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Development of Metoprolol Tartrate Orally Disintegrating Tablets 50 mg using Design of Experiments.

Rakesh K. Patel[1*], Mukesh C. Patel[1], Mukesh R. Patel[1,2]

1. S.K.P.C.P.E.R., Dept. of Pharmacy, Ganpat university, Ganpat Vidyanagar, Mehsana-382711, India

2. Restech Pharmaceuticals, National highway no 8A, moraiya, Ahmedabad, India

ABSTRACT

The objective of the current study was to develop and optimize an orally disintegrating tablet formulation of Metoprolol tartrate which is an effective drug in the treatment of hypertension. Metoprolol tartrate orally disintegrating tablets were prepared by direct compression method using different ingredients such as Mannitol, Microcrystalline cellulose, Aspartame, Crospovidone, Sodium starch glycolate, Croscarmellose sodium, Powder flavours Strawberry, peppermint & orange, Colloidal silicon dioxide and Magnesium stearate. Tablets were evaluated for the physical properties, out of which disintegration time and wetting time were considered as responses in a 3^2 full factorial experimental plan. Results were statistically examined using design expert software and polynomial mathematical equations; found to be statistically significant ($p<0.05$) for disintegration time and wetting time data. The obtained results were used to generate optimized overlay plot. The physical data from the numerical optimization were verified and found to be very close to those predicted from the regression analysis. Accelerated stability study was also performed on the optimum formulation. All results were in accordance with the requirements of a orally disintegrating tablet.

Keywords: Metoprolol tartrate; orally disintegrating tablet; 3^2 full factorial design; Optimization

*Corresponding Author Email: rakesh.patel@ganpatuniversity.ac.in

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INTRODUCTION

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually[1]. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms**.** To fulfill these medical and commercial needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water[16-19]. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[6-8]**.**

Orally disintegrating tablets contain a wide variety of pharmaceutical actives covering many therapeutic categories, and can be particularly good applications for pediatric and geriatric treatments. The time for disintegration of orally disintegrating tablets is generally considered to be less than one minute[1-5], although patients can experience actual oral disintegration times that typically range from 5-30 seconds. Orally disintegrating tablets are characterized by high porosity, low density, and low hardness. When administered, an in-situ suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed[11-14].

Solubility of drug candidate in water is desirable for being a good candidate for ODTs. Metoprolol tartrate is having higher solubility (16.9 mg/ml) in water and hence is found to be suitable candidate for ODTs. BCS class gives the hint about drug molecule's suitability as ODTs, and Meteprolol Tartrate is BCS Class I drug, shows its suitability for ODTs. LogP value (>1) of drug indicates its ability to diffuse and partition into the epithelium of the upper GIT. Metoprolol Tartrate has LogP value 1.72. According to this criterion Metoprolol tartrate was found to be acceptable molecule for ODTs. Bioavailability of any drug molecule via oral route becomes important to know with a view to selection of drug candidate for ODTs. Metoprolol tartrate having 50% Bioavailability via oral route makes it promising molecule to be formulated as ODT [9,10].

The objectives of this study are to produce a fast disintegrating tablet, which has sufficient hardness for handling and can be manufactured by commonly used production methods and equipment. To formulate, optimize & evaluate Orally Disintegrating Tablets of selected

antihypertensive drug, basically a solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is also known as fast dispersing dosage form or mouth dissolving tablets. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. Experimental design, also called design of experiments (DOE), is an approach in the development and optimization of drug delivery devices. By this method, it is feasible to obtain the desired formulation as quickly as possible while avoiding unnecessary experiments[15]. 3^2 full factorial design was utilized to develop Metoprolol tartrate orally disintegrating tablets. Average Weight (mg), Hardness (kp), Thickness (mm), Disintegration Time (min: sec), Wetting time (min: sec) were used as evaluation tool.

MATERIALS AND METHODS:

Materials:

Metoprolol tartrate was received from Alembic Ltd. The other materials were as follows: Mannitol USP (pearlitol SD 200, roquette pharma), Microcrystalline cellulose USPNF (Avicel PH 102, FMC biopolymer), Aspartame USPNF, Crospovidone USPNF (Polyplasdone XL-10, ISP), Sodium starch glycolate (Glycolys, roquette pharma), Croscarmellose sodium (Ac-Di-Sol), Powder flavours Strawberry, peppermint & orange (Firmenich), Colloidal silicon dioxide USPNF (Aerosil 200, degussa) and Magnesium stearate USPNF (Ferro). Design Expert 8.0.7 (State-Ease, Inc) was used for statistical design of experiments.

Methods:

Preparation of Metoprolol Tartrate Tablets by direct compression method

Direct compression method was used to prepare Metoprolol tartrate ODTs 50 mg. Initially exploratory trials were taken using Crospovidone USPNF (Polyplasdone XL-10), Sodium Starch Glycolate, and Croscarmellose Sodium as superdisintegrants. Mannitol USP (pearlitol SD 200), and Microcrystalline Cellulose USPNF (Avicel PH 102) were used as diluents. Aspartame USPNF was used as sweetner. Mixure of Strawberry, Peppermint & Orange were used as flavours to help in mouth feel improvement. Colloidal Silicon Dioxide USPNF (Aerosil 200) and Magnesium Stearate USPNF (Ferro) were used as glidant and lubricant respectively.

Metoprolol tartrate (MTPT) was mixed with excipients except Colloidal silicon dioxide and magnesium stearate; and passed through #30 mesh sieve. This mixture was blended with #60 sieve passed colloidal silicon dioxide for 10 minutes. Resulting blend was lubricated with #60 sieve passed magnesium stearate for 5 minutes. Lubricated blend from above step was subjected for tabletting by direct compression method on 16 station rotary tablet press (Cadmach). Tablet

Compression process was carried out using 8.0 mm round standard concave D type tooling. The composition of batches S1 to S6 are shown in Table 1.

Table 1. Formulation of trial batches using different superdisintegrants

Parameter / B. No.	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**
Composition	**mg/Tablet**					
Metoprolol tartrate	50	50	50	50	50	50
Mannitol (Pearlitol SD 200)	68	62	68	62	68	62
Aspartame	10	10	10	10	10	10
Microcrystalline cellulose (Avicel PH 102)	44	40	44	40	44	40
Crospovidone (Polyplasdone XL-10)	20	30	-	-	-	-
Crosscarmellose sodium	-	-	20	30	-	-
Sodium starch glycolate	-	-	-	-	20	30
Powder Flavour Strawberry	0.6	0.6	0.6	0.6	0.6	0.6
Powder Flavour Pippermint	0.8	0.8	0.8	0.8	0.8	0.8
Powder Flavour Orange	0.6	0.6	0.6	0.6	0.6	0.6
Colloidal silicon dioxide (Aerosil 200)	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2
Total (mg)	**200**	**200**	**200**	**200**	**200**	**200**

3^2 full factorial design

A 3^2 Full Factorial Design was used in this study. In this design, 2 factors were evaluated, with 3 levels, and experimental trials were performed at all 9 possible combinations[7,8]. The amount of Crospovidone (X1) and the amount of Mannitol (X2) were selected as independent variables and disintegrating time and wetting time were selected as dependent variables. The polynomial equation generated by this experimental design is as follows:

Polynomial equation

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1^2 + b22X2^2 \quad (1)$$

where Y is the dependent variable, b0 is the arithmetic mean response of the nine runs, and b1 is the estimated coefficient for the factor X1. The main effects (X1 and X2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms ($X1^2$ and $X2^2$) are included to investigate nonlinearity. The composition of 3^2 full factorial design batches F1 to F9 are shown in Table 2.

Evaluation of Tablet Properties:

Average weight

Average weight was measured by weighing 10 tablets individually, by using analytical balance (Mettler Toledo).

Table 2. 3^2 full factorial design

Factor/ Trial	Crospovidone		Mannitol (Pearlitol SD 200)		Disintegration Time (seconds) (±SD)	Wetting time (seconds) (±SD)
	Level	mg/tab	level	mg/tab		
1	0	30	1	62	24.00 (0.89)	28.17 (1.72)
2	0	30	0	56	21.83 (1.17)	23.17 (0.75)
3	0	30	-1	50	25.00 (1.10)	26.00 (1.10)
4	1	34	1	62	23.17 (0.75)	26.17 (1.60)
5	1	34	0	56	19.67 (1.37)	20.83 (1.47)
6	1	34	-1	50	24.17 (0.75)	23.50 (1.05)
7	-1	26	1	62	30.33 (1.37)	36.33 (1.03)
8	-1	26	0	56	27.83 (1.17)	29.17 (1.72)
9	-1	26	-1	50	32.17 (0.98)	33.00 (0.89)
Check point	--	32	--	53	21.50 (1.64)	22.17 (0.98)

Table 3. Composition of 3^2 full factorial design batches

Strength	50 mg	Batch size: 1000 Tablets								
Batch no.	F1	F2	F3	F4	F5	F6	F7	F8	F9	Check point
Ingredients	mg/Tablet									
Metoprolol tartrate	50	50	50	50	50	50	50	50	50	50
Mannitol (Pearlitol SD 200)	62	56	50	62	56	50	62	56	50	53
Aspartame	10	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose (Avicel PH 102)	40	46	52	36	42	48	44	50	56	47
Crospovidone (Polyplasdone XL-10)	30	30	30	34	34	34	26	26	26	32
Powder Flavour Strawberry	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Powder Flavour Pippermint	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Powder Flavour Orange	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Colloidal silicon dioxide (Aerosil 200)	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Total (mg)	200	200	200	200	200	200	200	200	200	200

Thickness

The thickness was measured in mm by placing tablet between two arms of the Vernier caliper (Mitutoyo). 10 tablets were taken and their thickness was measured.

Friability

The friability of a sample of whole tablet corresponding to about 6.5 gm. was measured using a Roche Friabilator (Electrolab). Pre-weighed tablets were rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were then reweighed after removal of fines & dusts from it. The percentage of weight loss was calculated.

Hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Dr. Schluniger hardness tester, which applies force to the tablet diametrically. Hardness of 10 tablets was measured in kp.

Disintegration time

Disintegration time was measured using a modified disintegration method (n = 6). For this purpose, a petridish was filled with 10 ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted. For disintegration time determination of marketed product, one tablet was placed in each tube of disintegration apparatus (ED2, Electrolab). Disintegration test was carried out using purified water at 37°±0.5°C.

Wetting time

The wetting time of the tablets can be measured using a simple procedure (n=6). Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Stability study

Accelerated stability test was conducted on the optimized formulation at 45°C and 75% relative humidity for 3 months and tablet properties including hardness, disintegration time, friability and wetting time were determined at the end of each month.

RESULTS AND DISCUSSION:

Metoprolol tartrate orally disintegrating tablets were prepared by direct compression method. Preliminary trials were done to select best superdisintegrant and diluents amongst different superdisintegrants like Sodium Starch Glycolate, Crospovidone, Croscarmellose sodium and diluents like Mannitol USP and Microcrystalline cellulose (MCC) USPNF at various concentrations and the formulations were evaluated for hardness, thickness, friability, weight variation, disintegration time and wetting time. All the formulations were found to pass the weight variation. The hardness was constantly maintained between 4-5 kp during compression. Friability for all the formulation shown less than 0.02% which is in the acceptable limits which indicates formulations have good mechanical strength. Water insoluble diluent, MCC, was selected as secondary diluent to avoid feeling of grittiness in the mouth. Water soluble diluent, Mannitol, was selected as a primary diluent considering its advantages in terms of easy

availability and negative heat of solubilization. The disintegrating time and wetting time were determined for all the formulations prepared. The evaluation of various batches was shown in Table 4.

Table 4. Evaluation parameters for screening trials

B. No.	S1	S2	S3	S4	S5	S6
Average Weight (mg) (±SD)$	200.60 (1.65)	200.10 (1.91)	200.50 (1.84)	199.80 (1.55)	201.00 (1.63)	198.90 (1.52)
Hardness (kp) (±SD) $	4.91 (0.77)	4.88 (0.79)	4.18 (0.96)	4.67 (1.08)	4.62 (0.97)	4.09 (1.10)
Thickness (mm) (±SD) $	3.91 (0.05)	3.87 (0.05)	3.89 (0.06)	3.92 (0.06)	3.91 (0.04)	3.90 (0.04)
Friability (%w/w)	Nil	0.01	Nil	Nil	0.01	0.02
Disintegration Time (seconds) (±SD)*	44.83 (2.79)	24.17 (1.33)	90.33 (1.37)	45.67 (2.07)	141.33 (2.80)	52.67 (2.50)
Wetting time (seconds) (±SD)*	47.33 (1.75)	28.33 (4.08)	94.67 (2.66)	50.17 (3.43)	144.50 (2.95)	55.00 (2.28)

$ N=10 units, * N=6 units

On the basis of the results obtained in the preliminary screening studies, the batch containing crospovidone showed the fastest disintegration. The results (Table 4) shows that the disintegrating time and wetting time were found within the acceptance criteria for crosprovidone containing batches S1 & S2 and hence it was considered for further studies for optimization. Also selection of Mannitol was done on the basis of its higher solubility, which helps in faster water uptake and hence facilitates wicking action of Crospovidone in bringing about faster disintegration. By considering amount of crospovidone and Mannitol as independent factors with 3 levels, 3^2 full factorial design was applied and evaluation of batches were shown in Table 5.

Table 5. Evaluation parameters for 3^2 full factorial design batches

Batch no.	F1	F2	F3	F4	F5	F6	F7	F8	F9	Check point
Average Weight (mg) (±SD)$	200.10 (1.20)	199.80 (1.62)	200.40 (1.90)	200.10 (1.85)	200.90 (1.73)	198.90 (1.52)	200.50 (2.64)	199.80 (2.10)	200.20 (2.30)	200.60 (2.01)
Hardness (kp) (±SD) $	4.33 (0.82)	4.78 (0.21)	3.90 (0.75)	4.31 (0.70)	4.30 (0.80)	3.52 (0.45)	3.99 (0.84)	4.04 (0.79)	4.45 (0.71)	4.20 (0.89)
Thickness (mm) (±SD) $	3.91 (0.03)	3.93 (0.02)	3.87 (0.03)	3.93 (0.02)	3.91 (0.01)	3.90 (0.02)	3.91 (0.04)	3.91 (0.05)	3.89 (0.03)	3.92 (0.02)
Friability (%w/w)	0.02	0.01	Nil	0.02	Nil	Nil	0.01	Nil	0.01	Nil
Disintegration Time (seconds) (±SD)*	24.00 (0.89)	21.83 (1.17)	25.00 (1.10)	23.17 (0.75)	19.67 (1.37)	24.17 (0.75)	30.33 (1.37)	27.83 (1.17)	32.17 (0.98)	21.50 (1.64)
Wetting time (seconds) (±SD)*	28.17 (1.72)	23.17 (0.75)	26.00 (1.10)	26.17 (1.60)	20.83 (1.47)	23.50 (1.05)	36.33 (1.03)	29.17 (1.72)	33.00 (0.89)	22.17 (0.98)

The Table 6 & Table 7 shows combined effect of Crospovidone and Mannitol on disintegration time and wetting time respectively. The figure 1 & figure 2 Shows that highest concentration of

Crospovidone (34mg) has lowest disintegration time with all the levels of Mannitol. At 50 mg and 56 mg of Mannitol, it shows faster solubilization and helps in achieving lowest disintegration time. But at 62mg it forms hard slug during compaction; hence reduces surface area and increases solubilization time. So concentration of Crospovidone (34mg) and Mannitol (56mg) were selected for further data analysis.

Table 6. Effect of Crospovidone & Mannitol concentration on Disintegration time

Crospovidone (mg/Tab) Mannitol (mg/Tab)	**26**	**30**	**34**
	Disintegration time (Seconds)		
50	32.17	25.00	24.17
56	27.83	21.83	19.67
62	30.33	24.00	23.17

Table 7. Effect of Crospovidone & Mannitol concentration on wetting time

Crospovidone (mg/Tab) Mannitol (mg/Tab)	**26**	**30**	**34**
	wetting time (Seconds)		
50	33	26	23.5
56	29.17	23.17	20.83
62	36.33	28.17	26.17

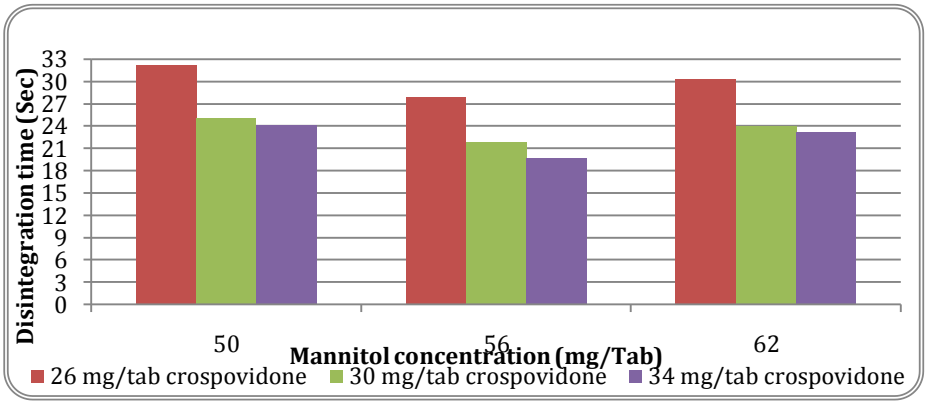

Figure 1. Effect of Crospovidone & Mannitol concentration on Disintegration time

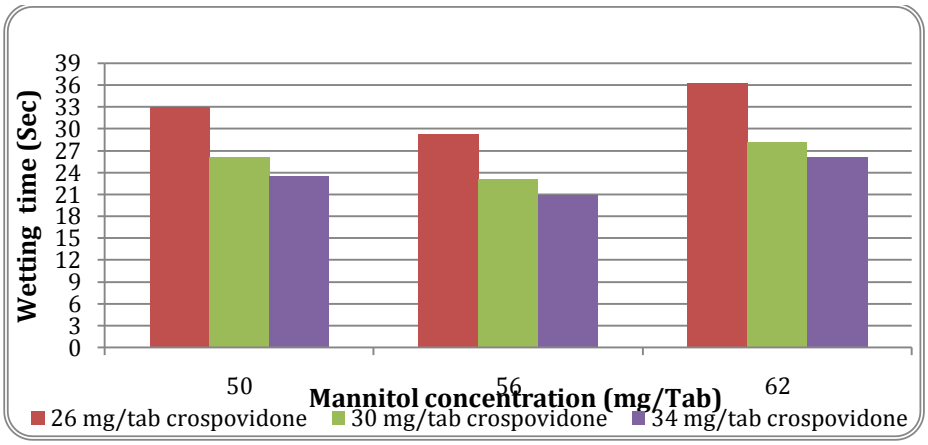

Figure 2. Effect of Crospovidone & Mannitol concentration on wetting time

$Y=B0+B1X1+B2X2+B1^2X1^2+ B2^2X2^2+B1B2X1X2$

Y=511.17-360.38-574.15+167.25+262.36+14.84 (Theoretical) (X1-32, X2-53)

DT=21.09

Disintegration time = +511.17481

-11.26167 *Crospovidone

-10.83287 *Mannitol

+8.75000E-003 *Crospovidone* Mannitol

+0.16333 *Crospovidone^2

+0.093426 * Mannitol^2

$Y=B0+B1X1+B2X2+B1^2X1^2+ B2^2X2^2+B1B2X1X2$ (X1-32, X2-53)

WT=557.322-311.42-714.39+152.78+348.88-11.66

WT=21.51

Wetting Time =+557.32185

-9.73167 *Crospovidone

-13.47866 *Mannitol

-6.87500E-003 *Crospovidone* Mannitol

+0.14917 *Crospovidone^2

+0.12421 * Mannitol^2

The statistical analysis of the design batches were performed by multiple linear regression analysis using Microsoft Excel®. The coefficients showing p value >0.05 were removed from the regression to generate reduced model. The refined model may be used for calculations of residuals or for drawing contour plots using design expert®. The summary of results of regression analysis of full and refined models ($p<0.05$) for disintegration time (DT) and wetting time (WT) are shown in Table 8. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. Those coefficients were found to be insignificant at $p > 0.05$, their values were omitted from the full model to generate the reduced model. The high values of correlation coefficient for DT and WT indicates a good fit.

Disintegration Time

$$Y = 511.17 – 11.26X1 – 10.83X2 + 0.16X1^2 + 0.093X2^2 + 0.008X1X2 \quad (2)$$

Wetting Time

$$Y = 557.32 – 9.73X1 – 13.47X2 + 0.14X1^2 + 0.12X2^2 – 0.006X1X2 \quad (3)$$

Table 8. Results of Regression Analysis for design batches

Response variables	Model	B_0	B_1	B_2	B_1^2	B_2^2	B_{12}	R^2
Disintegration Time	FM	21.37	-3.89	-0.64	2.61	3.36	0.21	0.995
	RM	21.37	-3.89	-0.64	2.61	3.36	---	0.994
Wetting Time	FM	22.80	-4.67	1.36	2.39	4.47	-0.17	0.993
	RM	22.79	-4.67	1.36	2.39	4.47	---	0.993

Table 9 shows the results of ANOVA, which was carried out to identify insignificant factors. From the results of ANOVA for the measured responses, it was found that the amount of crospovidone and Mannitol had a significant effect on disintegration time and wetting time of the system ($p < 0.05$). The calculated value of F are less than their critical value, it may be concluded that those interaction term do not contribute significantly can be omitted from the full model.

Table 9. Results of ANOVA

Source	Df	SS	MS	F-value	R^2	Significance F
Disintegration Time (DT)						
Regression	4	76.44	19.11	68.8	0.985	0.00060
Residual	4	1.33	0.27			
Wetting Time (WT)						
Regression	4	192.66	48.16	144.5	0.993	0.000141
Residual	4	1.33	0.33			

Effect of X1 and X2 on disintegration time

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The coefficient obtained shows that coefficient b_1, b_2 were negative and b_1^2, b_2^2 and b_{12} were positive (Table 8). The negative sign for b_1, b_2 indicated that crospovidone and mannitol were significantly affecting disintegration time in opposite manner. As the concentration of crospovidone and mannitol increased, disintegration time decreased. The magnitude of coefficient showed that X1 has more effect than X2 on disintegration time. This is due to wiking effect of superdisintegrant Crospovidone. The response surface plot and contour plot of effect of Crospovidone and Mannitol on disintegration time are shown in Figure 3 and Figure 4 respectively.

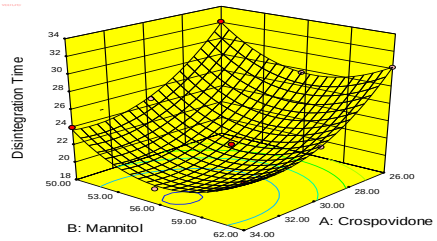

Figure 3. Response surface plot showing effect of Crospovidone & Mannitol on Disintegration time

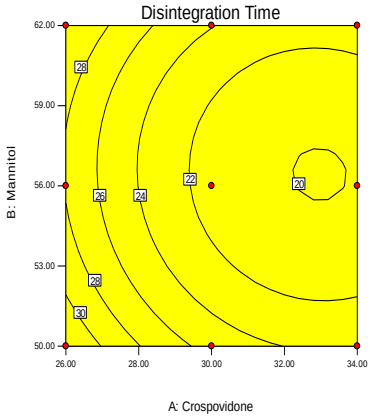

Figure 4. Contour plot showing effect of Crospovidone & Mannitol on Disintegration time

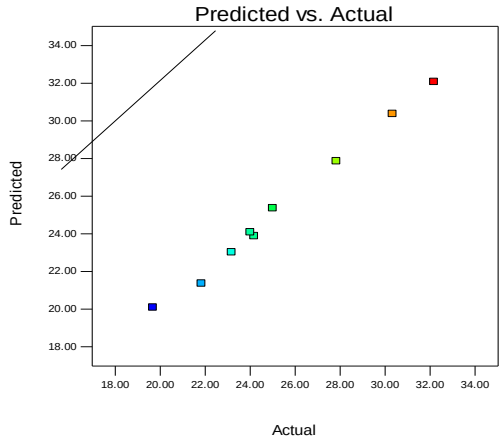

Figure 5. Predicted vs. Actual plot for Disintegration time

Effect of X1 and X2 on wetting time

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. The coefficient obtained shows that coefficient b_1, b_{12} were negative and b_2, b_1^2 and b_2^2 were positive (Table 8). The negative sign for b_1 indicated that crospovidone was significantly affecting wetting time in opposite manner. As the concentration of crospovidone increased, wetting time decreased. This is due to water uptake and swelling property of crospovidone. The positive sign for b_2 indicated that as the mannitol concentration increased, wetting time also increased. Mannitol is sugar alcohol having crystalline nature so it forms hard slug during compaction; hence reduces surface area and increases solubilization time. The effect of mannitol on distintegration time & wetting time depends on its soluble characteristic not on swelling property. The magnitude of coefficient showed that X1 has more effect than X2 on wetting time but in negative manner. The response surface plot and contour plot of effect of Crospovidone and Mannitol on wetting time are shown in Figure 6 and Figure 7 respectively.

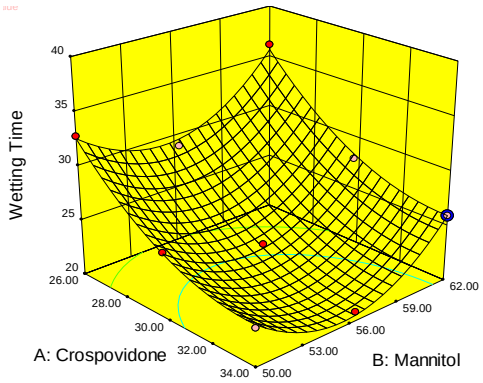

Figure 6. Response surface plot showing effect of Crospovidone & Mannitol on Wetting time

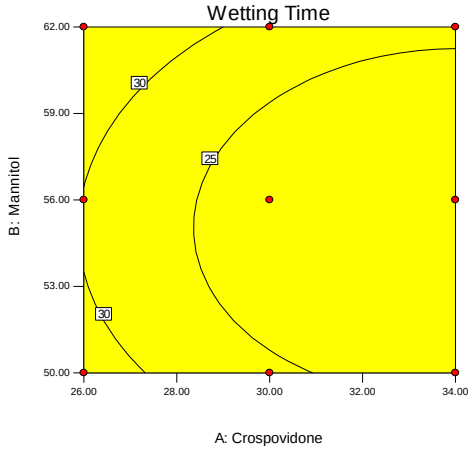

Figure 7. Contour plot showing effect of Crospovidone & Mannitol on Wetting time

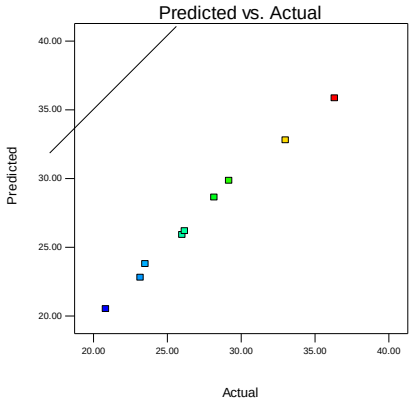

Figure 8. Predicted vs. Actual plot for Wetting time

Stability studies:

The data related to stability studies of optimized batch was shown in Table 10. The study was performed at 40°C/75% RH for 1, 2 & 3 months. Average weight, hardness, thickness, friability, disintegration time & wetting time were evaluated during each station of stability. Data of stability study reveals that optimized formulation is stable during accelerated stability testing.

Table 10. Results of stability study

Batch No. – F5	**Stability at 40°C/75%RH**			
Test	**Initial**	**1 month**	**2 month**	**3 month**
Average Weight (mg) (±SD)$	200.90 (1.73)	200.8 (1.81)	200.6 (1.96)	200.3 (1.83)
Hardness (kp) (±SD) $	4.30 (0.80)	4.16 (0.86)	4.1 (0.82)	4.11 (0.83)
Thickness (mm) (±SD) $	3.91 (0.01)	3.921 (0.01)	3.912 (0.02)	3.925 (0.03)
Friability (%w/w)	Nil	Nil	0.01%	0.04%
Disintegration Time (sec) (±SD)*	19.67 (1.37)	20.83 (1.17)	21.83 (1.72)	21.50 (1.97)
Wetting time (seconds) (±SD)*	20.83 (1.47)	20.67 (1.63)	21.17 (0.75)	22.33 (1.51)

$ N=10 units, * N=6 units

Design Space:

Overlay plot representing design space to operate within mannitol and crospovidone to get desired disintegrating time & wetting time is graphically expressed in Figure 9. At this stage, the defined desirable areas of both responses were superimposed and the region of interest was generated. It shows desired area for both responses explained by yellow region in the plot.

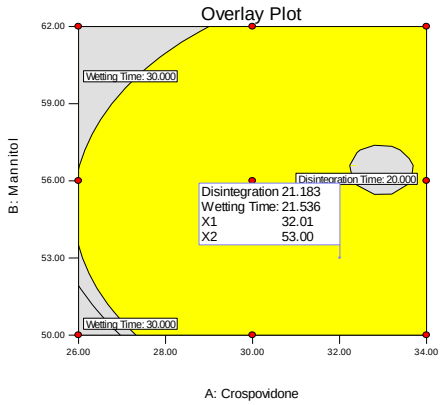

Figure 9. Overlay plot representing design space

Table 11. Market product comparison

Product Name: Metoprolol tartrate immediate release Tablets 50 mg				
Brand name: Betaloc - 50 (Batch no. BF-K-016)				
Sr. No.	**Average wt. (mg)**	**Thickness (mm)**	**Hardness (kp)**	**Disintegration time (Min: second)**
1	179.0	3.44	8.6	9:54
2	183.1	3.45	7.7	9:50
3	179.9	3.45	8.4	9:52
4	181.5	3.46	8	9:48
5	178.2	3.44	8.5	9:55
6	178.7	3.45	8.3	10:00
Average	180.07	3.45	8.25	9:53
±SD	1.89	0.01	0.34	4.21

Comparison with marketed immediate release tablet

The Table 11 shows characterization of marketed product Metoprolol Tartrate IR Tablets 50 mg

(Betaloc – 50). As the market formulation is immediate release Tablets, so we can see significant difference in D.T. as compared to optimized formulation of Metoprolol tartrate ODT.

CONCLUSION:

An optimized formulation of Metoprolol tartrate orally disintegrating tablets was found and prepared in this study by direct compression method. Formulation and optimization procedure was facilitated using 3^2 full factorial design. Physico-chemical characteristics and accelerated stability results of the optimum formulation also met all pharmaceutical requirements. Concentration of crospovidone has opposite effect on disintegration time & wetting time; as the concentration increased disintegration time & wetting time decreased. Mannitol initially decreases disintegration time & wetting time but at high concentration it increases disintegration time & wetting time.

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