Pharmaceutica Analytica Acta
ISSN: 2153-2435

Lokesh et al., Pharmaceut Anal Acta 2012, 3:9
DOI: 10.4172/2153-2435.1000195

Review Article Open Access

Design, Development and Formulation of Orodispersible Tablets of a Model Drug Using Response Surface Methodology

Lokesh PNV, Abdul Althaf S* and Sailaja PB

Division of Pharmacy, Sri Venkatswara University, Tirupati, Andhra Pradesh, India

Abstract

The present investigation deals with preparation of Fast Dissolving Tablets (FDT) of Model drug (Telmisartan) 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. Glycine and SLS are used as wetting agent. Various superdisintegrants like Croscarmellose, Sodium starch glycolate, Crospovidone, Crospovidone-XL10 and Polacrallin potassium were screened to find the best formulation with good friability and disintegration values. Employing a 3^2 factorial design, the joint influence of two formulation variables like superdisintegrant concentration and ratio of diluents (MCCP: MANNITOL) on the disintegration time and friability were determined. The drug excipient compatibility studies were performed by FTIR and solubility changes are observed by dissolution using HPLC. The physical characteristics were analyzed by X-ray diffraction and supported by DSC studies. The multiple linear regression analysis was used to find the effect of these variables on physical properties of final formulation. Finally, a check-point batch is prepared to prove the validity of evolved method. Using the contour plot, 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: Telmisartan; Fast dissolve tablet; Kyron; 3^2 Factorial designs; Contour plot

Introduction

The aim and objective of the present study is to develop and evaluate FDT of Telmisartan and enhance the onset of action of Telmisartan and also to study the influence of excipients on the physical characteristics of the tablets by applying three level two factor factorial designs taking Telmisartan as model drug which is used in the treatment of the hypertension. The study was intended to select the best possible diluents and the superdisintegrants combination to formulate the dispersible tablets among all the diluents and disintegrants used. Finally the impact of the diluents ratio and superdisintegrants on various properties of the tablet were also determined [1].

The basic approach in the development of the fast dissolving tablet is the use superdisintegrants. Croscarmellose, sodium starch glycolate, crospovidone, polacrallin potassium are the best used superdisintegrants globally. In this study all the above mentioned superdisintegrants are selected and best one is selected for further studies. Another approach used in developing FDT's is freeze drying and vacuum drying, but both are cumbersome and they yield a fragile and hygroscopic product. Therefore it was decided to adopt the Direct Compression Technique to prepare FDT in an easy and comfortable way as it requires less number of unit operations. Additionally a wetting agent is used to increase the wicking nature of the tablet.

Factorial Experiments

Factorial designs allow for the simultaneous study of the effects that several factors like concentration of superdisintegrants and diluent concentration 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].

Response Surface Design – Surface Plots

Using a surface plot one can visualize the response surface. Surface plots are useful for establishing desirable response values and operating conditions.

Equipments Used

Electronic digital balance-Sartorious BT 323S, Tapped density apparatus-Electrolab USP ETD 1020, Rotary tablet punching machine-Elit Jemkay Pvt Lt, Ahmedabad, Friability test apparatus-Electrolab, EF 2, Mumbai, Disintegration apparatus-Electrolab ED 2AL, Helium lamp (LOD)-Mettler-Toledo, Thickness (Vernier Calipers)-Mitutogo Vernier Calipers, Sieves, Jayanth test sieves, Mumbai, Hardness tester, Monsanto hardness tester, UV-Visible spectrophotometer-Shimadzu (uv-1601), Vernier calipers-Mitutoyo, Japan, Monsanto hardness tester-Scientific Eng Corp Delhi, Stability chamber-Neutronics, HPLC-Shimadzu, FTIR-Shimadzu, X-ray diffractor-Philips, DSC (Differential Scanning Colorimetry)-Shimadzu.

Materials Used

Telmisartan, Kyron T-314, Crosspovidone, XL 10, SSG, Croscarmellose, Strawberry Flavour, Aerosil, Neotame, Microcrystalline cellulose, Mannitol SD, Magnesium stearate, Glycine, Methanol (HPLC Grade), HCl, TEA(tri ethyl amine), Acetonitrile (HPLC Grade). All the chemicals were provided by KAPL Bangalore [4].

***Corresponding author:** Abdul Althaf S, Division of Pharmacy, Sri Venkatswara University, Tirupati, Andhra Pradesh, India, E-mail: abdul.althafi@gmail.com

Received November 06, 2012; **Accepted** November 19, 2012; **Published** November 25, 2012

Citation: Lokesh PNV, Abdul Althaf S, Sailaja PB (2012) Design, Development and Formulation of Orodispersible Tablets of a Model Drug Using Response Surface Methodology. Pharmaceut Anal Acta 3: 195. doi:10.4172/2153-2435.1000195

Plan of Work

The plan of work is to perform pre-formulation studies of the prepared formulation with excipients for their compatibility by FTIR studies and screening of various disintegrating agents for the preparation of rapidly integrating tablets. The best disintegrating agent was used and further evaluated by 3^2 factorial design and regression analysis. Dispersible tablets were prepared by direct compression technique for a model anti-hypertensive drug, telmisartan. Formulation of rapidly disintegrating tablets was carried out using different diluents ratio. 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 polynomial models. The optimized formulation was compared with the reference product by using similarity factor to assess the bioequivalence between the two products. Compatibility studies were performed for the final formulation by using DSC and also stability studies were performed on the most satisfactory formulation as per ICH guidelines [5].

Direct Compression Method

The disintegration and solubilisation of directly compressed tablets depends on action of the disintegrant and other excipients used like wetting agents. Disintegrant efficacy is strongly affected by tablet size and hardness. Large and hard tablets will have more disintegration time than usually required. As a consequence low values in hardness may lead to increased friability. This will affect the physical resistance on the tablet. Disintegrants have major role in the disintegration process of the mouth dissolving tablets made by direct compression. To ensure high disintegration rate, choice of suitable type and optimal amount of the disintegrant is important. All the ingredients were passed through #30 meshes separately. The drug and the diluents were mixed in small portions of both at each time and blended to get a uniform mixture. The ingredients are weighed and mixed in geometrical order. Flavouring agents followed by the lubricants were added at the end and were mixed thoroughly. The blend was compressed using 10 mm flat punch to get a tablet of 300 mg using 16-stationary rotary punching machine. Elit Jemkay Pvt Ltd., Ahmedabad [6].

Formulation of Telmisartan FDT's

The aim of the study is to formulate fast dissolving tablets of Telmisartan by direct compression technique using a wetting agent for fast wicking action and for the solubility enhancement of Telmisartan. Different disintegrants were selected for this study following literature survey. Superdisintegrants used are Croscarmellose sodium, Sodium starch glycolate, Crospovidone, Crospovidone XL 10 and Polacrallin potassium.

Method Development

Since Telmisartan had poor solubility and less bioavailability. Therefore, Addition of different Superdisintegrants were added to decrease the disintegration time thereby increasing the bioavailability and wetting agent was employed to enhance its solubility [7-21].

Method

For the drug Telmisartan, Superdisintegrants were added in different percentage concentrations. The Superdisintegrants and other excipients were mixed thoroughly. The blend was then compressed directly. All the Superdisintegrants were screened and the final formulations with favorable disintegration time and friability results were taken into account for solubility enhancement studies. Since it is already proved that addition of a wetting agent like Glycine will increase the solubility of water insoluble drugs, Glycine is added at a concentration of 3%w/w of the total tablet. The process for the formulation of Telmisartan fast dissolving tablets was developed in a systematic way. Trials were taken by conducting the dissolution studies of the tablets with Glycine, with 1% SLS and 3% SLS in which the drug is intended to show greater solubility (Tables 1-4).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Telmisartan	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Croscarmellose	3	9	18	-	-	-	-	-	-	-	-	-	-	-	-
SSG	-	-	-	6	15	24	-	-	-	-	-	-	-	-	-
Crosspovidone	-	-	-	-	-	-	6	10.5	15	-	-	-	-	-	-
XL 10	-	-	-	-	-	-	-	-	-	3	6	9	-	-	-
KYRON	-	-	-	-	-	-	-	-	-	-	-	-	1	8	15
Mg.stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Aerosil	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Glycine	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
SLS	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Neotame	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MCCP	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180
Peartilol qs to	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300

Table 1: Working formula of the preliminary batches from f1-f15 batches

Batch Code	Variables Levels In Coded Forms		Disintegration Time (Y_1)	% Friability (Y_2)
	X_1	X_2		
P1	-1	1	119	1.71
P2	0	1	58	1.45
P3	1	1	26	0.98
P4	-1	0	69	0.45
P5	0	0	24	0.28

P6	1	0	8	0.16
P7	-1	-1	45	0.53
P8	0	-1	25	0.49
P9	1	-1	15	0.39
Check point batch	0.5	-0.3	16	0.89

Table 2: Factorial design studies: 3^2 Full factorial design lay out.

NOTE: X_1 and X_2 are independent variable representing the concentration of Kyron and diluents ratio in the coded values. Y_1 and Y_2 are the dependent variables representing the responses like Disintegration time in seconds and % Friablilty. All the values of Y_1 and Y_2 are the taken from the following table.

Coded values	Actual values	
	X_1 (Kyron in mg)	**X_2 (MCCP:MANNITOL)**
-1	1	3:1
0	8	2:2
1	15	1:3

Table 3: Coded values and actual values of $X_1$and X_2 variables.

Ingredients	P1	P2	P3	P4	P5	P6	P7	P8	P9
Telmisartan	40	40	40	40	40	40	40	40	40
KYRON	1	8	15	1	8	15	1	8	15
Glycine	9	9	9	9	9	9	9	9	9
SLS	3	3	3	3	3	3	3	3	3
Neotame	1	1	1	1	1	1	1	1	1
Mg. stearate	3	3	3	3	3	3	3	3	3
Aerosil	8	8	8	8	8	8	8	8	8
Mccp: Peartilol	3:1	3:1	3:1	2:2	2:2	2:2	1:3	1:3	1:3
Total	300	300	300	300	300	300	300	300	300

Note: All the weights are expressed in milligrams.

Table 4: Analysis of factorial formulation: Working formula of factorial formulation.

Compatibility Studies of Telmisartan with Formulation Excipients

Compatibility analysis by FTIR spectrophotometer was performed.

Pre-compression parameters

It contains Bulk density, Tapped density, Compressibility index and hausner's ratio, Angle of repose.

Post-compression parameters include

Weight variation, Thickness and diameter, Apparent density, Physical appearance, Hardness, Friability, Disintegration Time, Wetting Time and Water Absorption Ratio, Assay [22-30].

***In vitro* dissolution studies:** *In vitro* dissolution studies for fabricated Mouth Dissolving tablet is carried out by using USPXX III Type II (Electro Lab dissolution tester) dissolution apparatus at 75 rpm in 900 ml of 0.1 N HCl as dissolution media, maintained at 37 ± 0.5°C. Mouth dissolving tablet of desired formulation were taken and placed in the vessels of dissolution apparatus. Sample of 10 ml were collected from the vessels at specified time intervals 10, 20, 30, and 60 min filtered and determined by liquid chromatography as described in the following procedure. Drug concentration was calculated from the standard and expressed as percentage of drug dissolved or released [9].

Stability Studies

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The choice of test conditions defined in the guideline ICH – Q1A (R2) is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States [31-39].

Dissolution Profile Comparison

Dissolution profiles may be considered similar by virtue of (1) overall profile similarity and (2) similarity at every dissolution sample time point. The dissolution profile comparison may be carried out using model independent or model dependent method [40].

Model Independent Approach Using a Similarity Factor

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles (Moore 1996). The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves [41-47].

Results

Standard plot of telmisartan

Regression analysis: Absorbance Y *vs.* Conc X (mcg/ml): The regression equation is Absorbance (Y)=0.01136(c)+0.05292 (m). Conc X (mcg/ml). Where, c=y intercept, m=slope of the regression equation; r^2=0.9993; R-Sq=99.93%; R-Sq (adj)=99.9% (Figures 1-15) (Tables 5-22).

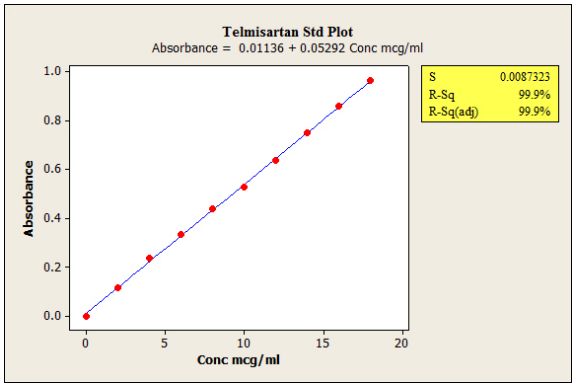


Figure 1: Standard plot of Telmisartan.

Polymorphism studies by x-ray diffraction

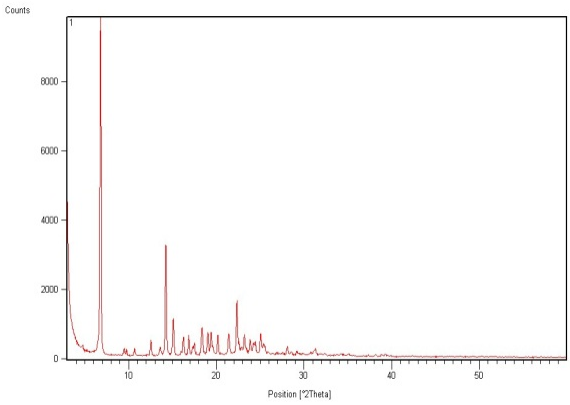


Figure 2: X-ray of pure API: (sample)

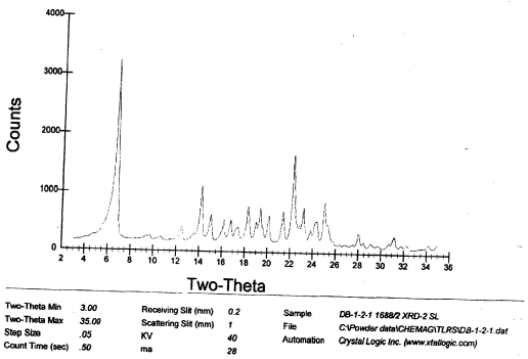


Figure 3: X-ray of reference API.

S.No	Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Status with Ref.
1	6.8203	9532.15	0.1338	12.96068	100.00	Complies
2	14.2584	3176.73	0.1506	6.21188	33.33	Complies
3	15.0878	1057.50	0.1338	5.87220	11.09	Complies
4	18.3679	803.62	0.1673	4.83028	8.43	Complies

5	22.3664	1589.01	0.1338	3.97499	16.67	Complies

Table 5: Peak list.

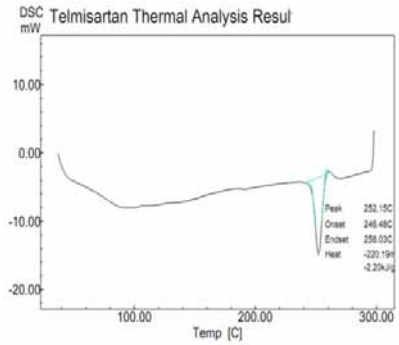


Figure 4: DSC Thermogram of pure API.

S.No	Ingredients	Ratio	Description			FTIR
			Initial	55°C (2 weeks)	40 ± 2°C / 75 ± 5% RH (4 weeks)	
1	API	1	Off white	No change	No change	Complies
2	Mannitol	1	White	No change	No change	Complies
3	Kyron T-314	1	Off white	No change	No change	Complies
4	Glycine	1	White	No change	No change	Complies
5	MCC PH 101	1	Off white	No change	No change	Complies
6	SLS	1	White	No change	No change	Complies
7	Aerosil	1	White	No change	No change	Complies
8	Magnesium stearate	1	White	No change	No change	Complies
9	API+Kyron	5:1	Off white	No change	No change	Complies
10	API+ MCC PH 101	1:5	Off white	No change	No change	Complies
11	API+Mannitol	1:5	Off-white	No change	No change	Complies
12	API+ SLS	10:1	Off white	No change	No change	Complies
13	API+Glycine	4:1	Off white	No change	No change	Complies
14	API+ Aerosil	5:1	Off white	No change	No change	Complies
15	API+ Mg. stearate	5:1	Off white	No change	No change	Complies

Table 6: Pre-Formulation Studies: Drug-excipient compatibility studies.

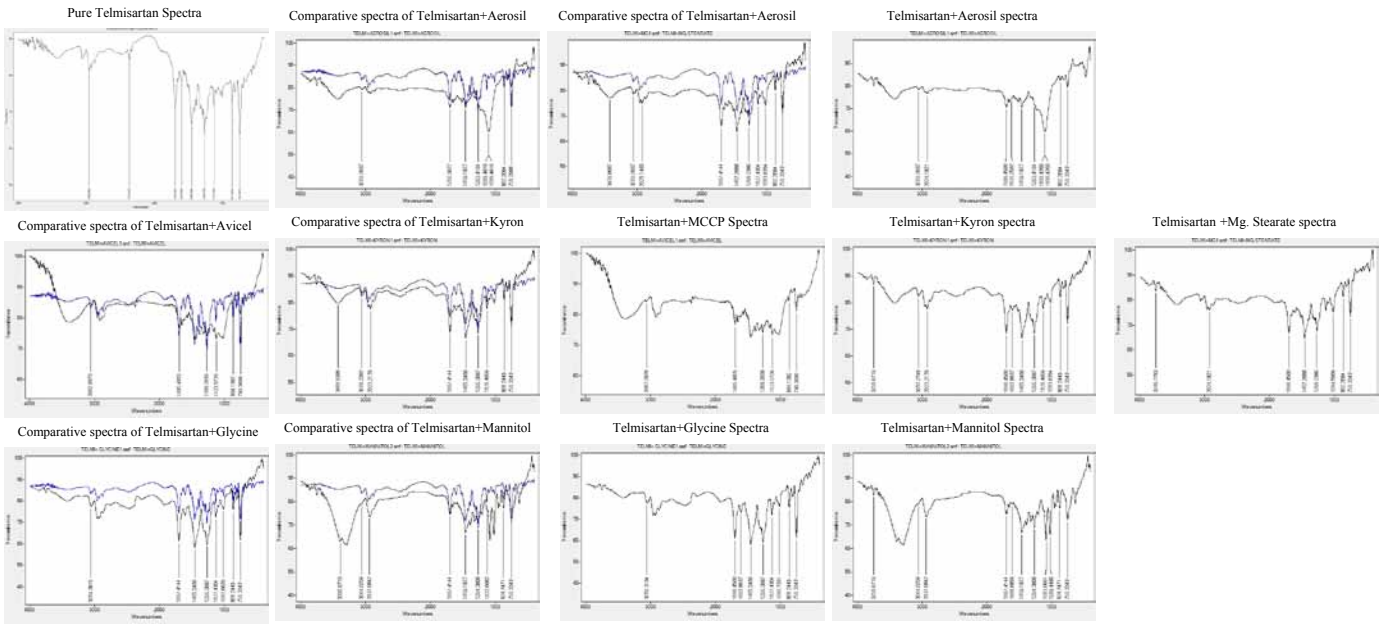


Figure 5: Compatibility studies by FTIR.

PRINCIPAL PEAKS						
Ingredients	**Aromatic C-H 'oop'**	**1°, 2° Amines N-H wagging**	**Amines C-N stretch**	**Arom.Amines C-N stretch**	**Carbonyls C=O stretch**	**Aromatics C-H stretch**
PURE API	749	861	1127	1269	1697	3060
API+Kyron	750.3	861.24	1126.4	1266.6	1697.44	3058.4
API+MCCP	749.3	864.13	1123.5	1269.2	1694.5	3062.09
API+Glycine	750	861.24	1127.43	1266.3	1696.45	3056.3
API+Mannitol	750.4	874.5	1083.06	1264.38	1697.41	3064
API+Mg.Stearate	750.33	862.5	1114	1268	1696	3064
API+Aerosil	751	862	1100.42	1263	1700.3	3059

Table 7: Principal Peaks in FTIR spectrum.

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Carrs Index (%)	Hausners Ratio	Angle of Repose (θ)
F1	0.47	0.59	20.3	1.25	32
F2	0.45	0.54	16.66	1.2	30.5
F3	0.50	0.62	19.3	1.209	30.2
F4	0.54	0.6	16.66	1.11	29.9
F5	0.50	0.62	19.3	1.24	29.1
F6	0.33	0.41	19.5	1.23	29.68
F7	0.36	0.44	18.18	1.22	31.5
F8	0.34	0.42	19.0	1.23	31.9
F9	0.43	0.52	17.3	1.209	31.6
F10	0.339	0.421	19.44	1.24	29.1
F11	0.341	0.429	20.51	1.26	31.2
F12	0.329	0.414	20.53	1.25	30.2
F13	0.32	0.385	16.1	1.19	31
F14	0.318	0.377	15.64	1.18	29
F15	0.313	0.371	15.6	1.15	31.1

Table 8: Pre-compression parameters of the preliminary batches F1-F15.

Disintegrant	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Cross Carmellose	3	9	18	-	-	-	-	-	-	-	-	-	-	-	-
SSG	-	-	-	6	15	24	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	6	10.5	15	-	-	-	-	-	-
XL 10	-	-	-	-	-	-	-	-	-	3	6	9	-	-	-
KYRON	-	-	-	-	-	-	-	-	-	-	-	-	1	8	15
Responses															
D T (Sec)	**65**	56	39	49	45	36	24	12	9	52	43	31	121	78	19
% Friability	**2.2%**	1.2%	0.9%	2.2%	1.6%	0.9%	1.9%	1.2%	0.7%	2.1%	1.8%	1.22%	0.94%	0.71%	0.45%

Table 9: Effect of the Disintegrating Agent with the Disintegration Time and % Friability.

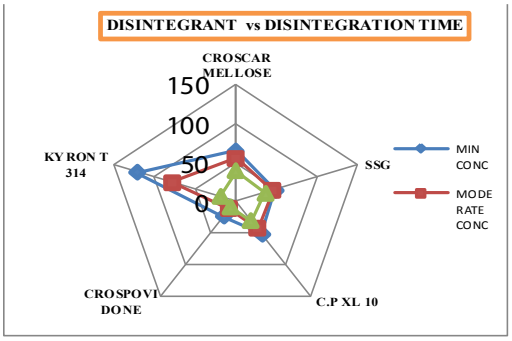
Batch code	Hardness (kg/cm²)	Friability	Weight. variation	Wetting time (Sec)	D.T. (sec)	W.A.R	Assay (%)
F1	3.9	2.2%	Pass	80	65	54.4%	99.6%
F2	4.0	1.23%	Pass	65	56	64.4%	101.3%
F3	4.0	0.89%	Pass	49	39	79.9%	101.1%
F4	4.1	2.24%	Pass	59	49	66.2%	103.3%
F5	4.0	1.55	Pass	49	45	80.9%	99.8%
F6	4.2	0.99%	Pass	42	36	89.1%	101.4%
F7	3.9	1.9%	Pass	28	24	45.3%	100.4%
F8	4.1	1.2%	Pass	21	12	56.4%	100.9%
F9	4.0	0.65%	Pass	16	9	79.6%	99.4%
F10	4.2	2.1%	Pass	69	52	69.5%	102.1%
F11	4.0	1.8%	Pass	47	43	79.5%	100.5%
F12	3.9	1.22%	Pass	37	31	94.6%	99.6%
F13	4.2	0.94%	Pass	140	121	89.3%	100.5%
F14	4.1	0.71%	Pass	67	78	96%	100.1%
F15	4.2	0.45%	Pass	22	19	101.3%	99.8%

Table 10: Post-compression parameters of the preliminary batches F1-F15.

S. No	Time	Condition	Tab. wt	Std Wt (gm)	Std absorbance	Spl Absorbance	% Purity	mg/Tab released	%Release
1	10	Glycine	0.306	0.0448	1456624.5	2764986	99.86%	37.902427	94.75607
2	10	1% SLS	0.307	0.0448	1456624.5	2774165	99.86%	37.892128	94.73032
3	10	3% SLS	0.2982	0.0448	1456624.5	2435898	99.86%	34.287098	85.71775
4	20	Glycine	0.306	0.0448	1456624.5	2866861	99.86%	39.324615	98.31154
5	20	1% SLS	0.3028	0.0448	1456624.5	2750950	99.86%	38.13345	95.33362
6	20	3% SLS	0.2982	0.0448	1456624.5	2482267	99.86%	34.939777	87.34944
7	30	Glycine	0.306	0.0448	1456624.5	2878330	99.86%	39.456147	98.64037
8	30	1% SLS	0.3028	0.0448	1456624.5	2790687	99.86%	38.684281	96.7107
9	30	3% SLS	0.2982	0.0448	1456624.5	2497834	99.86%	35.158894	87.89723
10	60	Glycine	0.306	0.0448	1456624.5	2902128	99.86%	39.78237	99.45592
11	60	1% SLS	0.3028	0.0448	1456624.5	2821973	99.86%	39.117965	97.79491
12	60	3% SLS	0.3016	0.0448	1456624.5	2578947	99.86%	35.891396	89.72849

Note: Average wt (weight) of the 20 tablets is 0.3037 mg; Std (standard); Spl (sample); Tab (Tablet).

Table 11: Screening the effect of glycine, 1% SLS and 3% SLS on solubility by dissolution apparatus.



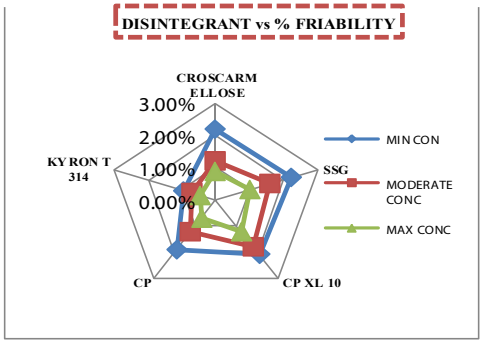


Figure 6: Left: Radar plot showing the effect of the Disintegrant on the Disintegration time.

Right: Radar plot showing the Effect of the Disintegrant on the % Friability.

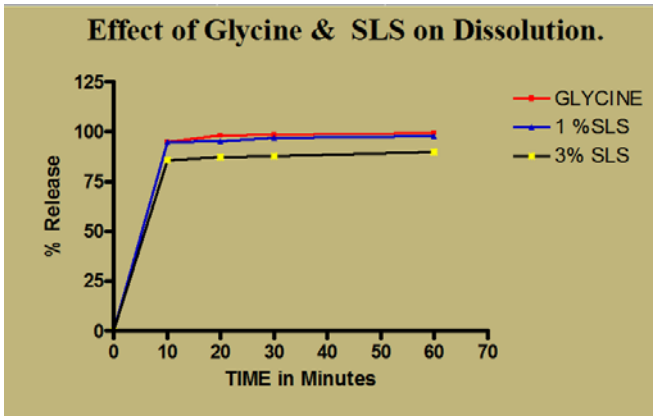


Figure 7: Effect of various wetting agents on the dissolution of the Telmisartan FDT's and comparative dissolution profile Telmisartan tablets with two different wetting agents.

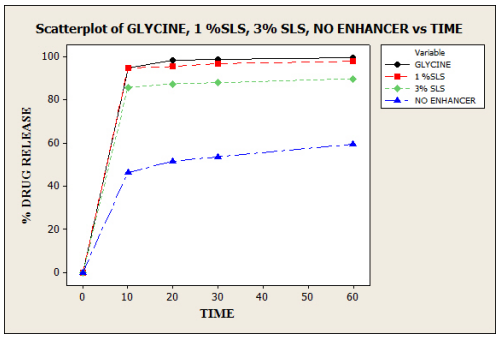


Figure 8: Comparative dissolution profile solubility enhancer *vs.* without enhancers.

Pre-Compression Parameters	P1	P2	P3	P4	P5	P6	P7	P8	P9
Bulk density	0.36	0.34	0.33	0.43	0.45	0.47	0.5	0.54	0.50
Tapped density	0.44	0.42	0.41	0.52	0.54	0.59	0.6	0.6	0.62
Carr's index	18.18	19.0	19.5	17.33	16.66	19.33	16.66	16.66	19.33
Hausner's ratio	1.22	1.23	1.23	1.209	1.21	1.25	1.2	1.11	1.24
Angle of repose	29.29	29.1	29.9	26.6	26.5	26.9	22.68	22.5	21.9

Table 12: Pre-Compression parameters of factorial formulations.

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Hardness	4	4.1	4.1	4.0	4.2	3.9	4.0	3.9	4
Thickness	3.96	3.94	3.95	3.38	3.39	3.39	3.05	3.04	3.04
Diameter	10.09	10.09	10.08	10.09	10.08	10.09	10.07	10.08	10.09
Density	0.95	0.95	0.95	1.24	1.11	1.06	1.24	1.239	1.24
Friability	1.71	1.45	0.98	0.45	0.28	0.16	0.53	0.49	0.39
Disint.time	119	58	26	9	24	8	45	25	15
Dispersion time	42	34	29	35	28	14	38	25	16
Assay (%)	99.7	100.3	100.9	102.2	101.1	100.4	103.3	100.1	98.9

Table 13: Evaluation of factorial formulations.

S.No	Time	Std Wt in gm	Tablet wt	Std absorbance	Sample Absorbance	% Purity	mg/Tab released	%Release
Smpl	10	0.0448	0.306	1456624.5	2790472	99.86%	38.27679	95.69%
Std	10	0.0458	0.221	1456624.5	2955804	99.86%	40.6888	101.7221
Smpl	20	0.0448	0.306	1456624.5	2816416	99.86%	38.60743	96.52%
Std	20	0.0458	0.221	1456624.5	2996819	99.86%	41.25344	103.1336
Smpl	30	0.0448	0.306	1456624.5	2859674	99.86%	39.22603	98.1%
Std	30	0.0458	0.221	1456624.5	2998622	99.86%	41.27826	103.1956
Smpl	60	0.0448	0.306	1456624.5	2904810	99.86%	39.84516	99.6%
Std	60	0.0458	0.2	1456624.5	3094804	99.86%	42.60228	106.5057

Note: Average wt of the 20 tablets is 0.3037 gm (P6 batch); Average wt of the 20 tablets is 0.2158 gm (Marketed batch); All the weights mentioned are in grams only.

Table 14: Dissolution data of the optimized batch and comparison with the marketed product.

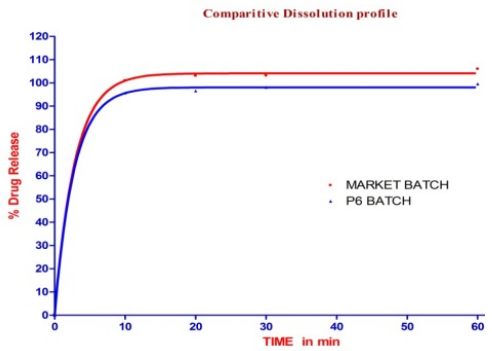


Figure 9: Comparative dissolution profile of Marketed batch *vs.* P6 Batch.

X1	X2	X1 X2	X_1^2	X_2^2	Y1
-1	1	-1	1	1	119
0	1	0	0	1	58
1	1	1	1	1	26
-1	0	0	1	0	69
0	0	0	0	0	24
1	0	0	1	0	8
-1	-1	1	1	1	45
0	-1	0	0	1	25
1	-1	-1	1	1	15

Table 15: Multiple regression analysis for response factor y1 (Disintegration time).

Predictor	Coefficients	P-value
Constant	26.11111	0.00242
X_1 Variable	-30.6667	0.000253
X_2 Variable	19.66667	0.000948
X_1X_2 Variable	-15.75	0.003299
X_1^2 Variable	11.33333	0.022047
X_2^2 Variable	14.33333	0.011606

Table 16: Summary of results of regression analysis for response factor y1 (Disintegration time):

S=3.66035 ; R-Sq=99.6%; R-Sq(adj)=98.9%; *Regression Analysis:* Y_1 *versus* X_1, X_2, X_1X_2, X_1^2, X_2^2; The regression equation is $Y_1=26.1-30.7X_1+19.7X_2-15.7X_1X_2+11.3\ X_1^2+14.3X_2^2$.

For D T (Y1)						
	df	SS	MS	F	Significance F	R^2
Regression	5	9623.361	1924.672	143.6521	0.000907	0.995841
Error	3	40.19444	13.39815			
Total	8	9663.556				

Table 17: Results of ANOVA for dependent variables.

Y_2 (Fraibility) *vs.* X_1 and X_2

X_1	X_2	X_1X_2	X_1^2	X_2^2	Y2
-1	1	-1	1	1	1.71
0	1	0	0	1	1.45
1	1	1	1	1	0.98
-1	0	0	1	0	0.45
0	0	0	0	0	0.28
1	0	0	1	0	0.16
-1	-1	1	1	1	0.53
0	-1	0	0	1	0.49
1	-1	-1	1	1	0.39

Table 18: Multiple Regression Analysis for Response Factor Y2 (% Friability):

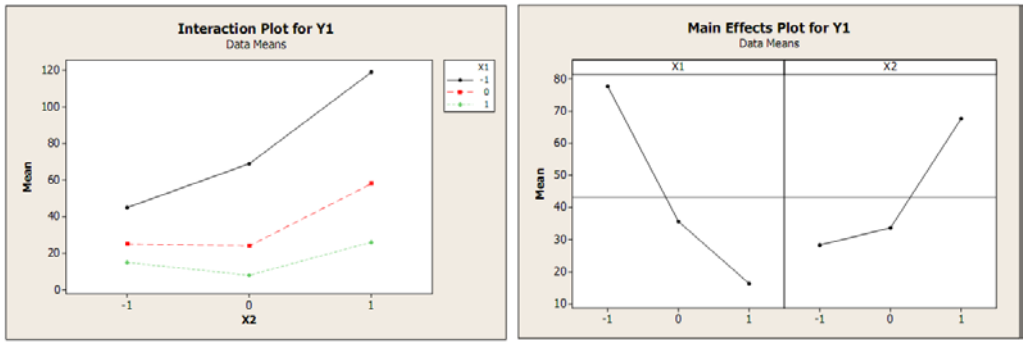


Figure 10: Right: Plot showing the level of interactions between the X1 and X2 at various concentrations.**Left:** Plots showing the effect of individual concentration of X_1, X_2 on the % Friability.

Predictor	Coefficients		P-value	
	FM	RM	FM	RM

Constant	0.321111	0.296667	0.007005	0.001157
X_1 Variable	-0.19333	-0.19333	0.005345	0.001578
X_2 Variable	0.455	0.455	0.000433	5.63E-05
X_1X_2 Variable	-0.1475	-0.1475	0.02005	0.008917
X_1^2 Variable	-0.03667	-	0.483493	-
X_2^2 Variable	0.628333	0.296667	0.000848	0.001157

Table 19: Summary of results of regression analysis for response factor Y_2 (% Friability).

S=0.0650285; R-Sq=99.5%; R-Sq(adj)=98.6% {FULL MODEL}

Regression Analysis: Y_2 versus X_1, X_2, X_1X_2, X_1^2, X_2^2 {FULL MODEL}. The regression equation is Y_2=0.321-0.193 X_1+0.455 X_2-0.147X_1X_2-0.0367 X_1^2+0.628X_2^2

S=0.0619980; R-Sq=99.3%; R-Sq(adj)=98.7% {REDUCED MODEL}

Regression Analysis: Y_2 versus X_1, X_2, X_1X_2, X_2^2 {REDUCED MODEL}. The regression equation is Y_2=0.297-0.193X_1+0.455X_2-0.147 X_1X_2+0.628X_2^2

For % Friability						
Full Model						
	Df	**SS**	**MS**	**F**	**Significance F**	**R^2**
Regression	5	2.345736	0.469147	110.9435	0.001333	0.994621
Residual	3	0.012686	0.004229			
Total	8	2.358422				
Reduced model						
Regression	4	2.343047	0.585762	152.3933	0.000127	0.993481
Residual	4	0.015375	0.003844			
Total	8	2.358422				

Table 20: Results of ANOVA of Full and Reduced Model for Dependent Variable.

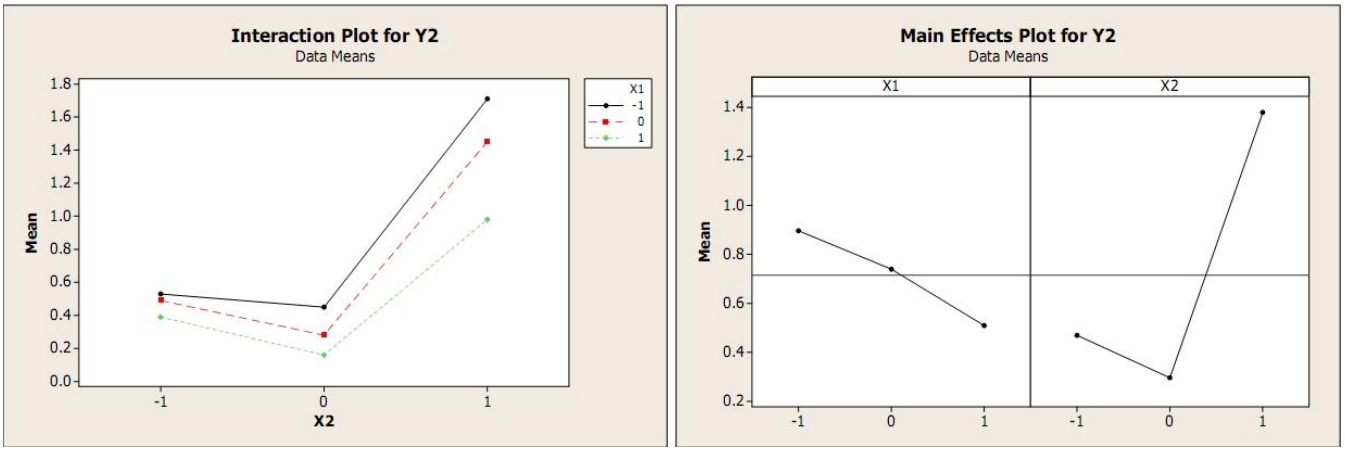


Figure 11: Right: Plot showing the level of interactions b/n the X1 and X2 at various Concentrations. **Left:** Plots showing the effect of individual concentration of X_1 and X_2 on % Friability.

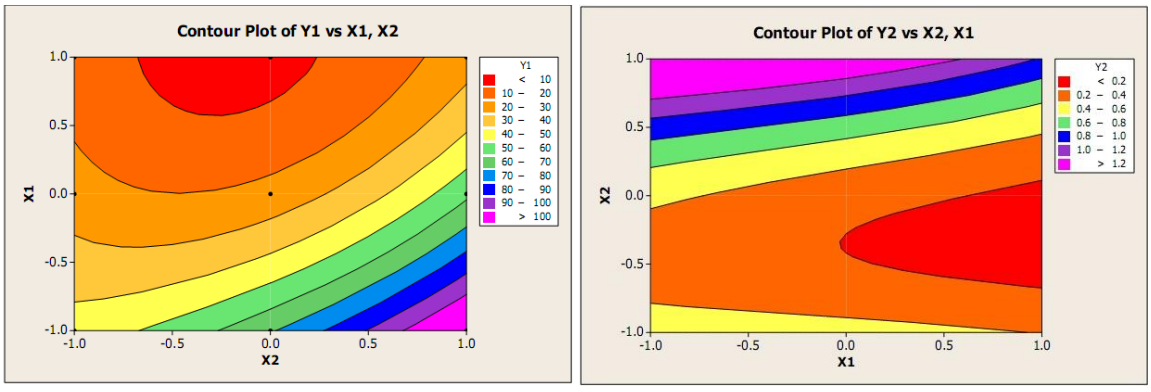


Figure 12: Right: Contour plot showing the effect of X1 and X2 on the % Friability. **Left:** Contour plot showing the effect of X1 and X2 on the % Friability.

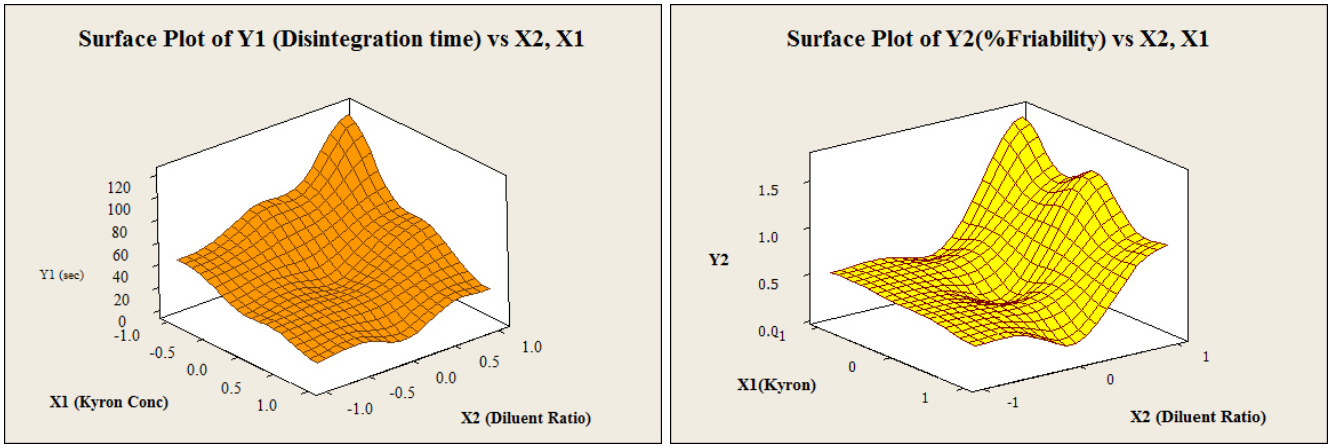


Figure 13: Right: Response Surface Plot of Y_1 *vs.* X_1 and X_2; Left: Response Surface Plot of Y_2 *vs* X_1 and X_2.

Figure 14: Diagramatic representation of invitro dispersion time of dispersible tablets: (P6 optimized batch).

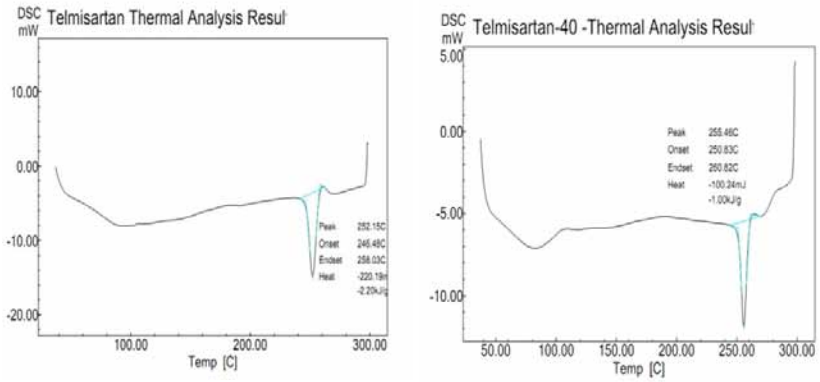


Figure 15: Final compatibility studies of telmisartan fast dissolving tablets using differential scanning colorimetry.

Stability data:

Parameter	Initial	1st	2nd	3rd	4th	5th	6th
Description	**Off white coloured round shaped uncoated tablets**	**No change**	**No change**	**No change**	**No change**	**No change**	**No change**
Avg.wt (mg)	301.9	302.2	302.4	302.3	302.2	302.2	302.3
Hardness (kg/cm²)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Thickness (mm)	3.39	3.39	3.39	3.39	3.39	3.39	3.39
Friability (%)	0.16	0.18	0.17	0.18	0.21	0.19	0.16
Assay (%)	99.98	100.5	99.47	100.2	100.7	99.98	99.69
Disintegration time	8 sec	8sec	8sec	9 sec	7 sec	8 sec	8 sec

Table 21: Physical and chemical parameters of Telmisartan fast dissolving tablets (P-6) after 1st and 2nd month at 40 ± 2°C/75 ± 5% RH (Packing: Blister packing).

Parameter	Initial	1st	2nd	3rd	4th	5th	6th

Description	Off white coloured round shaped tablets	No change	No change	No change	No change	No change	No change
Avg.wt (mg)	301.8	302.2	301.2	302.4	301.7	302.2	301.2
Hardness (kg/cm²)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Thickness (mm)	3.39	3.39	3.39	3.39	3.39	3.39	3.39
Friability (%)	0.16	0.19	0.16	0.18	0.17	0.18	0.21
Assay (%)	100.5	99.98	99.69	100.2	99.98	99.47	100.7
Disintegration time	8 sec	8 sec	9 sec	8 sec	8 sec	10 sec	9 sec

Table 22: Physical and chemical parameters of Telmisartan Fast Dissolving Tablets (P-6) after 1st – 6th month 25 ± 2°C and 60 ± 5% RH for 12 months (Packing: Blister packing).

Discussion

Melting point determination

By using melting point determination apparatus, the preliminary physical characteristics of the pure API like melting point, Telmisartan was found to be 255°C complies with literature standards.

X-ray diffraction studies and DSC studies

The X-ray Studies revealed that the API sample is only of pure polymorph A and there was no contamination of polymorph B which has less stability, poor flow than polymorph A which may cause degradation during the compression stages of tablets.

FT-IR studies

The excipient compatibility studies were conducted with the pure API and it was found to be compatible by comparative studies. Results revealed that there was no disturbance in the pure API.

HPLC studies

The solubility studies between without solubility enhancer, glycine and 1% SLS, 3% SLS were conducted. There was huge indirect relationship was observed that, increase in the concentration of SLS from 1% to 3% causes decrease in the solubility from 98% to 85%. And glycine has showed very good solubility of 99.97% which is comparatively higher than SLS which was observed by HPLC chromatograms.

DSC studies

Final compatibility studies of Telmisartan with all the excipients are performed and analyzed. The comparative thermogram of API and final blend results revealed that that there was no incompatibility between them. The clear peak at 252°C in the pure API thermogram was not disturbed after final blending was completed.

Experimental design

In the present study, a three level two factorial design was used to evaluate the effects of the selected independent variables on the responses, to characterize the physical properties of the tablet like disintegration time, the % friability and to optimize the procedure. This design is suitable for exploration of the quadratic responses and the second order polynomial models, thus helping to optimize the process by using a small number of experimental runs. This design resolves the two factor interaction effects of the individual terms and allows the mid-level setting (0) for the combination of factors.

Optimization results

The formulation was designed using 3^2 factorial design, the materials and compositions used are presented in table 4. In this study, formulation variables i.e,

Independent variables: X1=Disintegrant Concentration (Kyron T-314)

X2=Diluent ratio (MCCP: MANNITOL)

Dependent variables: Y1=Disintegration time,

Y2=% Friability.

Influence of independent variables on the final formulation

The preliminary trails were conducted by using five different Superdisintegrants like Croscarmellose, sodium starch glycolate, Crospovidone, XL-10 and kyron T-314. Three batches were using a single superdisintegrant. On the basis of the results obtained in the preliminary studies, the batch containing the Kyron T-314 is showing good correlation % friability and disintegration time. Hence it was selected for further studies. The hardness was adjusted to the 4 kg/cm². Wetting agent like glycine is used to increase the water availability for the superdisintegrant by its wicking action. The table of post compression parameters of F1 to 15 indicates that the concentration dependent disintegration was observed in the batches prepared by the different Superdisintegrants at different concentrations. Tablets with lower friability (≤ 0.5%) may not break during handling on machines and or shipping. In the first few attempts in preliminary batches a change in the filler ratio of (MCCP: Mannitol) causes changes in the friability values were observed and hence it is also considered as one of the important factor that effect friability. The use of superdisintegrant at

varied concentrations {along with change in the filler concentration/ratio} effecting the friability was also observed. Addition of colloidal silicon dioxide results in decreased friability and marginal effect on the disintegration time. As the magnesium stearate will form a layer around the tablet that may decrease the wicking action of the other excipients. It was decided to add the colloidal silicon dioxide that helps to restore the bonding properties of the other excipients. So, based on the observation it was decided to take superdisintegrant concentration and MCCP: MANNITOL (filler ratio) as the two independent variable that effecting the friability and disintegration time taken as the dependent variables. The disintegration time and % friability for the 9 batches from P1 to P9 showed wide range of variation (i.e., 8 sec to 119 sec and 0.16% to 1.71%) respectively. This indicates the disintegration time and friability are strongly dependent on the selected independent variables. The fitted equation (full and reduced model) relating the disintegration time and friability is shown in the table. The polynomial equation can be used to draw the conclusion after considering the magnitude of the coefficient and the mathematical sign it carries (positive or negative). Table 22 shows results of analysis of variance (ANOVA), which was performed to identify the insignificant factors. The high values of the correlation coefficient for disintegration time and % friability indicates a good fit.

Estimation of quantitative effects of the factors

A response regression analysis for each factor was performed by using the coded values of the factor levels (-1, 0, 1). In the table 18, 19, 21 and 22, the factor effects and associated *p-values* for the responses were presented. A factor is considered to influence the response if the effects significantly differ from zero and the *p*-value is less than 0.05. A positive sign indicates a synergistic effect, while a negative sign represents an antagonistic effect of the factor on the selected response.

Analysis of fitted data

Combinational effect on disintegration time: The results of linear multiple regression analysis reveal that on increasing the concentration of the superdisintegrant i.e. Kyron T-314, there is decrease in the disintegration time is observed as the coefficient of the X_1 bears the negative symbol. This may be due to an increase in the concentration might cause the increase in the water uptake by the superdisintegrant in the formulation causing the tablet to disintegrate rapidly by swelling. Similarly the X_2 coefficient positive symbol indicates that increase in the concentration of MCCP in the diluents ratio will increase the disintegration time was observed.

$$Y_1=26.1-30.7X_1+19.7X_2-15.7X_1X_2+11.3\ X_1^2+14.3X_2^2$$

The factor X_1, and interaction term $X_1\ X_2$ has antagonistic effect on the Y_1 response and these factors are found to be significant with a *p-value of* 0.0002 and 0.003. The factor X_2, and the nonlinearity factors X_1^2, X_2^2 have synergetic effect on the Y_1 and found to be significant with *p-values* of 0.001, 0.022 and 0.012. For estimation of the significance of the model, the analysis of variance ANOVA was applied. Using the 5% significance level, a model is considered to be significant if its *p-value (significant probability value)* is less than the 0.05. From the table 19, the value of *p* was found to be less than 0.05 and hence the model is considered was found to be significant to predict the influence of the independent variables on the responses or dependent variables i.e. disintegration time (Y_1).

Combination effect on % friability*:* As the concentration of the superdisintegrant led to decrease in the friability values because the coefficient of X_1 indicates negative sign. When an higher amount of the superdisintegrant is used, the adhesive nature may result in the increase in the inter particulate bonding strength such that decrease in the friability is achieved. Thus addition of polacrallin potassium not only favors the disintegration time but also the friability values. Tablets of low friability of 0.16% may not break during the handling, packing and shipping. Thus polacrallin potassium helps in producing the mechanically strong Fast Dissolving Tablets. In the same manner, the coefficient of the X_2 bears positive symbol indicating that increase in the MCCP in the filler ratio causes increase in the friability value. But from the graph the effect is in sigmoid fashion. This indicates that decrease in the concentration of MCCP will decrease the friability values up to certain extent i.e. when the MCCP: MANNITOL is 2:2. But the proportionality is observed up to the certain level i.e. up to the MCCP: Mannitol ratio is 2:2, after that again the reverse is observed because the X_2^2 nonlinearity factor was found to be more significant.

$$Y_2=0.321-0.193\ X_1+0.455\ X_2-0.147\ X_1\ X_2-0.0367\ X_1^2+0.628\ X_2^2 \{\text{Full model}\}$$

$$Y_2=0.297-0.193\ X_1+0.455\ X_2-0.147\ X_1\ X_2+0.628\ X_2^2 \{\text{Reduced Model}\}$$

The factor X_1 and interaction term $X_1\ X_2$ have antagonistic effect on the Y_1 response and these factors are found to be significant with a *p-value of* 0.005 and 0.02. The factor X_2, and the nonlinearity factor X_2^2 have synergetic effect on the Y_1 and found to be significant with *p-values of* 0.001 and 0.001. The nonlinearity factor X_1^2 was to found to be insignificant in predicting the % friability because its *p-value is* 0.483 and hence it was excluded in estimating the ANOVA of the model. For estimation of the significance of the model, the analysis of variance ANOVA was applied. Using the 5% significance level, a model is considered to be significant if its *p-value (significant probability value)* is less than the 0.05. From the tables 2 and 3, the value of *p* was found to be less than 0.05 and hence the model is considered was found to be significant to predict the influence of the independent variables on the responses or dependent variables i.e. % friability. The reduced model was tested to determine whether X_1^2 variable contribute significantly to predict the % friability or not. Since the *p-value* is <0.05, it was conclude that X_1^2 does not contribute significantly to predict the % friability.

Analysis of contour plots and response surface plots

Three-dimensional (3D) plots and Contour plots for the measured responses were formed, based on the model polynomial functions to assess the change of the response surface. Also the relationship between the dependent and independent variables can be further understood by these plots. Since the model has two factors, one factor was held constant for each diagram; therefore, a total of 2 response surface diagrams was produced one for each response. Response surface plots are presented using optimal levels of the factors studied. Considering the greatest difference in model

polynomial functions response, the surface plots for responses *Y*1 and *Y*2 are further presented (Figures 13 and 14). In Figure 14 (Right), response surface plots (3D) showing the effect of concentration of superdisintegrant (X_1) and ratio of diluents (X_2) on the response *Y*1 (Disintegration time of Telmisartan) and in figure 14 (Left), response surface plots (3D) showing the effect of concentration of superdisintegrant (X_1) and ratio of diluents (X_2) the response Y_2 (% Friability), respectively are presented. The influence of concentration of superdisintegrant (X_1) and ratio of diluents (X_2) are presented.

Conclusion

Oral disintegrating tablets (ODT) of TELMISARTAN was successfully prepared by using direct compression method The optimal batch P6 exhibited the disintegration time of 8 sec and friability of 0.16%. The method for immediate release of Telmisartan tablets with optimal release properties was determined using experimental design methodology. After determination of significant parameters by using three-level two-factorial design was applied. Analytical parameters investigated in this study were: concentration of superdisintegrant (X_1), ratio of diluents (X_2). The chosen responses were disintegration time and the % friability. The model reliability and estimation of quantitative effects of different levels of investigated factors was performed using the Minitab System statistical software, Release 16.0. 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 Telmisartan immediate release tablets was performed in a very short 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 3^2 factorial design revealed that the amount of superdisintegrant and the filler ratio significantly affect the dependent variables disintegration time and % friability. It is concluded that by adopting a systematic formulation approach, an optimum can be reached in the shortest time with minimum efforts.

References

1. Avani FA (2006) Emerging Trends in The Development of Orally Disintegrating Tablet Technology.
2. United States Publication (2006) Publication Number US 2006/0165781 A1.
3. Bhowmik D (2009) Design and characterization of fast dissolving tablet of telmisartan. IJPRR 1: 31-40.
4. James E De Muth (2006) Basic Statistics & Pharmaceutical Statistical applications. (2nd edn).
5. Sanford Bolton, Charles Bon. Pharmaceutical Statistics, Practical and Clinical Applications.
6. Gerald Van Belle Biostatistics- A Methodology for the Health Sciences. (2ndedn).
7. Kumari S, Visht S, Sharma PK, Yadav RK (2010) Fast Dissolving Drug Delivery System: Review Article. J Pharm Res 3: 1444-1449.
8. Parikh BN (2010) Formulation Optimization and Evaluation of Immediate Release of Telmisartan. Journal of Global Pharma Technology 2.
9. Jinichi F, Etsuo Y, Yasuo Y, Katsuhide T (2006) Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. International Journal of Pharmaceutics 310: 101-109.
10. Lefevre P, Duriez X, Joshi AA (2005) Screening and identifying optimal combinations of excipients and super-disintegrants in the development of orally disintegrating tablet (odt) formulations.
11. Ranch KM, Koli AR, Vyas BA, Parikh RK, Vyas RB, et al. (2009) Formulation, design and optimization of orodispersible tablets of atenolol. International Journal of PharmTech Research 1: 1559-1563.
12. Pandya VM, Patel DJ, Patel JK, Patel RP (2009) Formulation, characterization, and optimization of fast-dissolve tablets containing celecoxib solid dispersion. Dissolution Tech 16.
13. Gosai AR, Patil SB, Sawant KK (2008) Formulation and evaluation of oro dispersible tablets of ondansetron hydrochloride by direct compression using superdisintegrant. International Journal of Pharmaceutical Sciences And Nano Sciences 1: 106-111.
14. Gohel M, Patel M, Amin A, Ruchi A, Agarwal R, et al. (2004) Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech 5: Article 36.
15. Parikh BN (2010) Formulation optimization and evaluation of immediate release tablet of telmisartan. Journal of Global Pharma Technology 2.
16. Alanazi FK (2007) Evaluation of Spray And Freeze Dried Excipient Bases Containing Disintegration Accelerators For The Formulation Of Metoclopramide Orally Disintegrating Tablets. Saudi Pharmaceutical Journal 15: 105-119.
17. Swamy PV, Shahidulla SM, Shirsand SB, Hiremath SN, Younus Ali (2008) Orodispersible Tablets of Carbamazepine Prepared by Direct Compression Method Using 3^2 Full Factorial Design. J Pharm Sci 7: 1-5.
18. Narmada GY, Mohini K, Prakas Rao B, Gowrinath DXP, Kumar KS (2009) Formulation, evaluation and optimization of fast dissolving tablets containing *Amlodipine Besylate* by sublimation method. ARS Pharm 50: 129-144.
19. Prajapati BG, Patel DV (2010) Formulation and optimization of domperidone fast dissolving tablet by wet granulation techniques using factorial design. International Journal of PharmTech Research 2: 292-299.
20. Garala KC, Ekshinge VB, Jarag RJ, Shinde AJ (2008) Fast-disintegrating aceclofenac tablets: formulation development using simplex lattice design. Thai J Pharm Sci 32: 77-81.
21. Mahamuni SB, Shahi SR, Nandakishor VS, Agarwal GR (2009) Formulation and evaluation of fast dissolving tablets of promethazine HCL with masked bitter taste. International Journal of Pharma Research and Development 1-18.
22. Ashutoshkumar S, Arunachalam A, Kartikeyan M, Manidipa S, Ravishankar V, et al. Design and evaluation of sustained release tablet of Telmisartan. International Journal of Pharmaceutical Sciences 2: S146-156.

23. Chaudhari KU, Gaikwad PD, Bankar VH, Pawar SP (2004) Development and validation of UV-spectrophotometric method for simultaneous estimation of telmisartan and atorvastatin calcium in bulk and tablet dosage form. IJPT 255-257.

24. Gohel M, Patel M, Amin A, Agrawal R, Dave R, et al. (2004) Formulation, design and optimisation of mouth dissolving tablets of nimesulide using vaccum technique. AAPS Pharm Sci Tech 5: 10-15.

25. Desai, Kharede SV, Petkar KC, Kuchekar BS (2006) Orodispersible tablets of promithazine hydrochloride. Indian J Pharm Edu and Research 40: 172-174.

26. Vijay KSG, Mishra DN (2006) Rapidly disintegrating oral tablets of meloxicam. Indian Drugs 43: 117-121.

27. Chandrashekar NS, Kulkarni PK, Parimala P (2006) Formulation and evaluation of fast dissolving tablets of rofecoxib. Int J Pharma Excip 14-17.

28. Devi VK, Asha AN, Pai RS, Reddy MCH, Raghvendra MMAV (2006) Orodispersible fluconazole tablets-Preparation and Evaluation. Indian Drugs 43: 548-552.

29. Di Martino P, Martelli S, Wehrlé P (2005) Evaluation of different fast melting disintegrants by means of a central composite design. Drug Dev Ind Pharm 31:109-121.

30. http://www.rxlist.com/micardis-drug-center.htm

31. Fast Dissolving Drug Delivery System (2006).

32. Rowe RC (2009) Hand Book Of Pharmaceutical Excipients. (6thedn).

33. United states of pharmacopeia 32 - nf 27, Physical tests for solid dosage form.

34. Indian pharmacopeia (2010) III: 2186.

35. Banker GS, Rhodes CT (1996) Modern Pharmaceutics and the pharmaceutical sciences. (4thedn), 121: 329-330.

36. Manivannan R (2009) Oral Disintegrating Tablets: A Future Compaction. International Journal of Pharmaceutical Research and Development.

37. Chaudhari KU, Gaikwad PD, Bankar VH, Pawar SP. Development And Validation Of Uv Spectrophotometric method For Simultaneous Estimation Of Telmisartan And Atorvastatin Calcium In Bulk And Tablet Dosage Form. International Journal 0f Pharmacy & Technology.

38. Gordon MS, Chatterjee B, Chowhan ZT (2006) Effect of the mode of croscarmellose sodium incorporation on tablet dissolution and friability. J Pharm Sci 79: 43–47.

39. Guidance for the Industry – dissolution testing for the immediate solid oral release dosage forms.

40. www.ich.org/fileadmin/.../ICH.../Guidelines/.../Stability_Guideline_WHO.

41. http://www.drugbank.ca/drugs/DB00966

42. Theory and Practice of Industrial Pharmacy- Lachmann & Leibermann.

43. US Department of Health and Human Services (2000) Guidance for the Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutical Classification System. FDA.

44. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (2003) ICH Harmonized Tripartite Guidelines: Stability Testing of New Drug Substance and Products- Q1A (R2).

45. www.cipladoc.com/therapeutic/pdf_cipla/cresar_am.pdf

46. Wilson & Gisvold's Textbook of Organic Medicinal & Pharmaceutical Chemistry. (11thedn).

47. United States Patent Application Publication Adin et al. (2006) US_2006_0276525_A1, Processes of preparing highly pure telmisratan form A, suitable for pharmaceutical compositions.