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Study of processing parameters affecting dissolution profile of highly water soluble drug

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ABSTRACT

The main aim of present work was to investigate the influence of processing parameters which affect the dissolution rate of highly water soluble drug. Diltiazem HCl was selected as model drug and used to prepare SR formulation. First, proper sustained release tablet formulation was selected by using different amount of HPMC K15 M and Ethyl Cellulose as sustained release polymers. Dissolution test was performed in USP apparatus 2, at 100 rpm in water as dissolution media. Selection of formula was made based on USP criteria for Diltiazem SR. After that seven different parameters: milling time (2/10 min), pre lubrication mixing time (5/10 min), lubrication time (1/5 min), compression speed (10/30 rpm), temperature (25°C/37°C), stirrer rpm (50/100 rpm) and stirrer alignment (50/100 mm) were used at two different levels to select three most critical parameters which affect the dissolution profile of drug. Initial screening was done by using Plackett Burman Design by taking 8 batches. Three selected parameters were again investigated in detail by using Face Centered Central Composite Design with three levels taking Mean Dissolution Time as primary response. The model was then analyzed by ANOVA to check the significance difference. From seven different parameters, speed of stirring, lubrication time and compression speed were found as most critical parameters for Diltiazem HCl. The detail study on three selected most significant parameters has revealed that lubrication time is the most significant parameter for water soluble drug (Diltiazem HCl).

Key words: Diltiazem HCl, HPMC K 15M, Ethyl Cellulose, Extended Release, Plackett Burman Design, Face centered central composite design

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INTRODUCTION

Dissolution is the process by which a solid of only fair solubility characteristics enters into solution.**(1)**Dissolution Rate may be defined as the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Fundamentally, it is controlled by the affinity between solid and solvent.**(2)**

There are many factors which affect the dissolution rate of the drugs. Factors related to physico-chemical properties of drugs which affect the dissolution rate are solid phase characteristics (Amorphous/Crystalline) (4), polymorphism (5), Co-precipitation & / or Complexation(6), particle size (7), molecular weight (8) and salt formation (6).Factors related to drug product formulation which affect the dissolution rate are Diluent (1), Binder & granulating agent (1), Disintegrating agent (9), lubricant (1), surfactant (10) and coating component (11).Factors related to dosage form manufacturing which affect the dissolution rate are milling (12), mixing (13), drying (14), compression force (1), and ageing (15).Factors related to dissolution test which affect the dissolution rate are agitation [(16)], rotation of speed (17), stirring element alignment (1), flow pattern distribution (1), and sampling probe, position and filter (1), temperature(1) and dissolution medium(1).

In this study, HPMC and Ethyl cellulose were used as sustained release polymers. Here HPMC K 15M is hydrophilic polymer. It is non-toxic, available in different chemical substitution and viscosity grades and having good compressibility.Ethyl cellulose is water insoluble and hydrophilic in nature. Ethyl cellulose reduces the drug dissolution rate due to its hydrophilic nature. (18)

MATERIALS AND METHODS

2.1 Materials

All materials used in this study were of analytical grade. These include Diltiazem HCl (Sun Pharma Ltd. Vadodara, India), HPMC K 15M (Lobachem Inc. India), Ethyl Cellulose (Lobachem Inc. India), MCC (Chemdyed Corporation, India), PVP K30 (Chemdyed Corporation, India), Magnesium Stearate (Chemdyed Corporation, India) and Talc (Chemdyed Corporation, India).

2.2 Experimental Design

In the first step, proper tablet formula for Diltiazem HCl was selected. Table 1 shows the different formulations. From these formulations, one suitable formulation was selected. Here dissolution test was performed as per USP at 100 RPM in water at 37°C.

Here Batch Df1 was nearest to USP criteria (Table 2). So Batch Df1 was taken for further study.

Table 1 Different SR formulations for Diltiazem HCl

Ingredient	SR			
	Df1	**Df2**	**Df3**	**Df4**
Diltiazem	**120**	120	120	120
HPMC K15 M	**60**	40	60	40
Ethyl Cellulose	**60**	40	40	60
MCC	**36**	54	56	56
Talc (1%)	**3**	3	3	3
PVP K 30	**15**	15	15	15
Magnesium Stearate(2%)	**6**	6	6	6
Total Weight(mg)	**300**	300	300	300

Table 2 USP Criteria for Sustained Release Tablet

Time(hr)	Amount Dissolved
3	between 10% and 25%
9	between 45% and 85%
12	not less than 70%

Screening of most critical processing parameters was performed using Plackett Burman design. Here, two different levels were taken for screening the parameters which are most significant. Here, in the Table 3, seven parameters were shown with two different levels.

Table 3 Screening of Processing Parameters

Factor	Associated Variable	Lower limit (-1)	Upper limit (+1)
Milling Time	(X1)	2 min	10 min
Pre Lubrication Mixing Time	(X2)	5 Min	10 Min
Lubrication Mixing time	(X3)	1 min	5 min
Compression Speed	(X4)	10 RPM	30 RPM
Effect of Temperature	(X5)	25 °C	37 °C
RPM of Paddle	(X6)	50 RPM	100 RPM
Stirring Element Alignment	(X7)	50 mm	100 mm

Table 4 Plackett Burman Design for Diltiazem HCl

Batch	(X1)	(X2)	(X3)	(X4)	(X5)	(X6)	(X7)
PDf1	**+1**	**-1**	**-1**	**+1**	**-1**	**+1**	**+1**
PDf 2	**+1**	**+1**	**-1**	**-1**	**+1**	**-1**	**+1**
PDf 3	**+1**	**+1**	**+1**	**-1**	**-1**	**+1**	**-1**
PDf 4	**-1**	**+1**	**+1**	**+1**	**-1**	**-1**	**+1**
PDf 5	**+1**	**-1**	**+1**	**+1**	**+1**	**-1**	**-1**
PDf 6	**-1**	**+1**	**-1**	**+1**	**+1**	**+1**	**-1**
PDf 7	**-1**	**-1**	**+1**	**-1**	**+1**	**+1**	**+1**
PDf 8	**-1**	**-1**	**-1**	**-1**	**-1**	**-1**	**-1**

In the Table 4, different Plackett Burman Screening batches were shown. Here batch was manufactured and dissolution test was performed by keeping the processing variable at low or high level as given in Table 4.

In this study, Lubrication mixing time, Compression speed and RPM of paddle were found to be most significant parameters.

Most significant parameters were further studied using Face centered Central Composite Design (Table 5). Here, 17 runs (14 non central points+3 central points) were taken. This design was generated using Design Expert 8.0.7.1 software (Table 6). Three center points (run CDf4, CDf9, and CDf14) were added to estimate the experimental error.

Table 5 Significant Processing Parameters

Independent Factor	Unit	Level		
		Low	Mid-Point	High
Lubrication Mixing Time	Min	5	7.5	10
Compression Speed	RPM	20	30	40
Stirrer Rotation	RPM	25	50	75

Table 6 Face Centered Central Composite Design

Run	LubricationTime (Min)	Compression Speed (RPM)	Stirrer Speed (RPM)
CDf 1	5	20	25
CDf 2	5	30	50
CDf 3	10	40	25
CDf 4	7.5	30	50
CDf 5	7.5	30	25
CDf 6	10	20	75
CDf 7	7.5	30	75
CDf 8	10	20	25
CDf 9	7.5	30	50
CDf 10	7.5	40	50
CDf 11	5	20	75
CDf 12	10	40	75
CDf 13	5	40	75
CDf 14	7.5	30	50
CDf 15	10	30	50
CDf 16	7.5	20	50
CDf 17	5	40	25

2.3 Manufacturing Process

Tablet was prepared by direct compression method. In the first step, drug was milled in Ball Mill (Hicon Lab. India) for specific time. Then it is mixed with other excipients using Double Cone Blender (Hicon Lab. India) for certain time. The blended powder was directly compressed using Rotary Tablet Punching Machine (Krishna Engineering India) at predetermined RPM speed.

2.4 Release study

For selection of proper SR formulation, release of prepared tablet was studied at 100 RPM of stirrer at 25 mm alignment from bottom using water as dissolution medium (As per USP).

For Plackett Burman Design, release study of prepared tablet was performed by keeping the processing variables at high or low level as shown in Table 4.

For Face Centered Central Composite Design, prepared tablet was further studied for dissolution testing at predetermined level of Stirrer rotation at 37°C at 25 mm stirrer alignment (USP standards).

2.5 Kinetic modelling of drug release (19)

The dissolution profile of a dosage form was ascertained statistically by measurement of the amount of the drug substance dissolved in the dissolution liquid.

(a) Mathematical Release Model

The dissolution profile of all the batches can be fitted to zero order, first order, Higuchi, Korsmeyer-Peppas to ascertain the kinetic modelling of drug release and the model with the highest correlation coefficient is then considered to be the best model.

⦿Zero Order (Time Vs. %CDR)

⦿First Order (Time Vs. log % CDR)

⦿Higuchi release (Square-root of time Vs. % CDR)
⦿Korsmeyer-Peppas (log time Vs. log % CDR)

(b) Mean Dissolution Time
The arithmetic mean value of any dissolution profile is called 'mean dissolution time' (MDT).The parameters MDT has been used not only to describe dissolution or residence Profiles with the aim to reduce the data, but also to calculate the in vitro/in vivo correlation of dissolution profiles to mode1 the input function of the drug absorption to test the equivalence of two dissolution profiles or to compare different profiles statistically. All these play an important role in the pharmaceutical dosage form development.

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

Wherejis the sample number, *n* is the number ofdissolution sample times, $t\hat{}$ is the time at midpoint between*t* and t_{j-1} (easily calculated with the expression $(t_j+t_{j-1})/2$) and ΔMiis the additional amount of drug dissolved between t_j*and*t_{j-1}

(c) Dissolution Efficiency
The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It can be calculated by the following equation:

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$

Where y is the drug percent dissolved at time t.

RESULTS AND DISCUSSION

3.1 Selection of Suitable SR Formulation of Diltiazem HCl

Here release study of Df1 to Df4 has been shown.

Table 7 Release study of Batch Df1 to Df4

Time (Hr)	%CDR			
	Df1	Df2	Df3	Df4
1	1.33	12.16	2.80	1.55
2	6.02	23.72	7.20	6.98
3	**14.10**	**32.49**	**12.35**	**10.96**
4	18.10	41.32	16.62	15.96
5	24.70	51.39	20.45	21.25
6	30.45	61.84	22.74	26.77
7	36.84	70.16	25.02	34.48
8	44.20	80.36	28.84	41.11
9	**51.41**	**94.32**	**32.88**	**47.44**
10	57.57	100.98	36.71	53.62
11	66.39		41.85	58.78
12	75.95		45.83	66.20

Table 8 Evaluation parameters for Batch Df1 to Df4

Batch	r2 Zero	%CDR	MDT (Hr)	DE%	Hardness	Weight Variation	Friability
DF1	0.9895	75.95	10.55	35.59	5.57±0.21	299.7±3.09	0.10%
DF2	0.9982	100.98	7.26	56.87	4.83±0.15	300.5±4.40	0.23%
DF3	0.9949	45.83	9.37	24.44	5.3±0.1	299.6±3.83	0.13%
DF4	0.9913	66.2	10.26	32.09	5.07±0.11	299.3±4.00	0.10%

Here, from Table 7, it can be concluded that batch Df1 is nearest to USP criteria (Table 2) for sustained release tablet. So it is selected for further study of processing parameters.

From Table 8, it can be shown that batch Df1 follows zero order release model. Mean dissolution time of Df1 is also high as compared to other three formulations. So sustained release of water soluble drug (Diltiazem HCl) has been achieved.

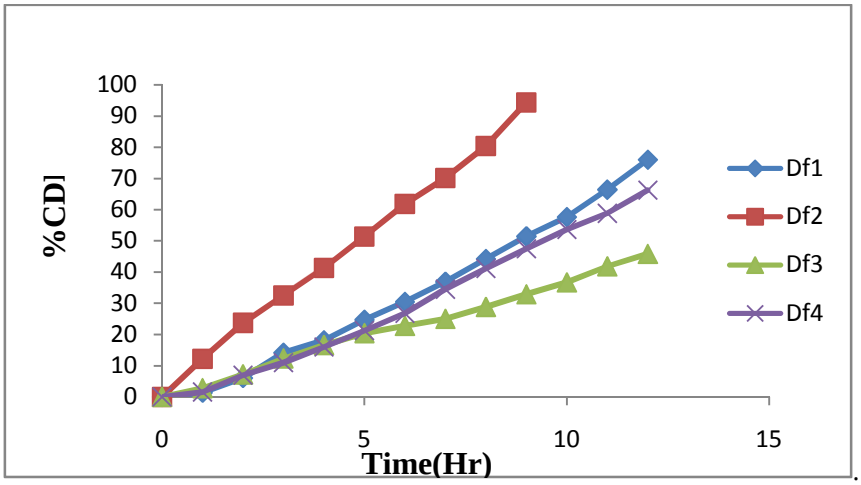

Fig.1. Dissolution profile of Batch Df1 to Df4

Here, from the fig.1. It can be seen that batch Df2 gives faster release than other batches. This is due to low amount of polymers in Df2 batch. Batch Df4 gives slow release than other batches. This is due to high amount of Ethyl Cellulose which is hydrophobic in nature and due to this, it retard the dissolution rate of Diltiazem HCl.

3.2 Screening of Processing Parameters by Plackett Burman Design

Effect of the processing parameters on the release of Diltiazem HCl has been shown on optimized Df1 SR formulation.

Dissolution profile of Plackett Burman batches has been shown below.

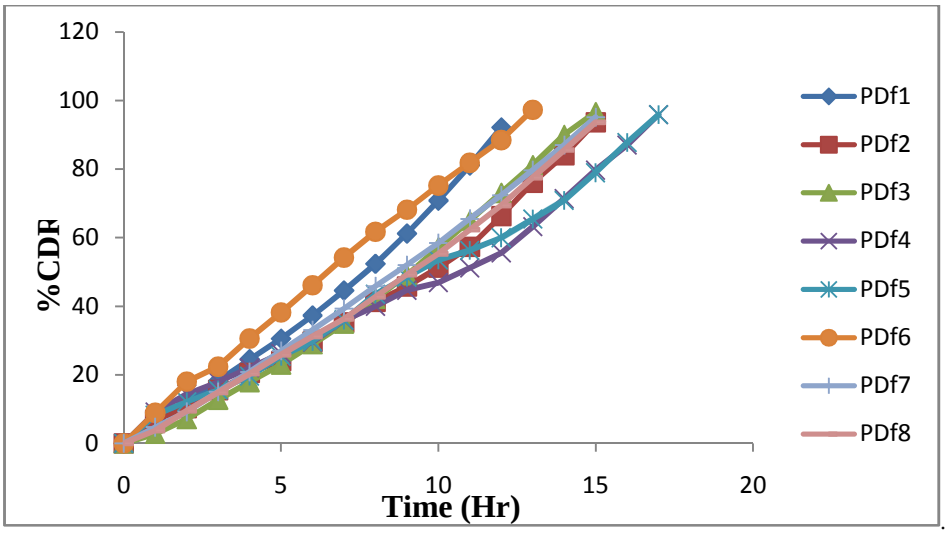

Fig.2. Dissolution profile of Batch PDf1 to PDf8

Table 9 Evaluation Parameters of Plackett Burman Design Batches

Batch	%CDR	MDT	DE	Hardness	Weight Variation	Friability
PDf1	91.39	6.95	44.4	4.63±0.06	301.9±4.17	0.76%
PDf2	93.61	8.47	43.83	5.37±0.15	299±2.21	0.53%
PDf3	96.57	8.45	45.36	5.26±0.15	296.6±2.72	0.17%
PDf4	95.82	9.25	46.47	4.96±0.1	299.4±3.53	0.20%
PDf5	95.08	9.17	46.43	4.76±0.05	300.8±4.69	0.40%
PDf6	93.61	6.39	53.16	5.06±0.21	299.4±4.60	0.20%
PDf7	93.62	8.57	46.98	5.1±0.06	301.4±3.81	0.27%
PDf8	97.3	8.71	47.74	5.06±0.2	299.2±3.53	0.30%

Here, from the Table 9, it can be concluded that as the MDT increases, Dissolution Efficiency decreases. This is due to decrease in drug dissolution rate.

Table 10 Kinetics of PDf1 to PDF8 Batches

Batch	r2			
	Zero	First	Higuchi	Korsmayer
PDf1	0.9878	0.7975	0.8706	0.826
PDf2	0.9948	0.7803	0.9008	0.8113
PDf3	0.9948	0.7886	0.8991	0.8192
PDf4	0.9923	0.7366	0.9548	0.7366
PDf5	0.9941	0.7511	0.9191	0.7871
PDf6	0.9898	0.8454	0.8643	0.8692
PDf7	0.9976	0.6862	0.9585	0.7331
PDf8	0.9979	0.8102	0.8983	0.8504

From Table 10, it can be concluded that Plackett Burman batches follows the zero order release model.

Table 11 Analysis of PDf1 to PDf8 Batches

SR NO	Factor	Co-efficient	Std. Error	P Value
1	Intercept	8.376	0.306	
2	Milling Time	-0.104	0.306	0.746
3	Mixing Time	0.0268	0.308	0.935
4	Lubrication Time	0.496	0.233	0.077
5	Compression Speed	-0.186	0.299	0.556
6	Temperature	0.0237	0.309	0.941
7	Stirrer Speed	-0.524	0.223	0.057
8	Stirrer Alignment	-0.0662	0.307	0.837

By running the Plackett Burman design, we obtain the equation which is given below.

$$Y_1 = 8.376 - 0.104X_1 + 0.0262X_2 + 0.496X_3 - 0.18X_4 + 0.02377X_5 - 0.5241X_6 - 0.0662X_6$$

From above table it can be concluded that the stirrer speed has P value of 0.05. So it is the significant parameter. Other parameters are non-significant. For further study the three most significant parameters are selected based on P value.

Those three parameters are Stirrer speed, lubrication time and compression speed.

(a) Effect of Milling Time (X1):

From polynomial equation, it can be concluded that milling time has negative effect on Mean Dissolution Time. As the milling time increases, MDT decreases due to higher dissolution. This may be due to micronization of the drug particles.

(b) Effect of Pre lubrication Mixing Time (X2):

From polynomial equation, it can be concluded that mixing time has positive effect on Mean Dissolution Time. As the pre lubrication mixing time increases, MDT increases due to low dissolution. As the pre lubrication mixing time increasing, more uniformly binder mix in the powder. So hardness of tablet increases. So ultimately release of drug decreases.

(c) Effect of Lubrication Time(X3):
From polynomial equation, it can be concluded that lubrication time has positive effect on Mean Dissolution Time. As the lubrication mixing time increases, MDT increases due to low dissolution. As the lubrication mixing time increasing, more uniformly lubricant mix in the powder.As lubricant is hydrophobic in nature, the release of drug retarded. So ultimately dissolution of drug decreases.

(d) Effect of Compression Speed (X4):
From polynomial equation, it can be concluded that compression speed has negative effect on Mean Dissolution Time. As the compression speed increases, MDT decreases due to higher dissolution. This may be due to low Dwell Time of the tablet. So hardness decreases. So ultimately dissolution of drug increases.

(e) Effect of Media Temperature (X5):
From polynomial equation, it can be concluded that media temperature has positive effect on Mean Dissolution Time. As the media temperature increases, MDT increases slightly due to higher dissolution. This may be due to high temperature. So ultimately dissolution of drug increases.

(f) Effect of Paddle Rotation (X6):
From polynomial equation, it can be concluded that paddle rotation has negative effect on Mean Dissolution Time. As the paddle rotation increases, MDT decreases due to higher dissolution. This may be due to exchange of media around the dosage form at high speed. So ultimately dissolution of drug increases.

(g) Effect of Stirring Element Alignment(X7):
From polynomial equation, it can be concluded that stirring element alignment has positive effect on Mean Dissolution Time. As the paddle alignment increases, MDT increases due to higher dissolution. This may be due to exchange of media around the dosage form at low speed. So ultimately dissolution of drug increases.

3.3 Study of Most Significant Parameters on Dissolution Rate.
Further study was performed on the three most significant parameters which were screened out by running Plackett Burman Design.

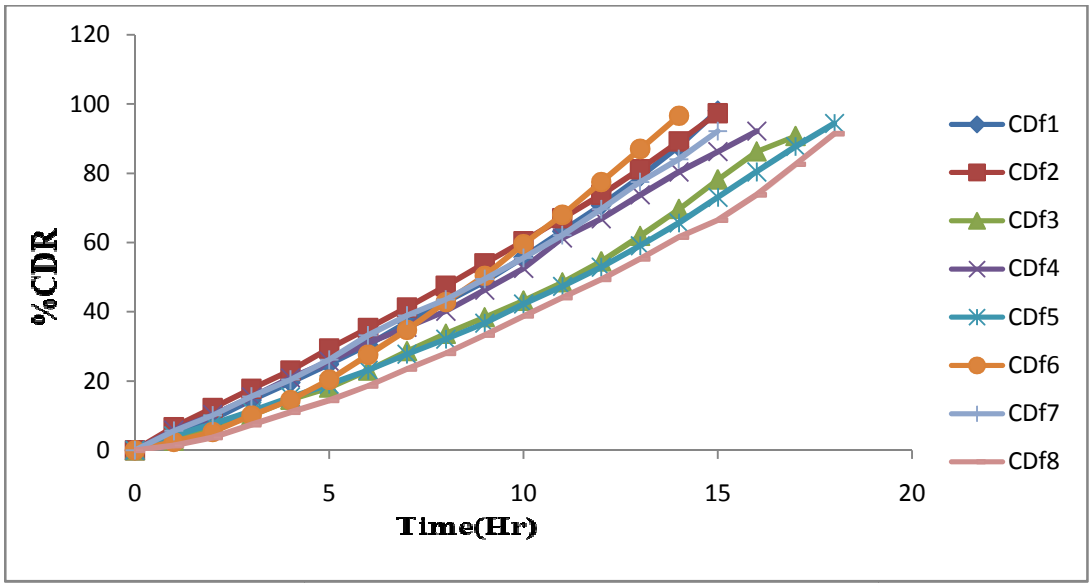

Fig.3. Dissolution profile of Batch CDf1 to CDf8

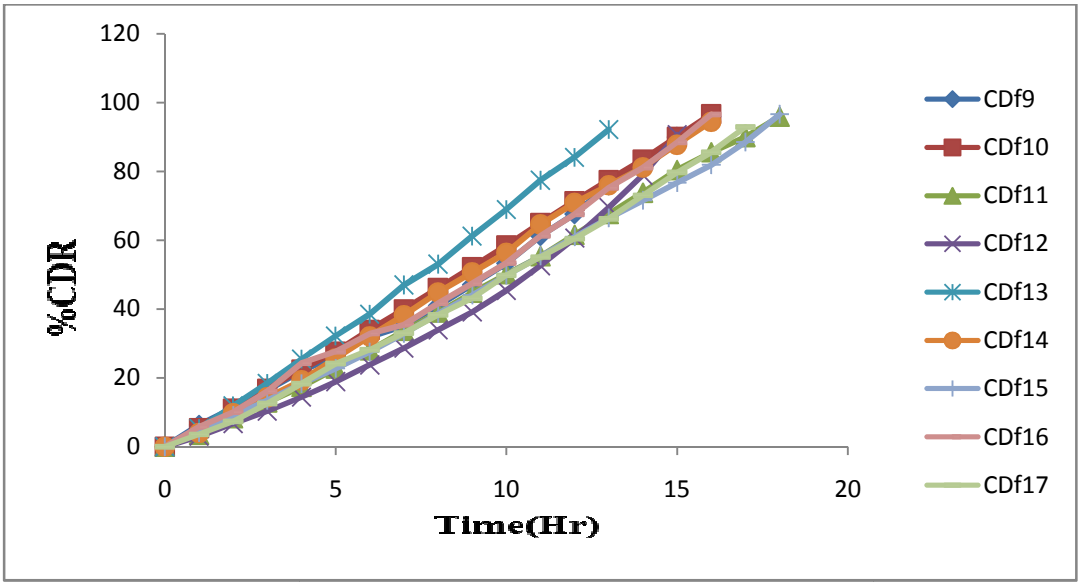

Fig.4. Dissolution profile of Batch CDf9 to CDf17

Table 12 Evaluation of CDf1 to CDf17 Batches

Batch	%CDR	MDT	DE	Hardness	Weight Variation	Friability
CDF1	98.02	8.51	45.61	5.27±0.23	298.8±3.93	0.13%
CDF2	99.67	7.94	49.03	4.13±0.23	299±3.43	0.47%
CDF3	90.69	8.9	41.69	4.13±0.11	301.8±4.10	0.23%
CDF4	92.16	8.42	46.5	4.33±0.30	296.9±3.66	0.5%
CDF5	92.15	8.4	46.61	4.33±0.30	300.1±2.81	0.53%
CDF6	96.55	8.32	42.6	5.23±0.25	300.9±3.90	0.09%
CDF7	92.15	8.08	45.57	4.67±0.11	301.7±4.99	0.46%
CDF8	91.41	10.79	39.13	5.1±0.17	300.8±4.07	0.33%
CDF9	94.36	8.34	48.09	4.67±0.11	299.1±2.64	0.2%
CDF10	96.57	8.24	49.82	3.97±0.05	300.5±3.83	0.57%
CDF11	97.28	8.83	43.22	5.2±0.2	299.1±2.33	0.1%
CDF12	90.65	9.14	37.43	4.13±0.23	298.6±3.74	0.27%
CDF13	92.14	6.87	47.83	4.27±0.30	298±3.13	0.33%
CDF14	96.56	8.58	47.79	4.56±0.06	299.9±2.88	0.37%
CDF15	96.56	9.6	47.7	4.4±0.4	300.3±2.86	0.73%
CDF16	95.84	9.42	48.33	5.13±0.23	301.4±4.24	0.07%
CDF17	92.16	8.42	46.5	4.33±0.30	296.9±3.66	0.005

Here, from Table 12 it can be concluded that Batch CDf8 has the highest Men Dissolution Time. So it gives the highest sustain release.

Table 13 Kinetics of CDf1 to CDf17 Batches

Batch	r^2			
	Zero	First	Higuchi	Korsmayer
CDF1	0.9944	0.8232	0.8845	0.8497
CDF2	0.999	0.7696	0.9188	0.8252
CDF3	0.9938	0.8612	0.8784	0.884
CDF4	0.9948	0.7886	0.8991	0.8692
CDF5	0.9966	0.7712	0.9186	0.806
CDF6	0.975	0.8974	0.8255	0.9156
CDF7	0.9979	0.7954	0.9033	0.8254
CDF8	0.9835	0.8951	0.8451	0.9159
CDF9	0.9964	0.819	0.8909	0.8471
CDF10	0.9992	0.7852	0.8176	0.8242
CDF11	0.8921	0.8621	0.8502	0.882
CDF12	0.9845	0.8688	0.856	0.8885
CDF13	0.9981	0.7892	0.9004	0.8215
CDF14	0.9945	0.7738	0.9115	0.8081
CDF15	0.9975	0.815	0.8984	0.843
CDF16	0.9976	0.8271	0.8955	0.8546
CDF17	0.9948	0.7886	0.8991	0.8692

Here, from Table 13 it can be concluded that all the batches from CDf1 to CDf17 follows the zero order release kinetics. There is no change occurs in the release pattern due to change in processing parameter level.

Table 14 ANOVA Analysis of CDf1 to CDf17 Batches

Source Model	SS	df	MS	F Value	P Value
Model	7.24	3	2.41	8.03	0.0028
Lubrication Time (A)	3.88	1	3.88	12.91	0.0033
Compression Speed(B)	1.89	1	1.89	6.29	0.0261
Stirrer Rotation(C)	1.47	1	1.47	4.88	0.0457

Here Table 14 shows that the model P value is <0.05. So model for lubrication mixing time, compression speed and stirrer rotation is significant. From the P value it can be concluded that all processing factors are more significant at high levels than lower limits.
Final Equation :

MDT = 8.63+0.62A-0.43B-0.38C

Here, A= Lubrication Mixing Time
B= Compression speed
C= Stirrer Rotation

3.4 Effect of Critical Parameters on MDT

Here, graphs obtained from the Face Centered Centeral Composite Design were shown. This helps to understand the relation between processing parameter and Mean Dissolution Time.

(i) Effect of Lubrication

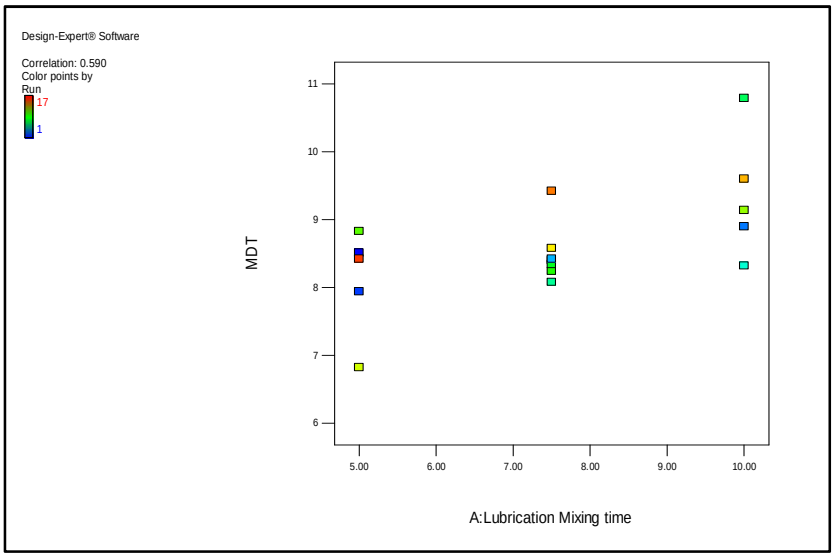

Fig. 5 Effect of Lubrication on MDT of Diltiazem HCl SR

From this graph it can be concluded that as the lubrication mixing time increase ,the mean dissolution rate of Diltiazem increase. As the mixing time increase, more uniformly Mg. Stearate (lubricant) mix and as it is hydrophobic in nature , the dissolution of drug decrease

(ii) Effect of Compression speed

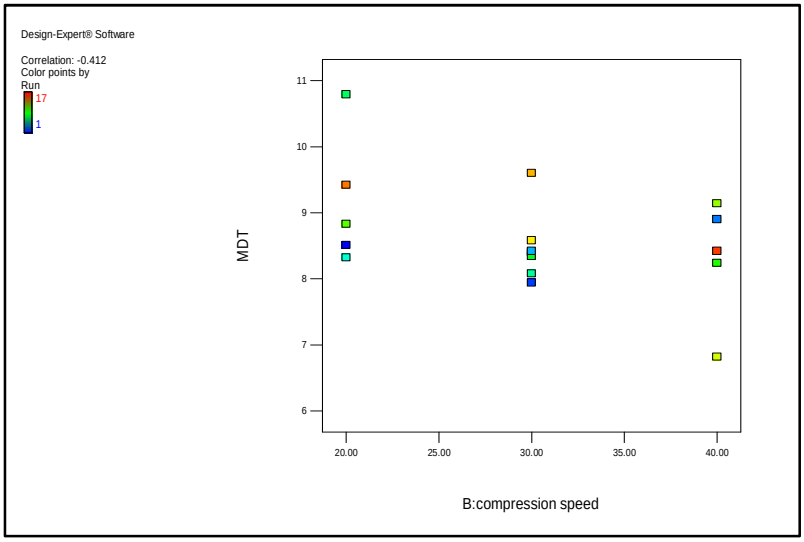

Fig. 6 Effect of Compression speed on MDT of Diltiazem HCl SR

From above graph, it can be concluded that as the compression speed increase, the mean dissolution time of drug decrease. So release of drug increases.This is due to decrease in dwell time.

(iii) Effect of Paddle Rotation

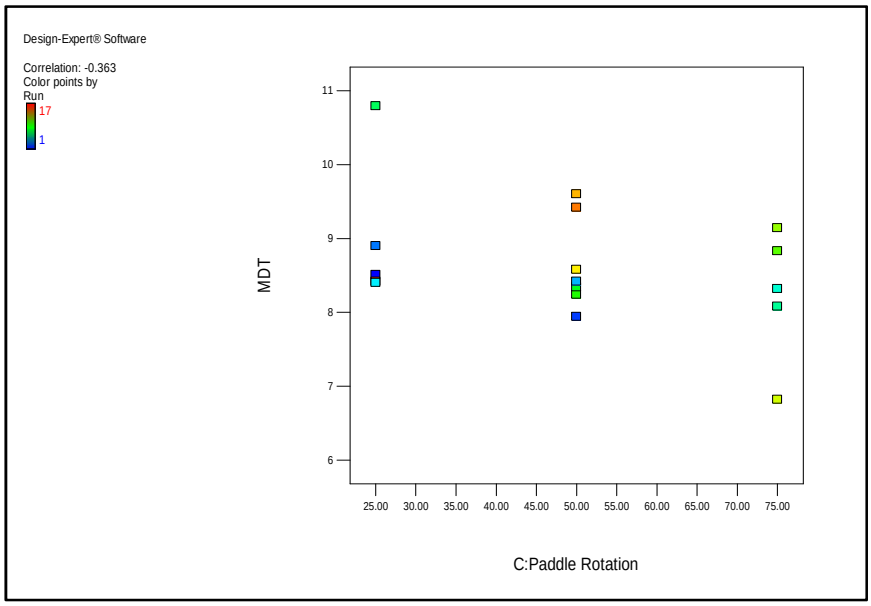

Fig. 7 Effect of Paddle Rotation on MDT of Diltiazem HCl SR

From above chart, it can be concluded that as stirrer speed increase, drug mean dissolution time decrease. This is due to continuous exchange of media around the dosage form.

3.5 Check Point Batch

By using Face Centered Central Composite Design, check point batch was found. This is given below.

Table 15 Check Point Batch

Independent Factor	Check point Batch
	DCP 1
Lubrication Mixing time	10
compression speed	20
Paddle Rotation	25

(i) Kinetic Model of Diltiazem HCl check Point Batch

Table 16 Kinetic Model of Check Point Batch

Batch	r^2			
	Zero	First	Higuchi	Korsmayer
DCP 1	0.9953	0.8407	0.8889	0.86

(ii) Evaluation parameters of Diltiazem HCl check Point Batch

Table 17 Evaluation parameters Check Point Batch

Batch	MDT	DE	Hardness	Weight Variation	Friability
DCP 1	10.18	42.21	5.06±0.21	299.4±4.60	0.20%

(iii) Comparison of Diltiazem HCl check Point Batch

Table 18 Comparison Check Point Batch

Batch	Value		% Error
	Observed Value	Predicted Value	
DCP 1	10.18	10.07	1.08

From table it can be concluded that there is less % Error. So check point batch is validated.

CONCLUSION

Statistical experimental designs are strongly recommended in identifying critical variables in the development of pharmaceutical products, particularly extended release dosage forms. Screening designs assists in isolating critical parameters that affect the desirable product response. The Plackett Burman Design allows the screening of critical parameters. The use of response surface designs allows to describe the release behavior in terms of variable study.

In summary, this study presents the screening of critical processing parameters affecting the dissolution profile of Diltiazem HCl (Class I) using Plackett Burman design and evaluation of critical parameters using Face Centered Central Composite design.

The stirrer rotation speed seems to be significant parameter affecting Mean Dissolution Time of Diltiazem HCl. With increase in stirrer speed from 50 to 100, the drug MDT decreases significantly. For Diltiazem HCl Lubrication time was found to be effective parameter. Compression speed is also having effect on Diltiazem HCl. Other less effective parameters, mixing time, media temperature and stirring element alignment was also performed. For Diltiazem HCl, stirrer speed, Lubrication time and compression speed was found to be most effective.

The further study was conducted on three most significant parameters using face centered central composite design by taking three different level. Based on ANNOVA analysis lubrication mixing time was found to be more effective at wide range than narrow range.

From this study, it can be concluding that without making changes in formulation composition, only by changing the processing parameters we can change the dissolution rate of the drug. So that burden on polymers can be reduced and it will be cost effective to sustained the release of water soluble drug.

The results of this study will provide a framework for developing QbD for Diltiazem HCl sustained release tablet

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