DESIGN, DEVELOPMENT AND OPTIMIZATION OF FAST DISSOLVING TABLET OF NEBIVOLOL HCL

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Abstract

The current research work involves preparation of fast dissolving tablets of nebivolol by direct compression method using different concentrations of superdisintegrants. A two-factor three-level (3^2) factorial design is being used to optimize the formulation. A total of 39 experimental run with 3 centre points were performed at all possible combination. The amount of % Disintegrating agent (X_1), Diluents concentration (X_2) and Disintigration agent (X_3) were selected as independent variable three levels (+1, 0, −1). The disintegration time and hardness were selected as dependent variable. All the active blends the tablets were evaluated for post compression parameters (weight variation, hardness, and friability, wetting time, disintegration time, water absorption ratio, and in vitro drug release studies). Formulation was selected by the Design-Expert software which exhibited DT (26 sec) and hardness (4 kg/cm^2). It was concluded that fast dissolving tablets with high mechanical strength and rapid disintegration without the use of superdisintegrant could be prepared, which provide better patient compliance.

Keywords: Nebivolol, Fast dissolving tablet, Optimization, Factorial design, Direct compression technique

Introduction

The oral route of administration is considered as the most widely accepted route. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients [1]. Thus, a new delivery system known as oral fast dissolving/disintegrating (FDDS)/melt-in-mouth tablets gaining importance. These oral dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water [2]. Elimination of bitterness is an important criterion in product formulation of mouth dissolving tablets [3].

The dissolution and bioavailability parameters of poorly soluble drug in a solid dosage form mainly depend upon excipients added to the formulation and their characteristics. According to these parameters the present study was proposed to formulate oral drug delivery dosage form in the form of fast dissolving tablet of nebivolol to increase its bioavailability. In the present investigation FDTs were prepared by direct compression method by using two approaches namely superdisintegrants and effervescent agent. The prepared tablets were subjected to both pre and postcompression parameters [4]. The main intention of present study was to prepare fast dissolving tablet of nebivolol using superdisintegrants and effervescent agent is to enhance the onset of action, improve dissolution and bioavailability [5].

The present study aims to formulate such a tablet that disintegrates rapidly and provides rapid dissolution of drug.

Material and method

Nebivolol HCl was kindly gifted by Glenmark Generics Limited (Colvale) Goa. PEG 6000, PVP K 30 and methanol were obtained from CDH Delhi. Avicel, lactose spray dried, mannitol, Magnesium stearate, Saccharin sodium used in the study were obtained commercially and used as received.

Methods

Preparation of solid dispersion

Solid dispersions of nebivolol: PVP K30 in different weight ratio (1:1, 1:3, 1:5, and 1:7) was prepared and characterized as per the previously published method [6]

Preparation of tablets by direct compression method

Fast dissolving tablets containing 5 mg of nebivolol were prepared by direct compression method and the formula used in the study is shown in Table 1. Different superdisintegrants such as polyplasdone xl-10, kyron T-314 and L-hpc were used. Saccharin sodium is a sweetening agent. Nebivolol was mixed in geometric proportions with sweeteners, diluents and lubricants. All the raw material were passed through a screen (60 mesh) prior to mixing. Tablets were compressed on a 10 station mini press tablet machine (Ratnakar Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Table 1: Composition of Nebivolol/PVP K30 Fast dissolving tablet by direct compression method

Batch	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
Nebivolol SD(1:7)	40	40	40	40	40	40	40
Kyron T-314	0	2	4	6	8	10	12
Avicel	35	34	33	32	31	30	29
Lactose	85	84	83	82	81	80	79
Mannitol	36	36	36	36	36	36	36
Magnesium stearate	2	2	2	2	2	2	2
Saccharin sodium	2	2	2	2	2	2	2
Total wt.(200mg)	200	200	200	200	200	200	200

Experimental design of Nebivolol HCL fast dissolving tablets

A randomized 3 level full factorial design using two factors was adopted to systematically study the formulation of FDT of Nebivolol HCL. A total of 39 experimental run with 3 centre points were performed at all possible combination (Table 3). The amount of % Disintegrating agent (X_1), diluents concentration (X_2) and Disintigration agent (X_3) were selected as independent variable (Table 2). The disintegration time and hardness were selected as dependent variable. The responses were analyzed for analysis of variance (ANOVA) using Design Expert version 8.0software.

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

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

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. [7-9]

Table 2: It shows variables in 3 level full factorial design

Independent variables-Factor	**Levels (%)**		
	Low(-1)	**Middle(0)**	**High(+1)**
X_1=% Disintegrating agent	1	3	5
X_2= Diluents concentration	40	60	80
X_3= Disintegrating agent			
Dependent variable-Response Y_1=Disintegration time (seconds) Y_2=Hardness(kg/cm^2)			

Table 3: It shows matrix of full factorial design

Run	% DT agent	Diluent concentration	DT agent
1	0	0	L-HPC
2	-1	1	L-HPC
3	1	1	Kyron T-314
4	0	0	Polyplasdone xl-10
5	0	0	L-HPC
6	0	1	Polyplasdone xl-10
7	-1	0	Polyplasdone xl-10
8	0	0	Kyron T-314
9	1	-1	Kyron T-314
10	0	-1	L-HPC
11	0	0	Polyplasdone xl-10
12	0	0	Kyron T-314
13	1	-1	Polyplasdone xl-10
14	0	1	Kyron T-314
15	-1	-1	L-HPC
16	0	0	Polyplasdone xl-10
17	-1	1	Kyron T-314
18	1	1	Polyplasdone xl-10
19	0	1	L-HPC
20	-1	0	L-HPC
21	1	-1	L-HPC
22	0	-1	Kyron T-314
23	0	0	Kyron T-314
24	0	0	L-HPC
25	0	0	Kyron T-314
26	1	0	L-HPC
27	0	0	Polyplasdone xl-10
28	1	0	Kyron T-314
29	0	0	L-HPC
30	1	0	L-HPC
31	0	1	L-HPC
32	1	0	Polyplasdone xl-10
33	0	0	Polyplasdone xl-10
34	0	0	Kyron T-314
35	-1	0	Kyron T-314
36	0	0	Polyplasdone xl-10
37	-1	-1	Kyron T-314
38	-1	-1	Polyplasdone xl-10
39	-1	1	Polyplasdone xl-10

Validation of statistical model

Levels of both the factors were selected at three different points and responses predicted by the statistical models were calculated. Fast dissolving tablets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

Response surface plots

Response surface plots were generated for each response to study the effect of both factors on each response.

Evaluation of tablet properties

Weight variation test

Weight variation test was performed as per specification given in I.P. on 20 tablets. The average weight of one tablet was determined from the collective weight. The maximum acceptable limit is ± 5% deviation of an individual mass from average mass.

Hardness

Hardness of the prepared FDTs was required to break a tablet in a diametric compression force and measured using a Pfizer hardness tester. Five tablets were chosen randomly and tested for hardness and the average was calculated. The limit for crushing strength of the tablets was kept in range of 3-4 kp.

Friability

The friability of the tablet was determined by Roche friabilator (Electro lab EF-2). Twenty tablets were weighed and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4min. The tablets were then weighed again and the percentage of weight loss was calculated. The limit of the percent friability was kept below 1%.

% Friability = $(W_0\text{-}W) / W \times 100$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Wetting time

The method was followed to measure tablet wetting time. Twice folded tissue paper was kept in a culture dish (internal diameter 5 cm) containing 6 mL of purified water. A tablet having a methyl red was added to Petri dish and tablet was carefully placed on the surface of the tissue paper. Three trials required for water to reach upper surface of the tablet was noted.

Disintegration test

The disintegration test of FDTs was studied using a modified disintegration method. Depending to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully places at the centre of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time.

Drug content

Drug content was determined by taking twenty tablets and amount of drug present in each tablet was determined. Randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 5 mg nebivolol was weighed and dissolved in 5 ml of methanol in volumetric flask, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 280 nm.

In vitro drug release study

The release rate nebivolol from fast dissolving tablets was determined using dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of pH 6.8 phosphate buffer, at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20, 25 and 30 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these solutions was measured at 280 nm using a Shimadzu UV-1800 UV/Vis double beam spectrophotometer.

Result and discussion

Evaluation of tablet properties

Nebivolol tablets were prepared by direct compression method using different concentration of superdisintegrant (0 - 6 %). To study the effect of different superdisintegrant types (polyplasdone xl-10, kyron t-314 and L-hpc) with different concentrations (0 - 6%) on the flowability of the powder blend and the physical properties of the prepared nebivolol fast dissolving tablet. Kyron T-314 displays best results among all superdisintegrents of the fast dissolving tablets. Tablets prepared with 0% kyron t-314 disintegrated in 65.16 seconds and release 71.64%. While with 6 % of kyron t-314 tablet disintegrated in 26.09 seconds and drug release was found to be 95.37% (Fig. 1). Considering disintegration time of tablets and drug release, tablets were optimally prepared using solid dispersion of drug in the ratio of drug/PVP K-30 at 1:7 and with 6 % kyron t-314. The hardness, friability, disintegration time, drug content and weight of formulated tablets are described in Table 4. All the parameters are within the acceptable range. Good uniformity in drug content was found amongst different batches.

Table 4: Technological characterization of Nebivolol/PVP K-30 SD (1:7) fast dissolving tablets

Parameter Formulation	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
T1	199.8±0.56	3.4±0.07	0.56±0.04	65.16±0.91	97.04±1.09
T2	198.8±0.35	3.7±0.38	0.59±0.09	55.13±0.54	98.02±1.07
T3	198.7±0.28	3.1±0.21	0.53±0.05	47.28±0.72	98.34±1.21
T4	200.2±0.35	3.7±0.14	0.55±0.08	42.02±1.06	99.15±1.44
T5	198.6±0.07	3.9±0.14	0.61±0.07	36.08±0.17	99.57±1.82
T6	199.3±0.14	3.2±0.28	0.51±0.03	30.01±0.05	98.96±1.37
T7	200.0±0.08	3.8±0.07	0.54±0.06	26.09±0.12	99.88±1.51

Data are expressed as mean ± S.D. (n = 3)

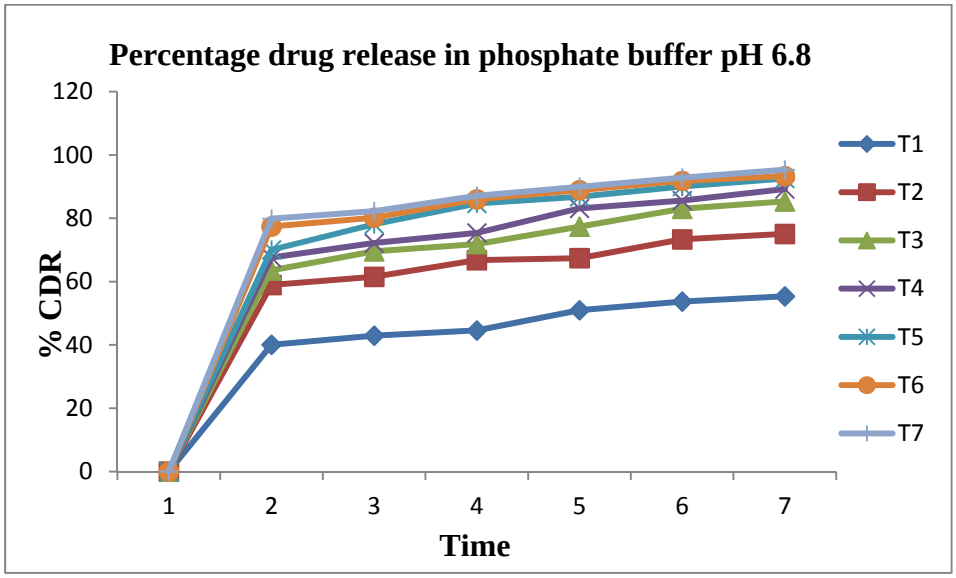

Fig 1. Dissolution profile of studies of Nebivolol/PVP K-30 SD (1:7) fast dissolving tablets

Responses for each experimental run

The optimization was carried out in different groups and each group consists of 39 formulations. The prepared formulations were evaluated for the disintegration time and percent friability.

After application of factorial design and with help of obtained polynomial terms the optimized tablet was produced which have targeted to the disintegration time 26 sec and percent friability 0.4 kg/cm^2. The optimized amount of the independent factors (amount of polymers/superdisintegrants) was incorporated in the tablet which was also used as the check point of the regression analysis model. A mathematical equation was generated for each response parameter. The mathematical models were tested for significance. Response surface plots were generated for each response to study the behavior of the system. The groups are tabulated below

Table 5 It shows responses for each experimental run

Run	Response[a]	
	Y_1(sec.)	Y_2(kg/cm^2)
1	35	3.7
2	54	3.8
3	34	4.0
4	32	4.2
5	36	3.8
6	30	4.3
7	51	3.9
8	30	4.1
9	35	4.3
10	34	3.5
11	31	4.2
12	29	4.0
13	30	4.3
14	36	3.6
15	53	3.3
16	31	4.1
17	55	3.5
18	31	4.5
19	38	3.8
20	52	3.6
21	34	3.9
22	35	3.6
23	30	4.1
24	34	3.6
25	30	4.2
26	30	4.1
27	33	4.2
28	29	4.4
29	35	3.7
30	33	4.0
31	34	3.7
32	29	4.4
33	32	42
34	30	4.1
35	35	3.5
36	32	4.0
37	51	3.2
38	57	3.7
39	56	3.7

[a]Data are expressed as mean±SD (standard deviation), n=3.

Y_1=Disintegration time (seconds), Y_2=Hardness (kg/cm^2)

The fitted equations (full and reduced) relating the responses to the transformed factor are shown in (Table 5). Analysis of variance (ANOVA) was carried out to identify the insignificant factors, which were then removed from the full model to generate the reduced model (Table 6) and (Table 7).

Table 6: It shows ANOVA for response surface reduced cubic model for disintegration time

Response model	Sum of square	df	Mean square	F value	P value	R^2	Adequate precision
DT	2969.88	16	185.62	43.50	<0.001	0.9694	20.128

The Model F-value of 43.50 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. "Adequate Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 20.128 indicates an adequate signal. This model can be used to navigate the design space.

Table 7: It shows ANOVA for response surface reduced quadratic model for hardness

Response model	Sum of square	df	Mean square	F value	P value	R^2	Adequate precision
Hardness	3.79	17	0.22	31.52	<0.0001	0.9623	24.163

The Model F-value of 31.52 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. "Adequate Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 24.163 indicates an adequate signal. This model can be used to navigate the design space.

Table 8: It shows summary of result of regression analysis for disintegration time

Model	b_0	b_1	b_2	$b_{3(1)}$	$b_{3(2)}$	b_{12}	$b_{13(1)}$	$b_{13(2)}$	$b_{23(1)}$
FM	31.60	- 8.33	0.33	3.02	0.39	-0.42	-0.39	-2.39	0.33
RM	-	-	0.33	-	-	-0.42	-	-	0.33
Model	$b_{23(2)}$	b_1^2	b_2^2	$b_1^2b_{3(1)}$	$b_1^2b_{3(2)}$	$b_1b_2^2$	$b_2^2b_{3(1)}$	$b_2^2b_{3(2)}$	
FM	-0.69	7.41	3.91	-0.58	2.87	-2.42	-2.01	-2.63	
RM	-0.69	-	-	-	-	-	-	-	

Table 9. Summary of result of regression analysis for hardness

Model	b_0	b_1	b_2	$b_{3(1)}$	$b_{3(2)}$	b_{12}	$b_{13(1)}$	$b_{13(2)}$	$b_{23(1)}$
FM	3.99	0.32	0.078	-0.28	0.20	-0.067	-0.100	-7.675	0.72
RM	-	0.32	0.078	-0.28	0.20	-0.067	-	-	-
Model	$b_{23(2)}$	b_1^2	b_2^2	$b_1^2b_{3(1)}$	$b_1^2b_{3(2)}$	$b_2^2b_{3(1)}$	$b_2^2b_{3(2)}$		
FM	5.556	0.019	-0.16	0.11	-0.083	0.090	0.10		
RM	-	0.019	-0.16	0.11	-0.083	0.090	0.10		

For disintegration time, the coefficients of X_1 and X_2 that is b_1, and b_2 respectively, bear a negative sign, thus on increasing the concentration of kyron T-314 and concentration of mannitol, a decrease in disintegration time is observed. For hardness, the coefficients of X_1 and X_2 that is b_1, and b_2 respectively, bear a positive sign and negative sign respectively, thus on increasing the concentration of kyron T-314 and concentration of mannitol, an increase and decrease in hardness is observed. When a higher percentage of mannitol is used, porosity in the tablet matrix is greater and thus assists in water uptake and subsequent disintegration. Further result showed that

kyron T-314 concentration had significant effect on tablet hardness, thus by using combination of kyron T-314 and mannitol provide tablets with high mechanical strength with low disintegration time.

6.7 Validation of statistical model

To validate the statistical model checkpoint batches, CP1 and CP2 were prepared according to the formula (Table 10). From the response surface plot (Fig. 3 and Fig. 4) and the calculations from the statistical equation obtained by regression, the results revealed the close match of the experimental results. Thus, we can conclude that the statistical model is mathematically valid. The best batch was selected after considering the requirements of an FDT.

Table 10 It shows comparison of predicted values and experimental values for check point batches

Formu--lation code	Predicted values (DT)	Experimental values (DT)	Residual	Predicted values (Hardness)	Experimental values (Hardness)	Residual
CP1	31.24	32.15±0.89	0.91	4.24	4.29±0.26	0.05
X1= +0.75						
X2= -0.75						
CP2	42.61	43.35±0.76	0.74	3.62	3.65±0.41	0.03
X1= -0.75						
X2= +0.75						

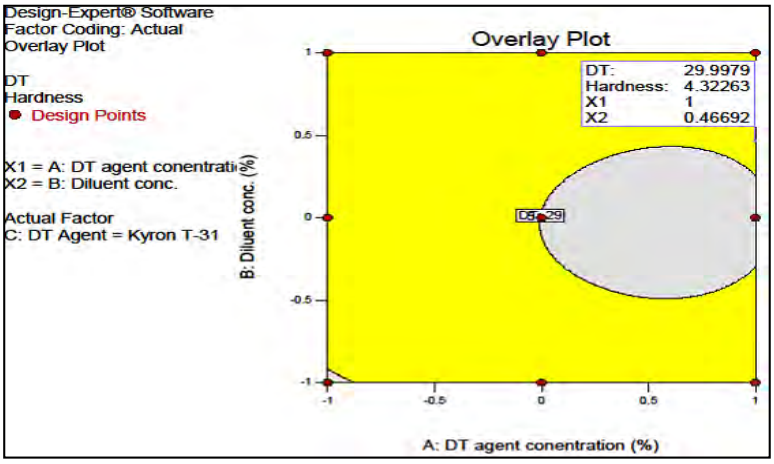

Fig. 2: It shows overlay plot eliciting the effect of X_1 (DT agent concentration) and X_2 (Diluent concentration)

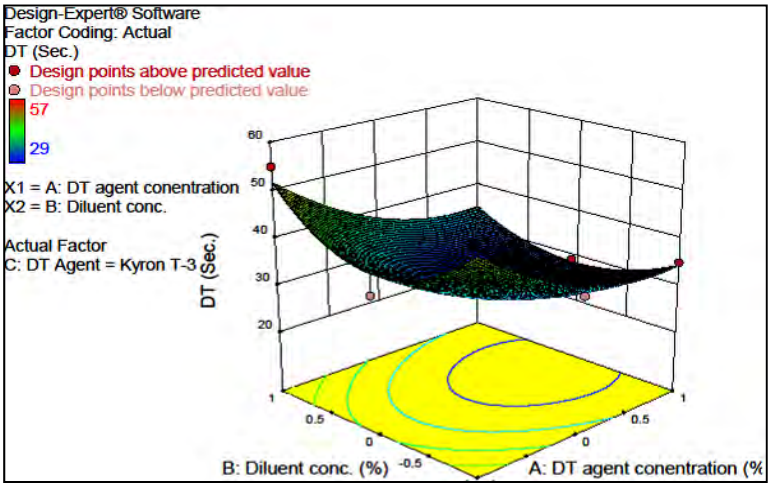

Fig. 3: It shows response surface plot eliciting the effect of X_1 (DT agent concentration) and X_2 (Diluent concentration) on Y_1 (DT)

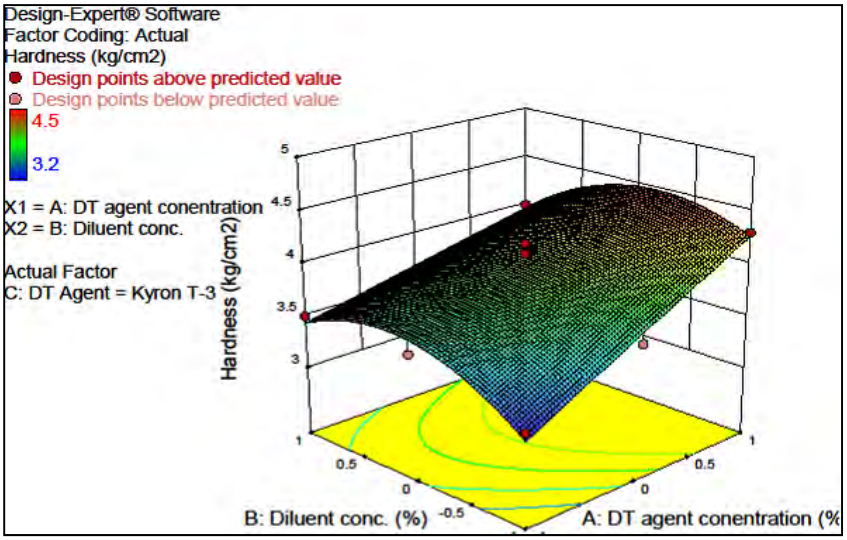

Fig. 4: It shows response surface plot eliciting the effect of X_1 (DT agent concentration) and X_2 (Diluent concentration) on Y_1 (Hardness)

To full fill these requirements, concentration of kyron T-314 was set maximum and concentration of mannitol 70%. Disintegration time and hardness were kept in range. The batches dissolution rates were also considered and batches with higher dissolution rates were given priority. Different constraints were applied; solution with desirability 1 was selected (Table 11).

Table 11: It shows predicted desirability

Number	**Kyron T-314**	**Lactose**	**Hardness**	**DT**	**Desirability**
1	**5%**	**70%**	**4.45**	**29.99**	**0.982**
Predicted responses at 95% confidence (n=1)					
Response	**Prediction**	**Std. Dev**	**SE (n=1)**	**95% PI low**	**95% PI high**
DT	29.99	2.065	1.46	24.75	35.25
Hardness	4.45	0.084	0.059	4.24	4.67

Friability of optimized tablet was below 1% which showed good mechanical resistance. All the parameters i.e. thickness, diameter, weight, friability, drug content and wetting time were under acceptable limits.

Table 12: It shows characterization of optimized tablet (FDT)

Parameter Formulation	**Thickness (mm)**	**Diameter (mm)**	**Weight (mg)**	**Friability (%)**	**Drug content (%)**	**Wetting time (seconds)**
FDT_s	3.1±0.43	9.0±0.18	200±0.56	0.41±0.03	99.61±1.68	24±0.49

[a]Data are expressed as mean±SD (standard deviation), n=3.

From the results of dissolution study of the optimized tablet revealed rapid release of drug in phosphate buffer pH 6.8 compared with pure drug. From in vitro dissolution data it was concluded that there may be rapid absorption (98.27%) of the drug formulation as compared with the pure drug in Fig. 5

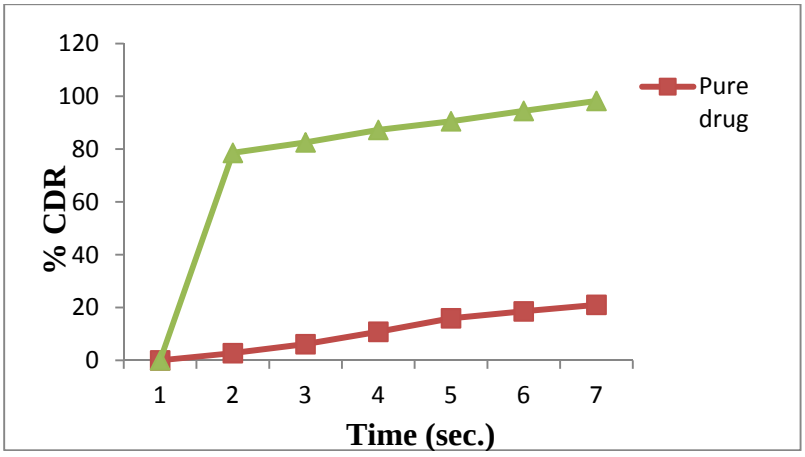

Fig. 5: It shows in-vitro release profile of optimized formulation (FDT) and pure drug

Comparison of predicted responses and observed values for the disintegration time and hardness were in close agreement (Table 13), and the models were found to be valid. Thus, full factorial design with two factors can be successfully used to optimize the formulations.

Table 13: It shows comparison between predicted and observed response

Predicted Values[a] (Disintegration time)	**Experimental Values[a] (Disintegration time)**	**Predicted Values[a] (Hardness)**	**Experimental Values[a] (Hardness)**
29.99±0.86	26±0.79	4.45±0.21	4±0.06

[a]Data are expressed as mean±SD (standard deviation), n=3

Conclusion

Fast dissolving tablets of nebivolol were formulated and optimized using 3^2 factorial designs. Two independent variables, that is, amount of Kyron T-314 and amount of lactose at three levels were selected on the basis of preliminary studies. Addition of superdisintegrant Kyron T-314 leads to significant effect on disintegration characteristics as well as drug release. But higher concentrations of Kyron T-314 had negative impact on drug release and disintegration time. In the present investigation Fast dissolving tablets of Nebivolol HCl having rapid disintegration and good mechanical strength was prepared using direct compression technique. Result of the study showed that disintegration time and hardness was strongly dependent on concentration of Kyron T-314 and mannitol. Comparison of predicted responses and observed values for the same showed close agreement, and the models were found to be valid. Hence, 3 level full factorial design and statistical models can be successfully used to optimize the formulations.

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