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# DESIGN, DEVELOPMENT AND FORMULATION OF DISPERSIBLE TABLETS CONTAINING ANTIRETROVIRAL AS A DARUNAVIR BY DIRECT COMPRESSION USING $2^3$ FULL FACTORIAL DESIGNS

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**Abstract:**
*The present investigation deals with preparation of Dispersible Tablets of Darunavir and to determine the influence of the certain excipients on physical properties of the tablets and solubility. Direct compression technique was used because of its ease of access and contains limited number of unit operations. A Superdisintegrant like Ac-di-sol, microcrystalline cellulose were screened to find the best formulation with good % drug release and disintegration values. Employing a $2^3$ Full factorial design, the influence of three factors variables like Superdisintegrant concentration (Ac-di-sol), glidant (Aerosil) and Lubricant (Magnesium stearate) on the disintegration time and % drug release were determined. The drug excipient compatibility studies were performed by physical compatibility observation using stability chamber. The multiple linear regression analysis was used to find the effect of these variables on physical properties of final formulation. Finally, a optimized batch was considered to prove the validity of evolved method. Using the contour plot and cube plot, the effect of the independent variables on the responses was represented graphically. The stability studies of the optimized formula were carried as per ICH guidelines.*

**Keywords:** *Ac-di-sol, $2^3$ Full factorial design, Contour plot, Prediction profiler, disintegration,% drug release.*

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## INTRODUCTION:

The aim and objective of the present study was to develop and evaluate Dispersible tablet of Darunavir and enhance the patient compliance of Darunavir is a second-generation protease inhibitor designed to have antiviral efficacy against HIV-1[1]. To study the influence of excipients on the physical characteristics of the tablets by applying two level and three factor factorial designs taking Darunavir as a drug which is used in the treatment of HIV-1 in pediatric. The study was intended to select the best possible Glidant, Lubricant and the Superdisintegrant combination to formulate the dispersible tablet. Finally the impacts of the Glidant ratio and Superdisintegrant on various properties of the tablet were also determined. The basic approach in the development of the dispersible tablet is the use of Superdisintegrant. Ac-di-sol, microcrystalline cellulose, Aerosil a glidant and Magnesium stearate the lubricant are the best used globally. In this study all the above mentioned excipients was selected and best one was selected for further studies. Another approach was decided to adopt the Direct Compression Technique to prepare Dispersible tablet in an easy and comfortable way as it requires less number of unit operations.

The objective of experimental design using Full factorial method is to plan and conduct experiments so that the experimental domain is systematically investigated with as few experiments as possible. The independent variables or factors are experimental variables that can be changed independently of each other. The factor settings define the experimental domain, i.e. the area to be investigated. The response variables, the dependent variables, are measured results of the performed experiments. The experiments should be performed in random order to eliminate the influence of systematic errors.

**Factorial Experiments**

Factorial designs allow for the simultaneous study of the effects that several factors like concentration of Superdisintegrant, Lubricant and Glidant may have on the physical characteristics of the tablets [2].

**Contour Plots**

Contour plot helps in visualizing the response surface. Contour plots are useful for establishing desirable response values and operating conditions [3].

**Cube plot** These plots are often used to summarize predicted values for the dependent variable, given the respective high and low setting of the factors [4].

**Equipment Used**

Electronic digital balance-Mettler Toledo (AB 2045), Tapped density apparatus-Electrolab USP ETD 1020, Tablet compression machine-Cadmach machinery co. Pvt Lt, Ahmedabad, Friability test apparatus-Electrolab, USP EF-2,Disintegration apparatus-Electrolab USP ED-2, Thickness (Vernier Calipers)-Mitutogo Vernier Calipers, Sieves, Jayanth test sieve, Hardness tester-Dr.Schleuniger Pharmatron Tablet tester 8M, UV-Visible spectrophotometer-Shimadzu (UV-1601), Stability chamber-Neutronics, HPLCShimadzu, Dissolution apparatus-USP TDL-08L,2100.

## MATERIAL AND METHOD:

**Materials Used:**

Darunavir, Ac-di-sol,lemon flavour, Aerosil, Aspartame, Microcrystalline cellulose, Magnesium stearate, Methanol (HPLC Grade), HCl,Sodium phosphate (monobasic). All the chemicals were provided by as a gift sample from Ranbaxy research and development center, Gurgaon.

**Plan of Work**

The plan of work is to prepared dispersible tablet of protease inhibitor of Darunavir and screening of disintegrating agents, Lubricant and Glidant for the preparation of rapidly integrating tablets. The best disintegrating agent was used and further evaluated by $2^3$ factorial design and regression analysis. Formulation of rapidly disintegrating tablets was carried out using Ac-di-sol, Aerosil and Magnesium stearate as a three factor which is evaluated at each two level i.e. Disintegration and % drug release. The prepared dosage form was subjected to pre- and post-compression parameters. Selection and optimization of the best formulation was carried out based on the above results. The results were subjected to ANOVA after the development of Actual v/s predicted model, and plotting contour plot and also prediction profiler. The optimized formulation was subjected to compatibility studies were compared with the initial value for the final formulation by using stability chamber as per ICH guidelines [5].

**Method**

For the drug Darunavir, All the excipient (Table-1) were added in different percentage concentrations. Darunavir and other excipients were mixed thoroughly. The blend was then compressed directly. The blend were screened and the final formulations with favorable disintegration time and %drug release results were taken .

**Table-1: Formulation design (Analysis of factorial formulation: Working formula of factorial formulation.)**

| Ingredient (mg/tablet) | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ADT-1 | ADT-2 | ADT-3 | ADT-4 | ADT-5 | ADT-6 | ADT-7 | ADT-8 | ADT-9 |
| Model drug | 81.3 | 81.3 | 81.3 | 81.3 | 81.3 | 81.3 | 81.3 | 81.3 | 81.3 |
| MCC pH 102 | 199.2 | 195.0 | 198.3 | 199.8 | 190.2 | 191.7 | 200.7 | 189.3 | 190.8 |
| Ac-di-sol | 6.0 | 10.5 | 6.0 | 6.0 | 15 | 15 | 6.0 | 15 | 15 |
| Aerosil | 0.6 | 1.05 | 1.5 | 1.5 | 0.6 | 0.6 | 0.6 | 1.5 | 1.5 |
| Magnesium stearate | 3.0 | 2.25 | 3.0 | 1.5 | 3.0 | 1.5 | 1.5 | 3.0 | 1.5 |
| Lemon flavour | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| Aspartame | 9.0 | 9.0 | 9.0 | 9.0 | 9.0 | 9.0 | 9.0 | 9.0 | 9.0 |
| Total | 300 mg | | | | | | | | |

**Evaluation of Tablet**

**Evaluation of Compressed Tablet of 1-9 batches:** Tablets were evaluated for the following parameters.

**Table-2 : Evaluation of factorial formulations**

| Formulation code | Thickness (mm) | Hardness (kp) | Disintegration(sec) | Friability (%) | % drug release at30 min | Weight variation test (gm) | Dispersion time(sec) | Dispersion fineness |
|---|---|---|---|---|---|---|---|---|
| Appearance | 300 mg, white colored, 10 mm, round flat on both sides tablet | | | | | | | |
| ADT-1 | 3.85±**0.07** | **6.05±1.1** | **21** | **0.15** | **82.1** | **0.3007±0.004** | **25** | **Pass** |
| ADT-2 | 3.84±**0.08** | **6.2±1.1** | **18** | **0.18** | **89.1** | **0.3032±0.006** | **22** | **Pass** |
| ADT-3 | 3.83±**0.04** | **6.0±1.1** | **20** | **0.06** | **89.5** | **0.3048±0.007** | **24** | **Pass** |
| ADT-4 | 3.84±**0.06** | **6.3±1.4** | **19** | **0.05** | **86.6** | **0.3045±0.005** | **24** | **Pass** |
| ADT-5 | 3.85±**0.07** | **5.4±1.5** | **14** | **0.08** | **87.6** | **0.3040±0.005** | **16** | **Pass** |
| ADT-6 | 3.78±**0.06** | **6.7±0.8** | **15** | **0.07** | **93.1** | **0.3037±0.006** | **18** | **Pass** |
| ADT-7 | 3.83±**0.03** | **6.4±0.9** | **21** | **0.07** | **86.0** | **0.3029±0.004** | **25** | **Pass** |
| ADT-8 | 3.84±**0.04** | **5.8±1.1** | **16** | **0.10** | **92.0** | **0.3030±0.006** | **18** | **Pass** |
| ADT-9 | 3.82±**0.07** | **5.7±1.4** | **15** | **0.07** | **92.6** | **0.3032±0.005** | **18** | **Pass** |

**Mean ± S.D., *- n=3 (all the values are the average of three determinations)**

**Dissolution Studies of Tablet**

**% drug release of the Dispersible tablet of Darunavir**

All the above prepared batches of dispersible tablet were subjected to dissolution for getting the result of % drug release at 30 min should not less than 80 %.

**Table-3: % drug release of factorial formulations**

| Formulation code | Cumulative % drug release (min) | | | | |
|---|---|---|---|---|---|
| | 0 min | 10 min | 20 min | 30 min | 45 min |
| ADT-1 | 0.0 % | 60.5 | 62.7 | 82.1 | 89.0 |
| ADT-2 | 0.0 % | 63.4 | 77.7 | 89.1 | 99.2 |
| ADT-3 | 0.0 % | 65.1 | 80.0 | 89.5 | 98.4 |
| ADT-4 | 0.0 % | 63.6 | 78.6 | 86.6 | 99.08 |
| ADT-5 | 0.0 % | 66.03 | 78.5 | 87.6 | 99.05 |
| ADT-6 | 0.0 % | 66.2 | 84.7 | 93.1 | 99.0 |
| ADT-7 | 0.0 % | 63.5 | 79.0 | 86.0 | 99.8 |
| ADT-8 | 0.0 % | 62.5 | 81.8 | 92.0 | 98.7 |
| ADT-9 | 0.0 % | 63.4 | 80.4 | 92.6 | 99.8 |

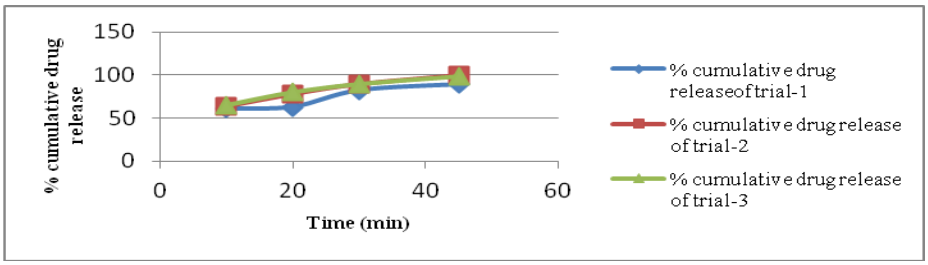



**Fig-1 : A plot of % drug release v/s Time of Formulation code ADT-1 To ADT-3**

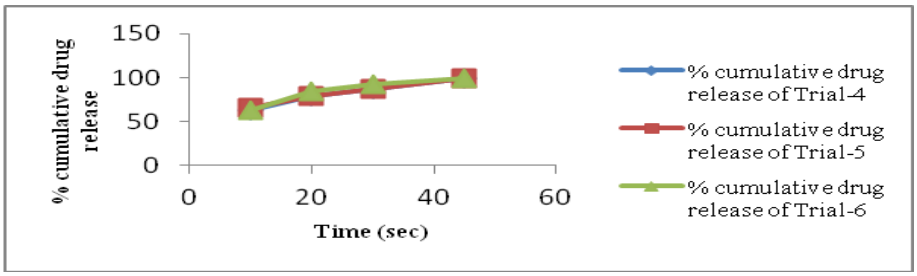



**Fig-2 : A plot of % drug release v/s Time of Formulation code ADT-4 To ADT-6**

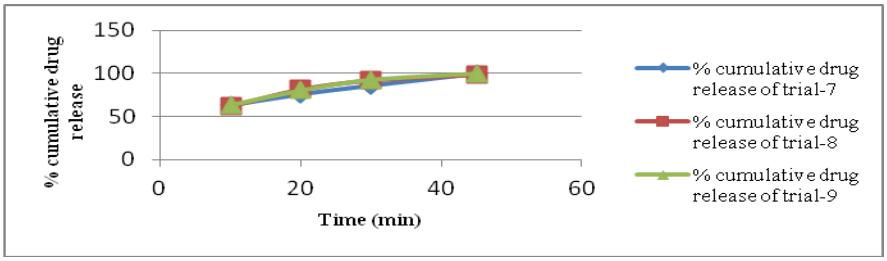



**Fig -3: A plot of % drug release v/s Time of Formulation code ADT-7 To ADT-9**

**Full factorial design pattern layout with resulting Response factor of Disintegration time (sec) & % drug release not more than 80 % at 30 min:** There are following result of response of selected factor.

**Table-4: Full factorial design pattern layout with resulting Response factor of Disintegration time (sec) & % drug release not more than 80 % at 30 min**

| **Full factorial design (2x2x2 Pattern) OR Independent Variable in coded form** | | | **Independent Variable in actual form** | | | **Dependent variable** | |
|---|---|---|---|---|---|---|---|
| Factor-1 | Factor-2 | Factor-3 | Ac-di-sol | Aerosil | Magnesium stearate | %drug release (NMT 80 % at 30 min) | Disintegration (sec) |
| + | – | + | 15 | 0.6 | 3 | 87.6 | 14 |
| + | + | – | 15 | 1.5 | 1.5 | 92.6 | 15 |
| 0 | 0 | 0 | 10.5 | 1.05 | 2.25 | 89.1 | 18 |
| – | + | + | 6 | 1.5 | 3 | 89.5 | 20 |
| _ | – | – | 6 | 0.6 | 1.5 | 86.3 | 21 |
| + | + | + | 15 | 1.5 | 3 | 92 | 16 |
| _ | + | _ | 6 | 1.5 | 1.5 | 86.6 | 19 |
| + | – | – | 15 | 0.6 | 1.5 | 93.1 | 15 |
| _ | _ | + | 6 | 0.6 | 3 | 82.1 | 21 |

**Table-5: Actual value of $2^3$ full factorial design lay out.**

| Coded Values | Actual Values of Factor (mg) | | |
|---|---|---|---|
| | Ac-di-sol | Aerosil | Magnesium stearate |
| **Low (-)** | 6 | 0.6 | 1.5 |
| **Center point (o)** | 10.5 | 1.05 | 2.25 |
| **High (+)** | 15 | 1.5 | 3 |

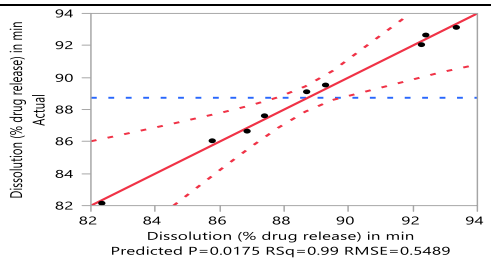
**Where:**

- ✓ values in the Pattern column describe the run each row represents
- ✓ − sign corresponds to the low limit of interest
- ✓ +sign corresponds to the high limit of interest
- ✓ 0 sign corresponds the average of the upper and lower limits is the midpoint of the interval of interest
- ✓ Responses - measurable outcomes of interest.
- ✓ Factors - controllable variable thought to have an influence on the response(s)
- ✓ Level - value of a setting of a factor
- ✓ Test run - set of factor level combinations for one experimental run

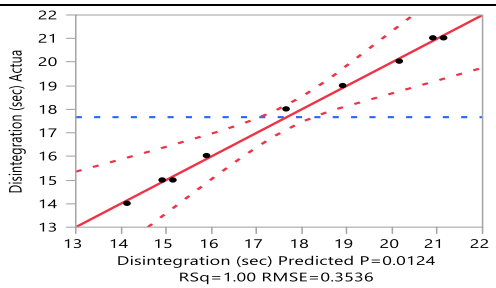
**Parameter**

**Response Dissolution (% drug release) in min Actual by Predicted Plot**

**(% drug release) in min Result**




**Response Disintegration (sec) Actual by Predicted Plot :**




**Summary of Fit**

*Table-6 . Summary of results of regression analysis for responses (% drug release*[30]

| Parameter | value |
|---|---|
| RSquare | 0.994135 |
| RSquare Adj | 0.976538 |
| Root Mean Square Error | 0.548862 |
| Mean of Response | 88.73333 |
| Observations (or Sum Wgts) | 9 |

*Table-7 . Summary of results of regression analysis for responses of disintegration of dispersible tablet*

| Parameter | value |
|---|---|
| RSquare | 0.995833 |
| RSquare Adj | 0.983333 |
| Root Mean Square Error | 0.353553 |
| Mean of Response | 17.66667 |
| Observations (orSum Wgts) | 9 |

**Analysis of Variance : (ANOVA)**

*Table-8 : Results of ANOVA for dependent variables*

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|---|---|---|---|---|
| Model | 6 | 102.11750 | 17.01196 | 56.4965 |
| Error | 2 | 0.60250 | 0.3013 | **Prob > F** |
| C.Total | 8 | 102.72000 | | 0.0175* |

*Table-9 : Results of ANOVA for dependent variables (for disintegration)*

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|---|---|---|---|---|
| Model | 6 | 59.750000 | 9.95833 | 79.6667 |
| Error | 2 | 0.250000 | 0.12500 | **Prob > F** |
| C. Total | 8 | 60.000000 | | 0.0124* |

**Parameter Estimates**

*Table-10: Estimation of quantitative effect of the factor*

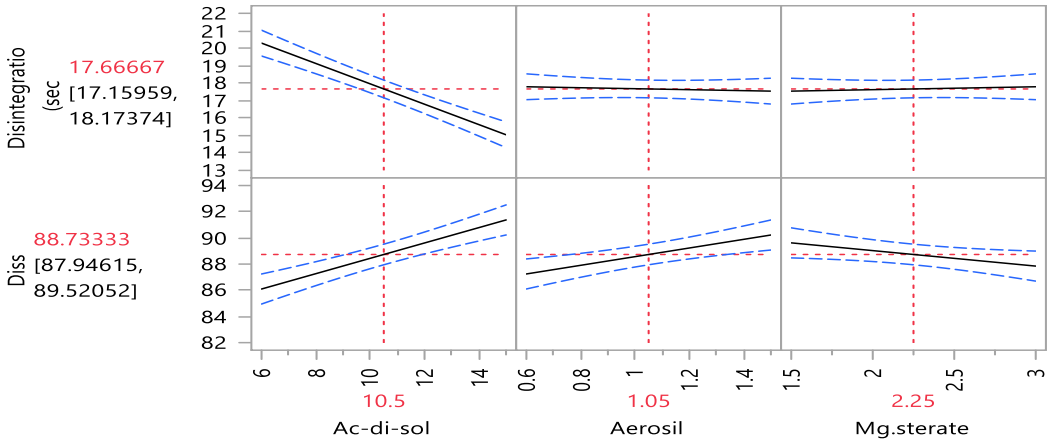
| Term | Estimate | Std Error | t Ratio | Prob >\|t\| |
|---|---|---|---|---|
| Intercept | 88.733333 | 0.182954 | 485.00 | <.0001* |
| Ac-di-sol(6,15) | 2.6375 | 0.194052 | 13.59 | 0.0054* |
| Aerosil(0.6,1.5) | 1.4875 | 0.194052 | 7.67 | 0.0166* |
| Mag.stearate(1.5,3) | -0.8875 | 0.194052 | -4.57 | 0.0446* |
| Ac-di-sol*Aerosil | -0.5125 | 0.194052 | -2.64 | 0.1184 |
| Ac-di-sol*Mag. stearate | -0.6375 | 0.194052 | -3.29 | 0.0815 |
| Aerosil*Magnesium stearate | 1.4625 | 0.194052 | 7.54 | 0.0172* |

*Table-11: Estimation of quantitative effect of the factor*

| Term | Estimate | Std Error | t Ratio | Prob >\|t\| |
|---|---|---|---|---|
| Intercept | 17.666667 | 0.117851 | 149.91 | <.0001* |
| Ac-di-sol(6,15) | -2.625 | 0.125 | -21.00 | 0.0023* |
| Aerosil(0.6,1.5) | -0.125 | 0.125 | -1.00 | 0.4226 |
| Magnesium stearate(1.5,3) | 0.125 | 0.125 | 1.00 | 0.4226 |
| Ac-di-sol*Aerosil | 0.625 | 0.125 | 5.00 | 0.0377* |
| Ac-di-sol*Magnesium stearate | -0.125 | 0.125 | -1.00 | 0.4226 |
| Aerosil*Magnesium stearate | 0.375 | 0.125 | 3.00 | 0.0955 |

**Prediction Profiler :** Prediction traces are displayed of each factor at each response as following.

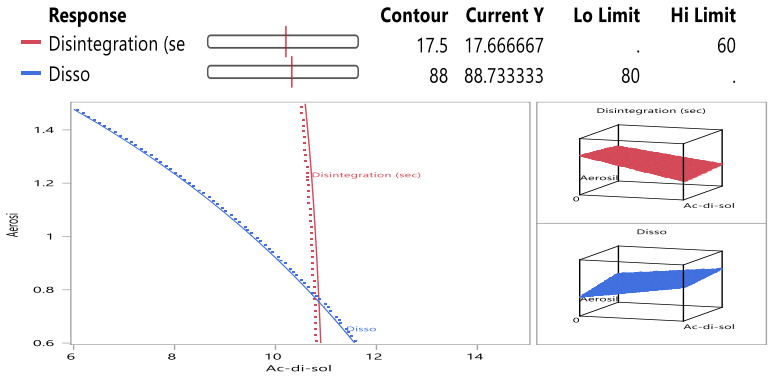
**Table-12: Prediction profiler of both response**




**Contour Profiler:**

| Horiz | Vert | Factor | Current X |
|---|---|---|---|
| ◉ | ○ | Ac-di-sol | 10.5 |
| ○ | ◉ | Aerosil | 1.05 |
| ○ | ○ | Magnesium stearat | 2.25 |

**Table-13: contour profiler of both response**




## RESULT AND DISCUSSION:

**Analysis of fitted data for selected factor on the response:**

**Combinational effect on % drug release at 30 min**: From the above table, AC-di-sol and Aerosil individually and shows the positive effect on selected response for the % drug release at 30 min and the p-value was less than 0.05 and hence it said to be model is significant. The Aerosil and Magnesium stearate also shown a synergistic effect on the selected response for the % drug release at 30 min and its p-value also supported that model is significant. But, Magnesium stearate, Aerosil with Ac-di-sol and Ac-di-sol with magnesium stearate has shown a antagonistic effect on % drug release at 30 min.

**Combinational effect on disintegration (NMT 60 sec.)** :From the above table, AC-di-sol, Aerosil and Ac-di-sol with Magnesium stearate shows the antagonistic effect on selected response for the disintegration (NMT 60 sec.) and the p-value of the Ac-di-sol was less than 0.05 shows that model is significant. But Aerosil and Ac-di-sol with Magnesium stearate does not shown model significance. The Aerosil and Magnesium stearate also shown a synergistic effect on the selected response for the disintegration (NMT 60 sec.) but its p-value does not supported that model is significant. But, Magnesium stearate, and Aerosil with Ac-di-sol has shown a synergistic effect on disintegration (NMT 60 sec.) but only Ac-di-sol with Aerosil supported the model significant.

**3-Analysis of Prediction profiler for selected factor on the response:** From the table12- A prediction profiler is the predicted response as one variable is changed while the others are held constant at the current values. Prediction profiler reveals the effect of Ac-di-sol that % drug release increases whenever concentration of Ac-di-sol increases and vice versa while When the concentration of Ac-di-sol increases, disintegration time decreases and vice versa. Effect of Aerosil on % drug release increases whenever concentration of Aerosil increases, while when the concentration of Aerosil increases, disintegration time decreases. The effect of Magnesium stearate on % drug release decreases whenever concentration of Magnesium stearate increases. however, When the concentration of Aerosil increases, disintegration time also increases and vice versa.

**4- Analysis of contour profiler for selected factor on the response :**The relationship between the dependent and independent variables can be further understood by these plots. From the Table-13, the appearance of the contour plot, the contour curves has been shown a considerable curvature, and so it was concluded that the Ac-di-sol and Aerosil term is significant and it is the two dominant factor that affect the response i.e. %drug release and Disintegration of formulation significantly. After plotting the contour plot, it was observed that there is no shaded region within the plot and hence, from the plot it was concluded that the value for the independent variables (factor) for each number of trial is robust for the preparation of dispersible tablet of model drug. Therefore, it was concluded that the trial of the centre point (Formulation code ADT-2) can be considered as the optimized batch and can be used in the formulation.

**Stability studies of the optimized formulation:** Stability studies are carried out to access self life of the prepared formulation. Tablets containing Darunavir were subjected to a short-term stability study (3 month, as per ICH guidelines 40°C/75 % RH) [6]. Stability testing was done to check the physical, chemical and physiological properties of the formulation. Accelerated stability testing was carried out as per ICH guidelines (40ºC/75% RH) to ascertain the product stability for long period in a short period of time. Tablets of the optimized

formulation were packed in HDPE bottles having silica gel were kept in a stability chambers. The tablet were withdrawn after every one month and analyzed and evaluated for change in physical characterization, thickness, friability, hardness, disintegration, dispersion time, fineness of dispersion, %drug release and the result were compared with initial sample.

**Table-14 : Evaluation of tablet of stability charged of optimized formulation code ADT-2**

| **Formulation code** | **Evaluated parameter** | **Initial observation** | **40°C/75 % RH (HDPE bottle)** | | |
|---|---|---|---|---|---|
| | | | **1-month** | **2-month** | **3-month** |
| **ADT-2 (Optimized formulation)** | Discription | White flat faced round uncoated tablet, plain on both sides. | White flat faced round uncoated tablet, plain on both sides. | White flat faced round uncoated tablet, plain on both sides. | White flat faced round uncoated tablet, plain on both sides. |
| | Thickness (mm) n=10 | 3.83±**0.04** | 3.83±**0.06** | 3.83±**0.08** | 3.81±**0.04** |
| | Hardness (kp) n=10 | 6.4±**0.42** | 6.7±**0.45** | 6.42±**0.42** | 6.47±**0.42** |
| | Disintegration (sec) n=6 | 17±**0.55** | 18±**0.55** | 20±**0.55** | 20±**0.55** |
| | Friability (%) n=10 | 0.16 | 0.18 | 0.21 | 0.24 |
| | Dispersion time(sec) | 23 | 24 | 25 | 25 |
| | Dispersion fineness | Pass | Pass | Pass | Pass |

**Table-15: % drug release of Dispersible tablet of stability charged of optimized formulation code ADT-2**

| **Formulation code** | **Condition (time in month)** | **Cumulative % drug release at required sampling point** | | | | |
|---|---|---|---|---|---|---|
| | | **0 min** | **10 min** | **20 min** | **30 min** | **45 min** |
| **ADT-2 (Optimized formulation** | **Initial** | **0.0%** | **63.5** | **77.3** | **88.8** | **99.7** |
| | 40°C/75 % RH (HDPE bottle) 1-month | **0.0** | **63.7** | **64.1** | **88.9** | **100.1** |
| | 40°C/75 % RH (HDPE bottle) 2-month | **0.0** | **63.9** | **64.5** | **88.5** | **99.8** |
| | 40°C/75 % RH (HDPE bottle) 3-month | **0.0** | **63.4** | **63.9** | **88.2** | **99.5** |

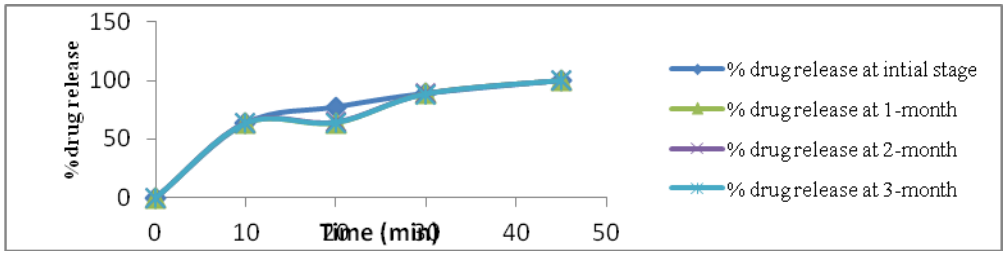



**Fig-4 : A plot of % drug release v/s Time of stability charged of optimized Formulation code ADT-2**

## CONCLUSION:

Dispersible tablet of Darunavir was successfully prepared by using direct compression method. The optimal formulation of code-ADT-2 exhibited the disintegration time of 18 sec and % drug release at 30 min of 89.1%. and passes the all specified limit. The method for Dispersible tablet of Darunavir with optimal release properties was determined using experimental design methodology. After determination of significant parameters by using two level and three factorial design was applied. Analytical parameters investigated in this study were: concentration of Superdisintegrant (Ac-di-sol), ratio of glidant (Aerosil) and Lubricant (Magnesium stearate). The chosen responses were disintegration time (NMT 60 SEC) and the % drug release at 30 min (NLT 80 %). The model reliability and estimation of quantitative effects of different levels of investigated factors was performed using the statistical software (**SAS JMP** 10) ). The levels of these factors were predicted to obtain an optimal response with reference to set constraints. The observed responses were close to the predicted values for the optimized drug release method. From the above results, it can be concluded that characterization and optimization of the Dispersible tablet of Darunavirl was performed in an very appropriate time period and with a small number of experimental runs. It is essential that experimental design methodology is a very economical way for extracting the maximum amount of complex information, a significant experimental time saving factor and moreover, it saves the material used for analyses and personal costs as well. The results of $2^3$ factorial design revealed that the amount of Superdisintegrant and the glidant ratio significantly affect the dependent variables i.e. disintegration time and % drug release. It is concluded that by adopting a systematic formulation approach, an optimum can be reached in the shortest time with minimum efforts.

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