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Article

Development of fast dispersing tablets of nebivolol: experimental and computational approaches to study formulation characteristics

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Formulation of FDT (fast dispersing tablets) of nebivolol was optimized and evaluated using simplex lattice design (SLD). The influence of type and concentration of three disintegrants *viz.,* Ac-Di-Sol, Primojel and Polyplasdone XL on hardness, friability and disintegration time of tablet was studied. Response surface plot and the polynomial equations were used to evaluate influence of polymer on the tablet properties. Results were statistically analyzed using ANOVA, and a $p < 0.05$ was considered statistically significant. Results reveal that fibrous integrity and optimal degree of substitution in Primojel and Ac-Di-Sol are mainly responsible for the hardness of the tablet. Use of Polyplasdone in higher percentage in tablet formulation may result in high friability. Increase in concentration of Ac-Di-Sol increases the disintegration time but increased concentration of Primojel in the tablet formulation decreases the disintegration time. This is also evident from model terms for disintegration time with a high '*F'* value of 14.69 and '*p'* value of 0.0031 (<0.05). The reason could be that Primojel has higher swelling properties and an optimum hydration capacity, which favors fast disintegration of a tablet. In conclusion, careful selection of disintegrant for FDT could improve their properties. Use of Simplex Lattice Design for formulation development could simplify the formulation process and reduce the production cost.

Uniterms: Nebivolol/fast dispersing tablets. Simplex lattice design. Tablets/fast dispersing/swelling capacity. Tablets/fast dispersing/hydration capacity. Tablets/fast dispersing/disintegration time.

Otimizou-se e avaliou-se formulação de comprimidos de dispersão rápida (CDR) de nebivolol, usando planejamento de grade simplex (PGS). Estudou-se a influência do tipo e da concentração de três desintegrantes *viz*, Ac-Di–Sol, Primojel e Poliplasdona XL, na dureza, friabilidade e tempo de desintegração do comprimido. O gráfico de superfície de resposta e as equações polinomiais foram utilizados para avaliar a influência do polímero nas propriedades do comprimido. Os resultados foram analisados estatisticamente por ANOVA, considerando-se $p < 0,05$ como estatisticamente significativo. Os resultados revelam que a integridade das fibras e o grau de substituição ótimo no Primojel e Ac-Di-Sol são os principais responsáveis pela dureza do comprimido. O uso de Poliplasdona em maior porcentagem na formulação pode produzir friabilidade elevada. O aumento de Ac-Di-Sol aumenta o tempo de desintegração, mas o aumento da concentração de Primojel na formulação diminui o tempo de desintegração. Isto é, também, evidente no modelo de tempo de desintegração com alto valor de "F" de 14,69 e "p" de 0,0031 (< 0,05). A razão poderia ser que o Primojel tem maiores propriedades de intumescimento e ótima capacidade de hidratação, favorecendo a desintegração rápida do comprimido. Em conclusão, a cuidadosa seleção de um desintegrante para CDR poderia aprimorar suas propriedades. O uso do PGS para o desenvolvimento da formulação poderia simplificar o processo de formulação e reduzir o custo de produção.

Unitermos: Nebivolol/comprimidos de dispersão rápida. Planejamento de grade simplex. Comprimidos de dispersão rápida/capacidade de intumescimento. Comprimidos de dispersão rápida/capacidade de hidratação. Comprimidos de dispersão rápida/tempo de decomposição.

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INTRODUCTION

Nebivolol is a selective beta-1 receptor antagonist used for the management of hypertension and angina pain. It reaches mean peak plasma concentration approximately in 1.5 to 4 h post oral administrations (Na, Larry, 2002). In such cases it is very essential to enhance onset of action of a drug.Therefore, in this work the goal has been set to formulate and evaluate fast dispersing tablets (FDT) of nebivolol. FDT improve bioavailability of drugs by rapid disintegration/dissolution/dispersion in oral cavity and by pregastric absorption of dispersed drugs that pass down into the stomach. The amount of drug which is subjected to first pass metabolism is also reduced from FDT as compared to conventional tablet(Tansel *et al.,* 2011; Shery, Arun, Anroop, 2009). Super disintegrant is the principle ingredient of the FDT to accommodate rapid disintegration time of the formulation. Efficiency of the formulation is varied according to the type and proportion of disintigrant in it (Deshika,Viness, Yahya, 2009; Alvaro,Consuelo, Ramón, 2011), since each disintegrant works on several unique properties, such as swelling properties (Zhao, Larry, Augsburger,2005), hydration capacity(Seong*et al.,*2008), among others. These properties in turn depend upon the basic nature of the polymer chain (Zhao, Larry, Augsburger, 2005), degree of cross linking (Bi Y*et al.,* 1996) and type of cross linking (Gohel *et al.,* 2004; Rashid *et al.,* 2008) along the polymer chain. Hence, selection of an ideal disintegrant for the formulation is a real challenging work. Three super disintegrants *viz.,* Ac-Di-Sol (Cross-linked carboxymethyl cellulose), Primojel (sodium salt of carboxymethyl ether of starch) and Polyplasdone XL (Cross-linked poly vinyl pyrrolidone) were tested individually and in combination. The experiment was executed using simplex lattice design (SLD) in order to simplify the formulation procedure and to optimize the formulation with limited number of trials (Zhou *et al.,*2011). SLD is useful when the trial - error approach may not be possible for the formulation design and the relationship between influential factors and output response in the work is complex.

MATERIAL AND METHODS

Material

Nebivolol HCl(Sanofi Aventis Pharma, Ltd, India) was received as a gift sample. Ac-Di-Sol, Primojel, Polyplasdone XL, (Loba chem. Pvt. Ltd. Mumbai) microcrystalline cellulose (MCC) and mannitol (Sisco Research Laboratories Pvt. Ltd) were purchased. All other chemicals used in the study were of analytical grade. Stat-ease Design-Expert® software is used to design the formulation.

Compatibility studies

Drug-excipient interactions were checked by performing FTIR study of nebivolol alone and its physical mixture with Ac-Di-Sol, Primojel and Polyplasdone XL on Bruker optics, Germany Model: Tensor 27. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}, represented as % transmittance *versus* wave number.

Simplex lattice design and statistical analysis

Simplex lattice design was adopted to optimize the formulation variables. Three dependent variables *viz,* hardness (kg/cm^2), friability (%) and disintegration time (sec) were evaluated by changing the concentrations of disintegrants (independent variables) *viz*; Polyplasdone XL (A), Ac-Di-Sol (B) and Primojel (C). Ten batches (F1-F10) of FDTs were prepared, considering one at each vertex (A, B, C), one each at the halfway point between vertices (AB, BC, and AC), one at the center point (ABC) and one each at the corner of the vertex (ABC, BAC, CAB) as shown in Figure 1. Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices and at corner represents a formulation containing the average of the minimum and maximum amounts of the 3 ingredients. The center point represents a formulation containing one third of each ingredient (Tadashi *et al*., 2011; Shirsand *et al.,*2010).

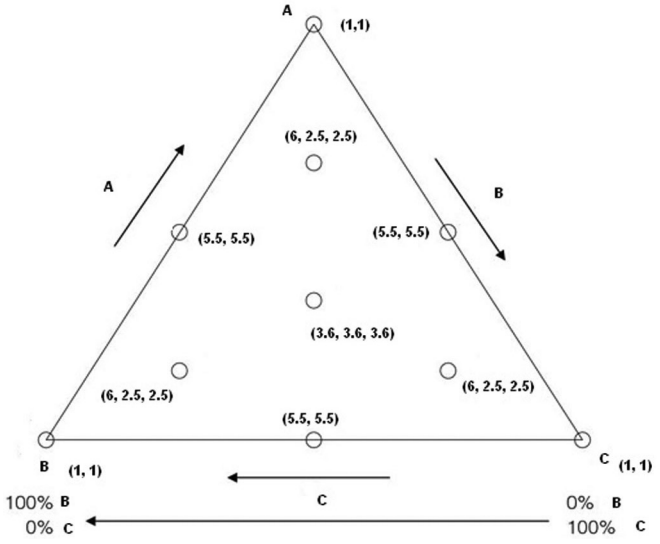

FIGURE 1 - Simplex lattice design for 3 components (A, B and C) system.

Analysis of variance (ANOVA) was performed to identify insignificant factors. The significance test for regression coefficients was checked using Student 't'test. Coefficient is significant if the calculated 't'value is greater than the critical value of't'(<0.05) (Gohel *et al.,*2007a).

Formulation development

The raw materials (Table I) of the formulation were passed through a #80 screen in dry state prior to mixing. Known quantities of drug, disintegrants, MCC and mannitol were weighed and mixed for the period of 10 min in a mortar. This powder mixture was lubricated with magnesium stearate, talc and then finally with vanillin. The lubricated powder was compressed into tablets with 10-station Rimek Minipress RSB-1 tablet punching machine using 7 mm concave punches. The dimensional specifications were measured using thickness gauge (Okimoto). Hardness of the tablet was measured using Monsanto hardness tester.

Drug content estimation

Standard calibration curve of nebivolol was constructed using UV-Visible spectrophotometer (Shimadzu-1700, Kyoto, Japan). Drug solution was prepared in 0.1 N HCl at the concentration range from 4 to 60 µg/mL, sonicated, filtered using 0.45 µ (Millipore) membrane filter. The drug content of standard drug solution and tablet formulation was measured at 281 nm against 0.1 N HCl as a blank solution (Lakshmana,Rajeswari, Sankar, 2010). This method was found to have good repeatability, reproducibility and relative standard deviation (RSD) was not more than 2%. The working curve equation was Y=0.016x with correlation coefficient value, $r^2 = 0.999$.

Friability test

Roche friabilator was used for testing the friability of all the batches of tablet formulation. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min the tablets were weighed and the percentage loss in tablet weight was determined.

% Friability = [Initial weight - Final weight / Initial weight] x 100 (2)

Disintegration test

Disintegration test was performed for six tablets selected randomly from each batch. USP disintegration apparatus without disc consisting 900 mL of simulated salivary fluid (pH 6.4, without enzyme) maintained at 37 ºC was used. The disintegration time in sec was recorded as mean±SD of 6 tablets.

In vitro drug release

The *in vitro* drug release studies of F1, F5, F10 and a check point batch F11 was conducted in USP dissolution testing apparatus II (Paddle type). The dissolution fluid is 900 mL of 0.1 N HCl maintained at

TABLE I - Simplex lattice design for formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Nebivolol HCl*	5	5	5	5	5	5	5	5	5	5
Primojel *	11	0	0	3.6	6	2.5	2.5	5.5	5.5	0
Polyplasdone XL*	0	11	0	3.6	2.5	6	2.5	5.5	0	5.5
Ac-Di-Sol*	0	0	11	3.6	2.5	2.5	6	0	5.5	5.5
Mannitol*	105	105	105	105	105	105	105	105	105	105
Magnesium stearate*	2	2	2	2	2	2	2	2	2	2
Talc*	1	1	1	1	1	1	1	1	1	1
Vanillin*	1	1	1	1	1	1	1	1	1	1
MCC Q.S*	150	150	150	150	150	150	150	150	150	150
Factors and corresponding level of disintegrant in the formulation										
Variable levels in coded form (Factor)					0.000	0.227	0.333	0.500	0.545	1
Actual disintegrant level (mg)					0	2.5	3.6	5.5	6	11

*All Quantities are in mg

37±0.5 ºC at an agitational speed of 75 rpm (Riikka, *et al.,* 2010; Botzolakis, Small, Augsburger, 1982). Samples equal to 2 mL were withdrawn at an interval time of 1min and up to 7 min, and the concentration was read on spectrophotometer at 281 nm.

RESULTS AND DISCUSSION

Compatibility studies

Drug-excipient interactions play a vital role with respect to biological performance and stability of the formulation. The characteristic absorption peaks obtained for drug alone and in presence of polymers (1:1 ratio) are depicted in Figure 2. From the spectra, it was observed that there were no changes in the main peaks of drug. Further, the frequencies of peaks were within the standard range, shown in Table II. This indicates that the drug was compatible with the selected disintegrants.

Simplex lattice design

The general equation for the response based SLD for three components system consisting terms for pure component and mixtures of component is

$$Y = b_o + b_1 A + b_2 B + b_3 C \qquad (3)$$

where, Y is the response variable and A, B and C are the proportions of formulation components. The b_0 is the arithmetic mean response of the 10 runs, and b_1, b_2 and b_3 are estimated coefficient for the factor A, B and C respectively. The coefficients can be calculated from the response (Y) of multiple regression equation. The fitted equations relating the hardness, friability, disintegration time to the transformed factor are shown in equation 4, 5, 6 respectively. These polynomial equations were used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The contour plot is also presented in

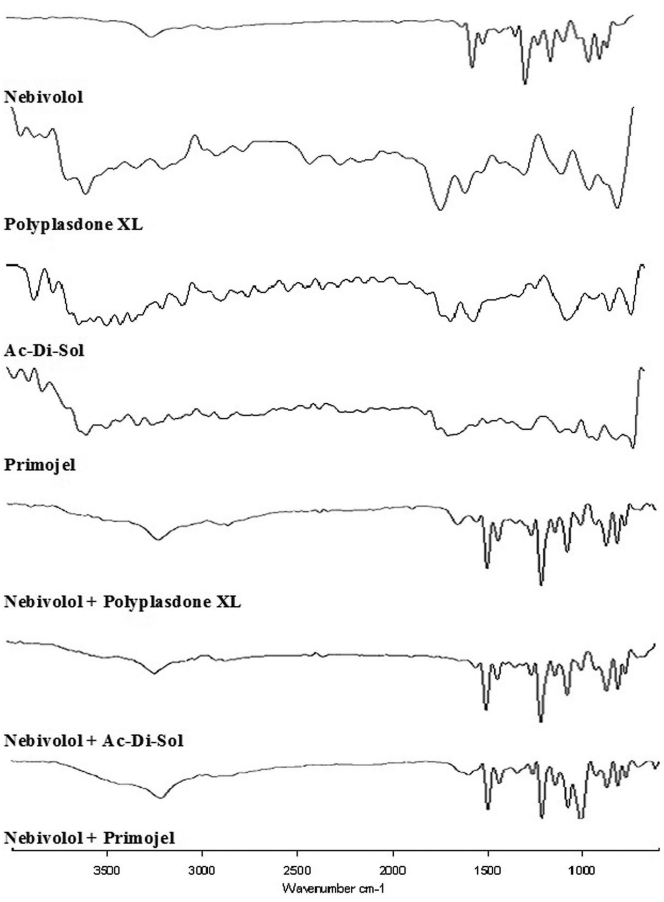

FIGURE 2 -FTIR spectra of nebivolol, Polyplasdone XL, Ac-Di-Sol, Primojel and physical mixture of drug with disintegrants.

Figure 3 to graphically represent the effect of independent variables on the responses. Table III shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors (Schwartz, 1996).

Effect of independent variables on hardness

The hardness of the formulations were found to be between 2.90±0.25 to 3.37±0.05 kg/cm^2(Table IV). FormulationsF2 and F6 resulted inlower hardness in which Polyplasdone XL is a principle disintegrant.This is also

TABLE II - Frequency of peaks observed in FTIR spectra for nebivolol and its physical mixture with disintegrants

Functional group	Nebivolol (cm^{-1})	Nebivolol and PolyplasdoneXL (cm^{-1})	Nebivolol and Ac-Di-Sol (cm^{-1})	Nebivolol and Primojel (cm^{-1})
O-H aromatic stretch	3444.86	3420.69	3453.62	2900-3600
Aromatic C-H stretch	3040.79	2976.74	2987.12	2922.74
N-H aromatic stretch	3189.30	3197.19	3197.94	3197.07
C-O aromatic stretch	1208.14	1211.66	1211.57	1211.73

TABLE III - Summary of ANOVA table for dependent variables from simplex lattice design

Source (Linear mixture)	Sum of squares	Degree of freedom	Mean square	'*F*' value	Probability '*p*' value
Hardness	0.020	2	0.010	2.27	0.1741
Friability	5.242E-003	2	2.621E-003	0.28	0.7660
Disintegration time	47.30	2	23.65	14.69	0.0031*

*p< 0.05 indicate model terms are significant

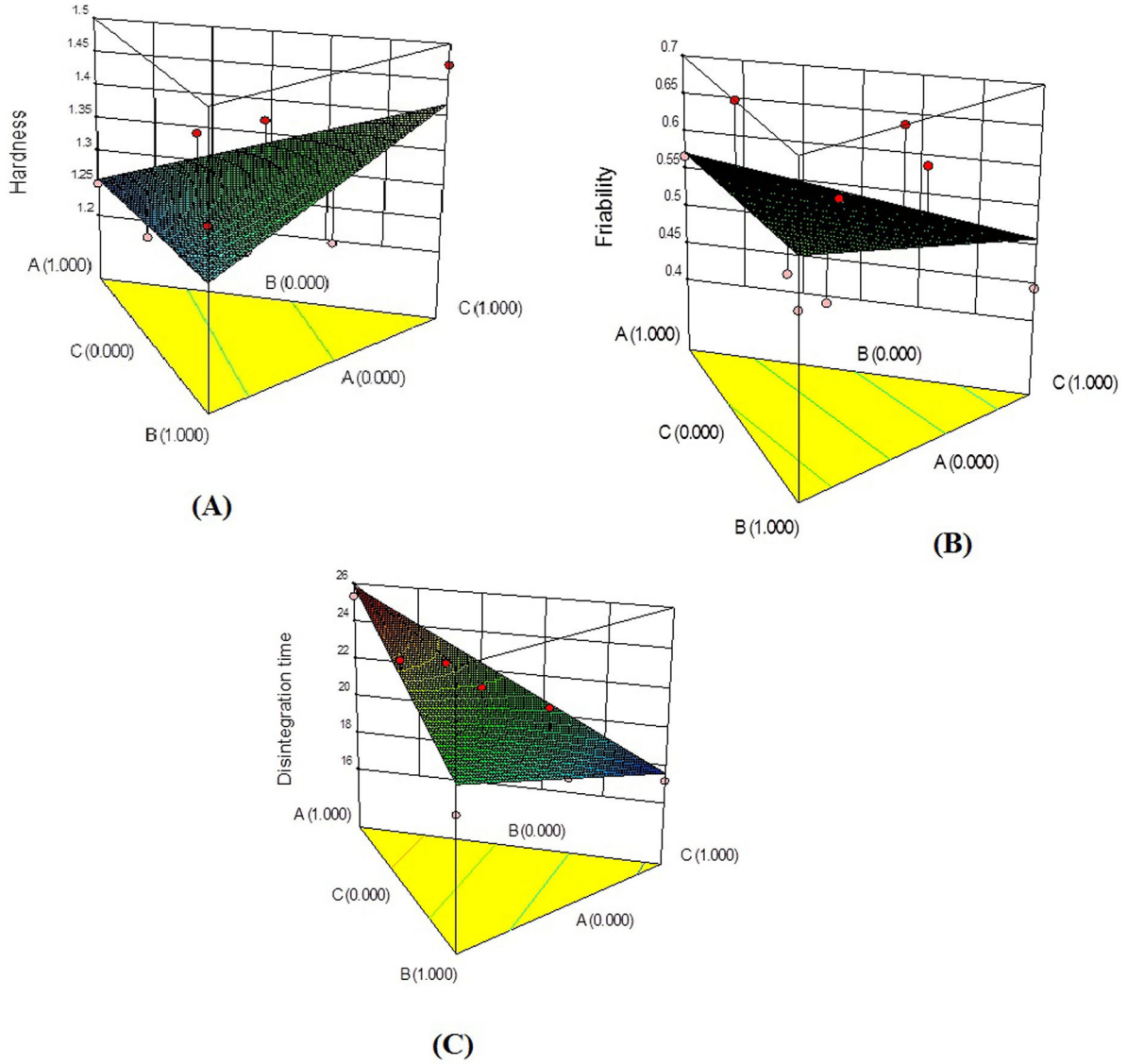

FIGURE 3 - Response surface plot showing the effect of concentration of Polyplasdone XL, Ac-Di-Sol and Primojel on (a) hardness (kg/cm^2), (b) friability (%) and (c) disintegration time (Sec).

evident from the polynomial equation for hardness shown below. However, the linear model terms for hardness on the polynomial equation is appers to be insignificant with a '*F*' value of 2.27 and '*p*' value of 0.1741 (<0.05).

Y1 (Hardness) = 2.25*A + 2.27*B + 2.41*C (4)

Above polynomial equation infers that concentration of factor 'A' has less contribution to hardness than B and C (Figure 3a). Reason would be that, Polyplasdone particles appear to be granular, highly porous and exhibit virtually no tendency to undergo binding and compaction (Sunil *et al.,* 2007). Whereas tablets made with Primojel (C) and

TABLE IV - Formulation characteristics

Formulation	Hardness (kg/cm²)*	Friability (%)	Disintegration time (sec)*	Drug content (%)	Tablet weight (mg)*	Thickness (mm)*
F1	2.25±0 .057	0.482	17.16±0.75	95.00	151.12±1.3	3.22± 0.021
F2	2.95 ± 0.22	0.628	21.33±0.51	97.85	149.40±1.0	3.21± 0.024
F3	3.17 ± 0.13	0.468	26.16±0.65	99.28	150.60±0.7	3.21± 0.023
F4	3.22 ± 0.20	0.574	23.03±0.81	96.42	150.40±1.2	3.21± 0.019
F5	3.47 ± 0.15	0.556	25.70±0.75	95.00	150.83±3.15	3.22± 0.022
F6	2.90 ± 0.25	0.672	22.33±0.54	96.42	149.80±1.89	3.21± 0.026
F7	3.42 ± 0.14	0.51	25.33±0.28	97.14	150.20±1.41	3.20±0.022
F8	3.25 ± 0.18	0.50	24.10±0.25	95.71	150.30±1.11	3.20± 0.21
F9	3.37 ± 0.19	0.526	21.16±0.75	97.85	149.90±1.09	3.20± 0.023
F10	3.27 ± 0.24	0.544	26.16± 0.75	98.57	150.50±1.18	3.21± 0.021

*Average of 6 determination ± standard deviation

Ac-Di-Sol (B) develops better hardness because of their fibrous integrity and optimal degree of substitution in the molecule (Komal *et al.,* 2011). These results infers that FDT made with Polyplasdone XL alone does not result with significant hardness.

Effect of independent variables on friability

The experimental results of friability of all the formulations were within 1% limit.

Y2 (Friability) = 0.59*A + 0.57*B + 0.50*C (5)

Equation 5 and Figure 3b indicates that the friability is not dependent on any specific variable chosen for the study. Also, model terms for friability were found to be insignificant on a linear model with a very less '*F'* value (0.28) and higher '*p'* value (0.766) than the critical value (<0.05). This infers that the selected disintegrants in the quantities does not promote friability of the tablet. However, least friability was observed with the formulation which chiefly contains either Ac-Di-Sol (B) or Primojel (C) or in combination. Highest friability was observed with formulations in which polyplasdone (A) is the main ingredient. Hence, it is understood that the use of polyplasdone (Parmar Shah, Sheth, 2011) in higher percentage may yield a tablet with high % of friability.

Effect of independent variables on disintegration time

The experimental results for the disintegration time showed a wide variation (Table IV) between the formulations. The formulation, which chiefly contains Primojel or combination of Primojel and Polyplasdone showed lowest disintegration time. This is well evident from the polynomial equation shown below.

Y3 (Disintegration time) = 20.74*A + 25.87 *B + 17.58 *C (6)

Magnitude of coefficients observed for disintegration time indicates that the effect of factor 'C' has significant and the factor B has insignificant effect on the disintegration time. This is also evident from response surface plot which indicates higher level of Primojel will decrease the disintegration time and the higher level of Ac-Di-Sol will increase the disintegration time (Figure 3c).The model terms are also significant with a higher '*F*' value of 14.69 and '*p'* value of 0.0031 (<0.05). The reason could be that Primojel can take up of water many times its own weight and swell powerfully without losing its fibrous integrity (Leonardi, 2007). The combination of rapid water penetration into tablets through the hydrophilic, fibrous particles and the subsequent development of a strong disintegration force make Primojel a very effective disintegrant (Achor,Oyi, Isah,2010).

Polyplasdone also performs better disintegrating action than the Ac-Di-Sol. Porous nature of Polyplasdone particles facilitates wicking of liquid into the dosage systems and causes rapid disintegration. Due to high crosslink density of Polyplasdone, it swells rapidly in water without gel formation than others. These properties make it a good disintegrant for oral administration (Kornblum,Stoopac, 1973).

Disintegration property of Ac-Di-Sol is based on

TABLE V - Coded quantities of the check point batch "F11" and their desirability

Constraints			
Name	**Goal**	**Lower limit**	**Upper Limit**
Hardness	Maximize	3.42±0.14	3.47±0.15
Friability (%)	Minimize	0.468	0.628
Disintegration time	Minimize	17.16±0.75	23.33±0.28
Primojel	Is in range	0	1
Polyplasdone XL	Is in range	0	1
Ac-Di-Sol	Is in range	0	
Solutions (Desirability)			
Parameter	**Primojel**	**Polyplasdone XL**	**Ac-Di-Sol**
Hardness (kg/cm^2)	6	2.5	2.5
Friability (%)	11	0	0
Disintgration time (sec)	0	5.5	5.5
Check point batch composition	2.5	3.6	5.5

*All values are mean of 6 readings ± SD

TABLE VI - Experimented and predicted values of check point batch 'F11'

Parameter	Predicted values	Experimented values*
Hardness (kg/cm^2)	3.47±0.15	3.85±0.23
Disintegration time (sec)	17.16±0.75	16.38± 2.31
Friability %	0.468	0.482

powerful water uptake and it takes up more than 20 times its own weight of water. Rapid water penetration into the tablets and powerful swelling results in rapid disintegration. However, Ac-Di-Sol fails to exhibit rapid disintegration of the tablet formulation because it exhibits virtually a tendency towards gel formation at high ratio. The formation of a viscous gel may impede water penetration into the tablet which is not favorable for orally disintegrating tablets. Hence tablet which chiefly contains Ac-Di-Sol may not show fast disintegration (Gohel *et al.,* 2007b).

A checkpoint batch F11 was also prepared (Table V) by considering the constraints and with a desirability to improve the *in vitro* performance of the formulation F1, F3, and F5 with respect to friability, hardness and disintegration time. The experimental results of formulation F11 were listed in the Table VI. Predicted results were almost similar to the observed experimental values indicates the accuracy of the design.

Drug release study

Formulations F1, F3, F5 and F11 were subjected for drug release study, have released 90% of drug within 5 min and drug release ranged from 93.81±0.73 to 98.58±0.01% (Figure 4).Drug release from the formulation F11is most satisfactory and it releases 98.58±1.2 of drug in 5 min. This

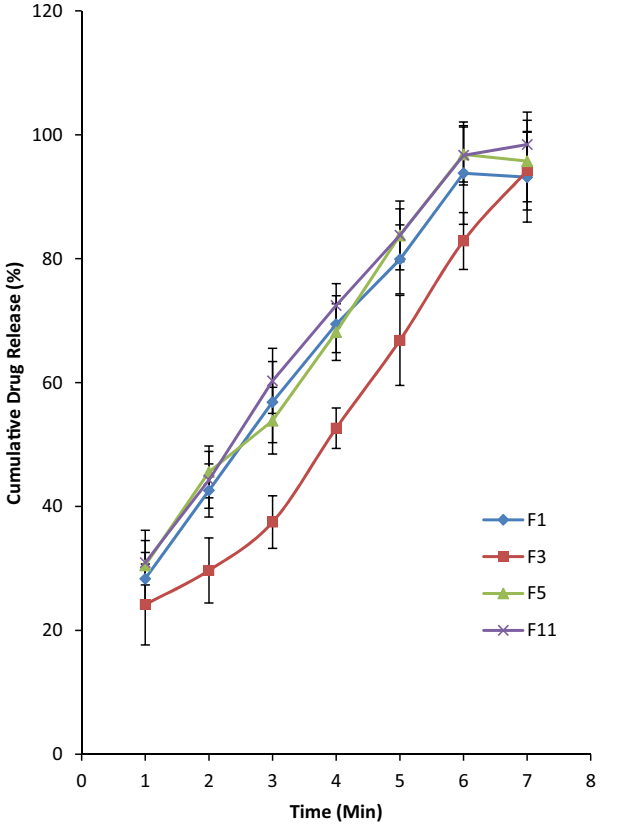

FIGURE 4 - Comparative drug release profile of FDT formulations.

signifies the incorporated disintegrants in the quantities doesn't affect the drug release. Based on above analysis, we decided to select formulation F11 as an optimized FDT of nebivolol HCl.

CONCLUSIONS

This research work signifies the importance of type and proportion of disintigrant in the performance FDT. Judicious combination of different disintegrants in a concentration may incorporate all the ideal characteristics such as optimal hardness, least friability and fast disintegration time. Optimal ratio of each disintegrant in the formulation can be optimized by adopting a systematic formulation approach in the shortest time with minimum efforts using SLD. Simplex lattice design could also reduce production costs and simplify the formulation process.

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