, Japan[12].

Weight Variation Determination

To study weight variation twenty tablets of the formulation were weighed using an Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation[13].

Hardness Testing

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined[14.]

In Vitro Drug Release Studies

The in vitro release of Metformin HCL from the formulated tablets was carried out in Tablet dissolution tester USP- Electro lab USP- TDT- 08L using 900 ml of dissolution medium maintained at 37.0 ±0.5°C and a stirring rate of 100 rpm. Six tablets from each formulation were tested individually in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer

(pH 6.8) for the following 10 h. At every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of DS resent in each sample was determined spectrophotometrically at 233 nm[15].

Kinetic Analysis of Release Data

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log (Q_0 - Q) v/st], Higuchi's square root of time (Q v/s $t_{1/2}$) and Korsmeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0 - Q) is the cumulative percentage of drug remaining after time t.

In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Statistical Analysis

The *in vitro* release data of the best formulations was subjected to statistical analysis by student's 't' test to find out the extent increase in the release rate[16].

RESULT AND DISCUSSION

Extraction and Evaluation of polysaccharides:

Both the polysaccharides obtained after extraction were creamish white in colour having viscosity of 12.46 cp & 10.34 cp and pH 6.2 & 7.1 for 1% w/v solution for Tamarind and Jackfruit polysaccharides, respectively.

Drug and excipients compatibility study:

Figure 1 shows the FTIR spectra of pure drug, pure individual polysaccharides and drug with excipients. The spectrum of the drug with excipients was compared with Metformin and the individual polysaccharide .The presence and absence of characteristic peaks associated with specific functional groups of the drug molecule was observed. The entire major peak observed in the pure Metformin was also found in the IR spectra of the physical mixture containing drug with excipients. This observation indicates that there is no well defined chemical interaction between drug molecule and the polysaccharides.

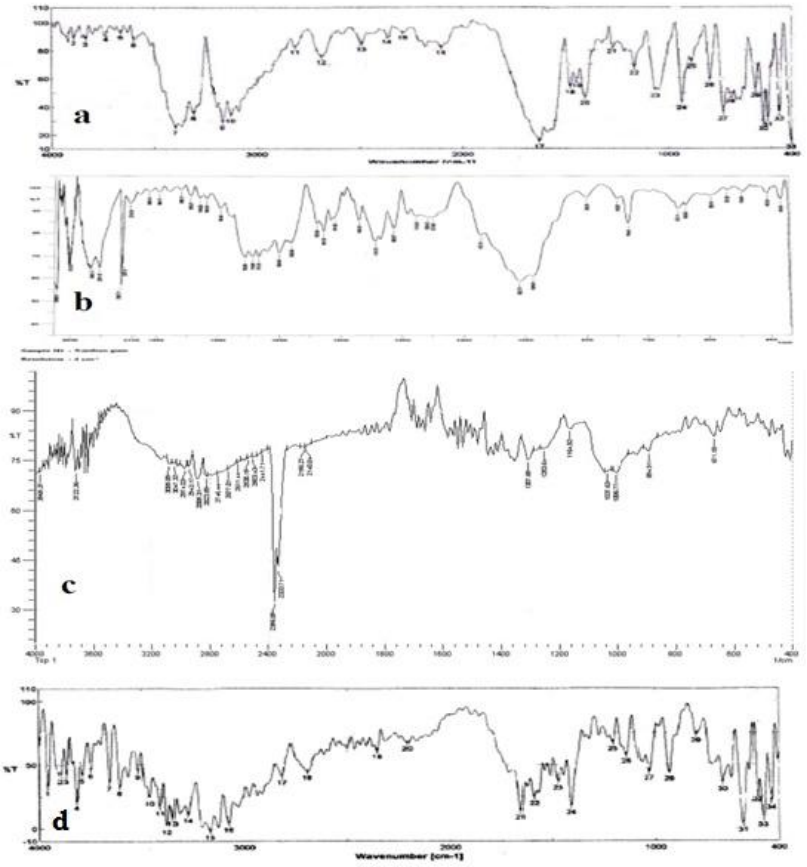

Figure 1. FTIR spectra of the a. drug (Metformin HCl), b. Jackfruit polysaccharides, c. Tamarind polysaccharide and d. Physical mixture

Optimization of Matrix Tablets

Traditionally, pharmaceutical formulators develop various formulations by changing one variable at a time, and the method is time-consuming. However, many experiments not succeed in their purpose because they are not properly thought out and designed, and even the best data analysis cannot compensate lack of planning. Therefore, it is essential to understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization [17]. A total of 9 trial formulations of Metformin HCl matrix tablets were proposed by the response surface factorial design for two independent variables: amounts of TPP (*A*, mg) and JSP (*B*, mg), which were varied at three different levels (-1, 0, +1). The effects of these independent variables on $T_{20\%}$, $T_{50\%}$ & $T_{80\%}$ were investigated as optimization response parameters in the current investigation. According to the design, various trial formulations of Metformin HCl matrix tablets were prepared by wet granulation method using ingredients stated in Table 1. Overview of the experimental trial and

observed responses is presented in Table 2**.** The results of the ANOVA indicated that these models were significant for all response parameters (Table 3). The Design-Expert 8.0.6.1 software provided suitable quadratic model equations involving individual main factors and interaction factors after fitting these data. The model equations as response became:

$T_{20\%}$ = + 2.68 + 0.80 * A + 0.32 * B - 0.058 * A * B - 0.15 * A^2 + 0.063* B^2

R^2 = 0.9999; F-value = 9503.03; P < 0.0001

$T_{50\%}$ = + 6.48 + 1.00 * A + 0.51 * B - 0.073 * A * B - 0.34 * A^2 +0.70 * B^2

R^2 = 0.9994; F-value = 955.58; P < 0.0001

$T_{80\%}$ = + 10.83 + 1.27 * A + 0.89 * B - 0.29 * A * B - 1.667E-003 * A^2 + 0.55 * B^2

R^2 = 0.9981; F-value = 319.17; P ≤ 0.0003.

Table 2: Factorial designs and their observed response values with drug contents in Metformin HCL matrix tablets

Formulation codes	Tamarind Pulp Polysaccharide (mg)(*A*)	Jackfruit Seed Polysaccharide (mg)(*B*)	Responses (Hours)		
			$T_{20\ \%}$	$T_{50\ \%}$	$T_{80\ \%}$
F-1	40 (+1)	26(+1)	3.67	8.3	13.2
F-2	40(+1)	19(0)	3.06	7.7	12.3
F-3	26 (0)	12(-1)	1.74	5.19	9.56
F-4	26(0)	19(0)	2.68	6.49	10.74
F-5	26(0)	26(+1)	3.33	7.1	12.2
F-6	12(-1)	19(0)	2.43	6.67	10.56
F-7	12(-1)	12(-1)	1.41	5.26	8.93
F-8	40(+1)	12(-1)	2.18	6.41	11.3
F-9	12 (-1)	26(+1)	3.13	7.44	12

A, and *B* represent the main effects (factors); (+1): higher value, (0): mid value and (−1): lower value.

Table 3: Summary of ANOVA for response parameters

Source	Sum of square	d.f.[a]	Mean square	*F* value	*P* value prob > *F*
For $T_{20\ \%}$					
Model	4.531536	5	0.906307	9503.027	< 0.0001 (S)
A	3.84	1	3.84	40264.08	< 0.0001(S)
B	0.627267	1	0.627267	6577.165	< 0.0001(S)
AB	0.013225	1	0.013225	138.6699	0.0013 (NS)
A^2	0.043022	1	0.043022	451.1068	0.0002(NS)
B^2	0.008022	1	0.008022	84.1165	0.0027(NS)
For $T_{50\ \%}$					
Model	8.737403	5	1.747481	955.5843	< 0.0001(S)
A	5.960067	1	5.960067	3259.176	< 0.0001(S)
B	1.540267	1	1.540267	842.2724	< 0.0001(S)
AB	0.021025	1	0.021025	11.49722	0.0428(NS)

A^2	0.226689	1	0.226689	123.9615	0.0016(NS)
B^2	0.989356	1	0.989356	541.0147	0.0002(NS)
For $T_{80\ \%}$					
Model	15.29494	5	3.058987	319.1678	0.0003(NS)
A	9.652017	1	9.652017	1007.07	< 0.0001(S)
B	4.69935	1	4.69935	490.3196	0.0002(NS)
AB	0.342225	1	0.342225	35.70698	0.0094(NS)
A^2	5.56E-06	1	5.56E-06	0.00058	0.9823(NS)
B^2	0.601339	1	0.601339	62.74234	0.0042(NS)

[a] d.f. indicates degree of freedom; T_{20}: Time in hours at 20 % Cumulative Percentage Release ; *A* and *B* represent the main effects (factors)—the amount of TPP and JSP in mg, respectively; *AB*, A^2 and B^2 are their interaction effects; S and NS indicate significance and nonsignificance, respectively.

Three-dimensional response surface plots and their corresponding contour plots to estimate the effects of the independent variables (factors) on each response investigated were presented in Figures 2, 3 and 4**.** The three-dimensional response surface plot is very useful in learning about the main and interaction effects of the independent variables (factors), whereas two dimensional contour plot gives a visual representation of values of the response [17]. The three-dimensional response surface plots and corresponding contour plots relating $T_{20\%}$, $T_{50\%}$ and $T_{80\%}$ indicate the relationship between T and all the independent variables. A numerical optimization technique based on the desirability approaches was adopted to achieve new optimized formulation with desired responses. The desirable range of these responses was restricted to $T_{20\%}$ = 3 hr, and 7 ≤ $T_{50\%}$ ≤ 7.5 and $T_{80\%}$ = 12 hr, whereas the ranges of factors were restricted to 12 ≤ A ≤ 26 mg and 12 ≤ B ≤ 40 mg. In order to evaluate the optimization capability of these models generated according to the results of selected factorial design, optimized Metformin HCl matrix tablet were prepared by wet granulation method using one of the selected optimal process variable settings proposed by the experimental design. The selected optimal process variable settings used for the formulation of optimized Metformin HCl matrix tablets were A = 18.92 mg and B = 38.12 mg. The numerical analysis was performed to acquire the optimal values of responses based on desirability criterion by the help of Design expert 8.0.6.1 software, which led to develop optimized Metformin HCl matrix tablets (F-10). Table 4 depicts the results of predicted values obtained from the mathematical model and practically observed (actual value). The results in terms of $T_{20\%}$, $T_{50\%}$ and $T_{80\%}$ of optimized Metformin HCl matrix tablets (F-10) showed acceptable results within small error values (less than 5), indicating that mathematical models achieved from the factorial design were well fitted.

Table-4. Results of experiments to assure optimization capability

Code	Tamarind Pulp Polysaccharide (mg) (*A*)	Jackfruit Seed Polysaccharide (mg) (*B*)	Responses (Hours)		
			$T_{20\ \%}$	$T_{50\ \%}$	$T_{80\ \%}$
F-10			Actual values		
	18.92	38.12	2.93	7.09	11.35
			Predicted values		
			3.00	7.44	12.00
	% Error		2.33	4.70	5.42

Actual values = mean

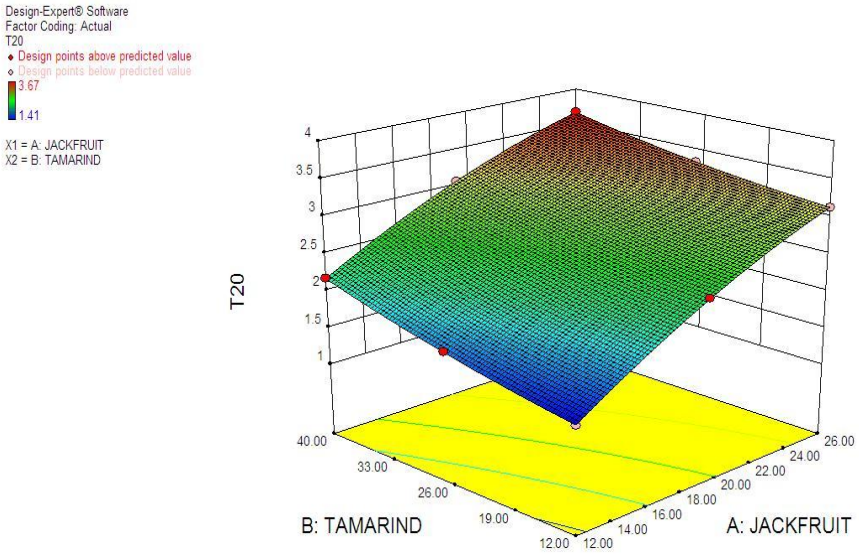

Figure-2(A). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{20\%}$ presented by response surface plot

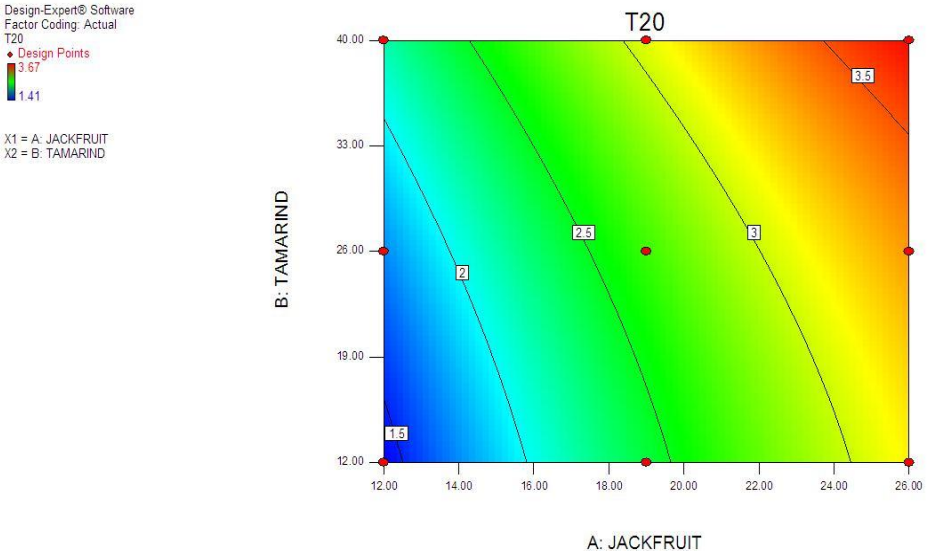

Figure-2(B). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{20\%}$ presented by contour plot

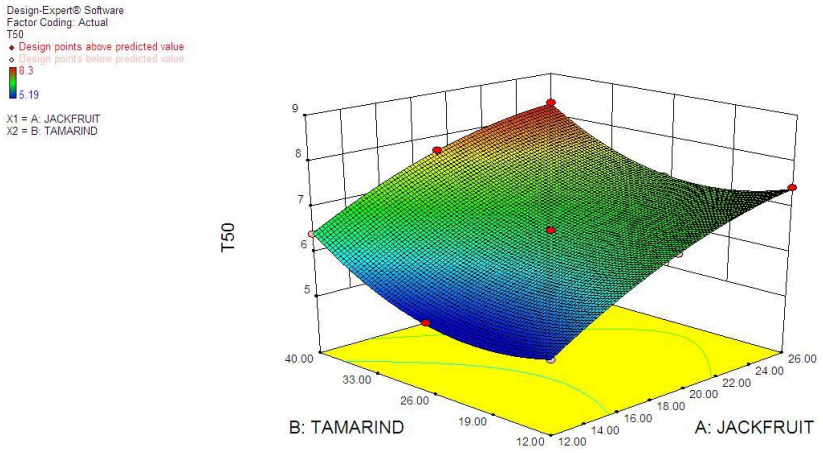

Figure-3(A). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{50\%}$ presented by response surface plot.

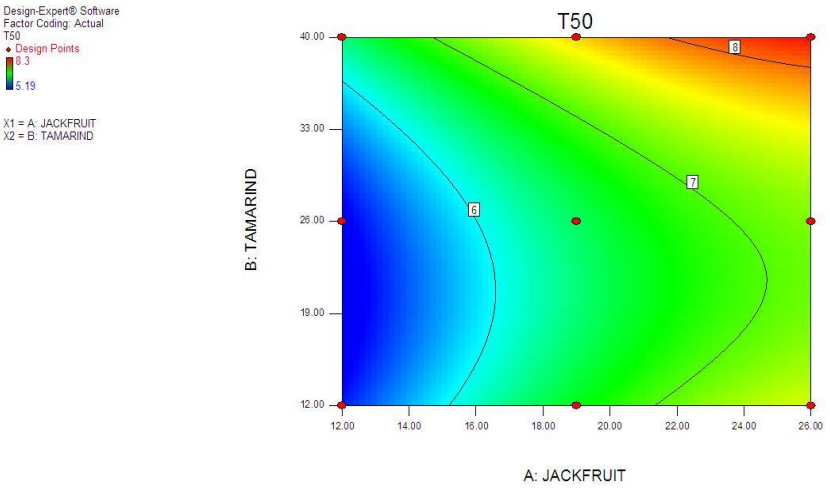

Figure-3(B). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{20\%}$ presented by contour plot

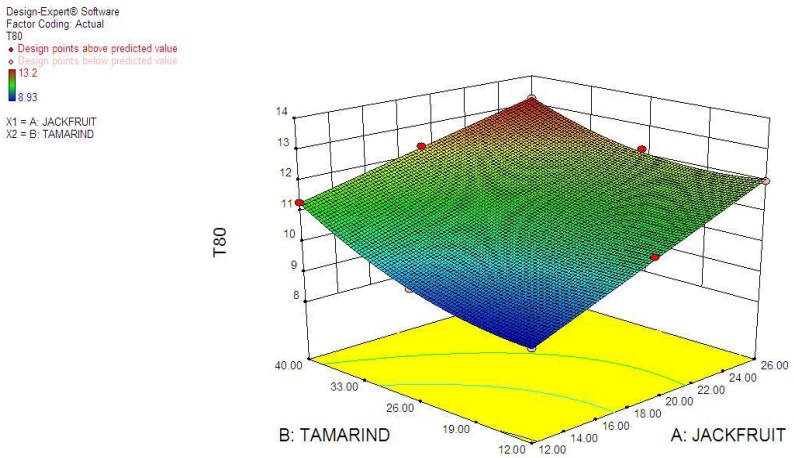

Figure-4(A). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{80\%}$ presented by response surface plot.

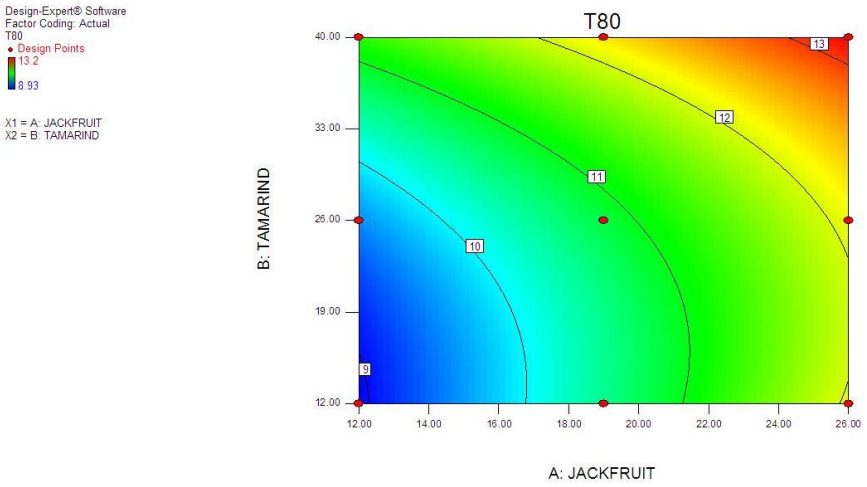

Figure-4(B). Effect of amounts of Tamarind (TPP) and Jackfruit (JSP) on $T_{80\%}$ presented by contour plot

Drug Content and Weight Variation

The percentage of drug content for all the formulated tablets was found to 97.11% to 99.79 % of Metformin HCL. It complies with official specifications. The results were shown in Table 5.

The percentage weight variations for all formulations were tabulated in Table 5. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Table 5: Post-compression characterization of Metformin HCL matrix tablet

Batch no.	Weight Variation (%) (n=20)	Hardness kg/cm2 (n=3)	Thickness mm (n=5)	Friability (%) (n=10)	Content Uniformity (%)
F-1	0.13	4.02	6.00	0.47	99.16
F-2	0.20	4.51	6.08	0.38	99.76
F-3	0.26	5.01	5.99	0.21	99.10
F-4	0.63	5.58	6.10	0.19	99.17
F-5	0.43	6.06	6.09	0.11	98.86
F-6	0.12	4.10	5.97	0.58	99.11
F-7	0.13	4.47	6.12	0.50	99.67
F-8	0.22	5.15	5.99	0.32	99.19
F-9	0.45	4.89	6.16	0.30	99.16
F-10	0.40	5.98	6.10	0.12	98.98

 # where n is number of Tablets.

Hardness

The measured hardness of tablets of each batch ranged between 4.01 to 6.11 kg/cm^2 (Table 5).This ensures good handling characteristics of all batches.

Table-6. *In vitro* drug release from various Metformin HCl matrix tablets (F-1 to F-10). Values are represented as (mean ± S.D., *n* = 3).

S. No	Time	% Cumulative Release									
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
1	30	0.34±0.03	2.33±0.09	0.99±0.43	4.36±0.52	3.71±0.23	5.35±0.40	11.5±0.09	9.74±0.05	4.75±0.98	3.50±0.23
2	60	4.49±0.13	4.57±0.49	3.10±0.41	6.78±0.63	7.06±0.48	11.04±0.52	15.49±0.43	17.02±0.34	14.35±0.19	5.89±0.62
3	120	10.78±0.13	12.07±0.20	5.25±0.52	17.51±0.26	13.78±0.62	14.41±0.17	23.47±0.18	20.59±0.61	24.45±0.44	15.65±0.57
4	180	17.07±0.31	18.56±0.55	14.89±0.63	23.95±0.86	18.49±0.76	24.79±0.68	34.44±0.12	26.15±0.68	33.87±0.56	19.41±0.19
5	240	23.37±0.43	24.058±0.48	24.53±0.39	32.39±0.77	26.21±0.41	30.16±0.62	42.42±0.27	34.72±0.33	40.65±0.09	24.17±0.61
6	300	29.66±0.21	32.55±0.43	33.17±0.26	39.82±0.34	36.92±0.72	39.54±0.47	48.4±0.29	39.29±0.42	46.89±0.36	35.93±0.53
7	360	37.95±0.46	38.04±0.33	37.80±0.83	45.26±0.37	41.64±0.46	48.91±0.81	52.38 ±0.48	45.85±091	53.67±0.21	39.69±0.85
8	480	47.54±0.16	48.03±0.20	49.08±0.71	64.13±0.34	52.07±0.68	64.66±0.54	74.33±0.47	63.99±0.83	68.34±0.78	50.21±0.29
9	540	53.84±0.483	57.52±0.13	58.71±0.44	69.57±0.49	58.78±0.86	71.04±0.82	83.31±0.33	68.56±0.46	75.82±0.41	59.98±0.71
10	600	65.13±0.23	68.01±0.46	69.35±0.51	75.00±0.91	67.49±0.85	79.41±0.31	87.28±0.32	74.13±0.27	87.38±0.63	68.74±0.59
11	720	74.72±0.62	81.00±0.42	82.62±0.35	91.88±0.87	78.92±0.23	92.16±0.26	94.25±0.55	87.26±0.18	96.53±0.55	95.27±0.87

Table-7. Results of curve fitting of the *in vitro* Metformin HCl release data from different Metformin HCl matrix tablets.

Formulation codes	Correlation coefficient (R^2)				Release exponent (*n*)
	Zero-order	First-order	Higuchi	Korsmeyer-Peppas	
F-1	0.9940	0.9481	0.8050	0.9962	1.075
F-2	0.9933	0.9355	0.8013	0.9965	1.092
F-3	0.9809	0.9120	0.7636	0.9928	1.189
F-4	0.9974	0.9459	0.8475	0.9982	0.960
F-5	0.9963	0.9616	0.8417	0.9967	0.972
F-6	0.9968	0.9387	0.8445	0.9973	0.966
F-7	0.9510	0.9556	0.9143	0.9898	0.764
F-8	0.9680	0.9570	0.8968	0.9895	0.813
F-9	0.9710	0.9584	0.9054	0.9957	0.803
F-10	0.9757	0.8922	0.7757	0.9837	1.157

In Vitro Drug Release

In vitro drug release from all Metformin HCl matrix tablets was in the 0.1N HCl (pH, 1.2) for the first 2 hours and then in phosphate buffer (pH, 7.4) for the next 4 hours. All these matrix tablets containing Metformin HCl showed prolonged sustained drug release over 12 hours. The cumulative drug release from these matrix tablets up to 12 hours of dissolution was within the range given in the table 6. The *in vitro* drug release data from various Metformin HCl matrix tablets were evaluated kinetically using various mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. The results of the curve fitting into these above-mentioned mathematical models are given in Table 7. When respective correlation coefficients of drug release from Metformin HCl matrix tablets were compared, it was found to follow the Korsmeyer-Peppas model (R^2 = 0.9928 to 0.9982) over a period of 12 hours. The value of release exponent (*n*) determined from *in vitro* Metformin HCl release data of various matrix tablets ranged from 0.764 to 1.189, indicating anomalous (non- Fickian) diffusion mechanism of drug release for F-4 to F-9 and case II transport for F-1 to F-3 including F-10.

CONCLUSION

Metformin HCl matrix tablets for sustained release application were successfully developed by response surface methodology based on factorial design. The effect of amounts of different polymers in the matrix tablets on the properties of Metformin HCl sustained release matrix tablet like drug release were analyzed and optimized. The three-dimensional response surface plots and corresponding contour plots indicated the same. These developed optimized matrix tablets showed prolonged sustained release of Metformin HCl over 12 hours, which might be beneficial over the conventional tablet to reduce the dosing frequency with improved patient compliance.

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