Available on line www.eijppr.com

International Journal of Pharmaceutical and Phytopharmacological Research

Int.J.Pharm.Phytopharmacol.Res. 2011, 1(1): 35-47

Development of Directly Compressible Co-excipient by Spray Drying Technique

Rajendra K. Surawase*, Santosh S. Surana, Avish D. Maru, Prashant S. Malpure

**Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Kalwan, Nashik-423 501*

Received on: *24/08/2011* ***Accepted on:*** *30/08/2011*

ABSTRACT

Co-excipients has multifunctional properties like good flow property, compressibility index and less moisture content and therefore it can be used in direct compression method to reduce many steps like granulation, blending and milling in wet. The aim of the present study was to develop co-processed directly compressible excipients using optimized spray drying technique. Experimental design was built to investigate the effect of three factors - Inlet temperature of spray dryer, Atomization pressure and Feed rate at two level using spray dried yield, moisture content and compressibility index of spray dried co-processed excipient as dependent variables. Box-behnken design was applied for optimization of spray dryer parameters. The Design Expert software has given the optimized parameters as Inlet temperature 120 ^{0}C, Atomization pressure 2 bar and Feed rate 5.01 rpm and using these optimized parameters one validation batch was taken and evaluated for its Scanning electronic microscopy (SEM) and Differential scanning calorimetry (DSC) study. Spray drying method was found to be suitable for the preparation of directly compressible co-processed excipient. This new technique will save the time and possible cost for the development of tablet dosage forms.

Key Words: Spray drying, Co-processing, Direct compression, Box-behnken design, Excipient.

INTRODUCTION

Despite many advanced dosage forms, the tablet remains the most widely used dosage form owing to its stability, dose uniformity and user acceptability. However, its formulation development is challenging owing to its multifarious manufacturing procedures. Many changes in tablet manufacturing process have taken place to overcome these challenges. Over the time, industries have become more interested in reducing both time and cost of drug production, which led to the introduction of new processes such as direct compression, fluidized-bed granulation, automatic capsule filling and film coating. In wet granulation and dry granulation techniques, various processing steps and manufacturing challenges are involved, leading to higher cost and time of tablet production. Most formulations contain higher amount of excipients compared to the active drug and, as a consequence, excipients play a major role in deciding the formulation's functionality and processability. Many improved grades of existing excipients such as spray dried Lactose, Microcrystalline cellulose (MCC), granular

dicalcium phosphate, Crosspovidone and pregel starch has been introduced in the market but performance improvement was achieved only up to a limited extent. On the other hand, co-processed excipients by virtue of combining properties of two different excipients fulfil the increasing demand of multifunctional excipients for direct tabletting[1].

Co-processing was initially used by the food industry to improve stability, wettability and solubility, and to enhance the gelling properties of food ingredients such as co-processed glucomannan and galactomanan. Co-processing is a novel concept of processing two or more established excipients by some appropriate means to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipient. The major advantages of co-processed excipient are the elimination of wet granulation production stages, avoidance of keeping and handling various excipients, and the synergetic effect of having homogenous free flowing directly compressible formulation of the required excipient. Co-processing of excipient cause them to interact at the subparticle level and lead to superior properties than simple physical mixtures of their components[1,2], Produce pharmaceuticals excipient with improved compressibility, such as lactose, to improve flow properties, to prepare free-flowing granules for tablet production, to improve the drug aqueous solubility and, consequently, their bioavailability. In addition, a number of formulation processes can be accomplished in one step in a spray dryer; these include complex formation and micro encapsulation. The fact that spray drying greatly reduces the labour-intensive formulation, drying and granulating of solid-dose pharmaceuticals gives cause to review the potential for this process in numerous instances. The pharmaceutical industry, however, is coming under ever-increasing pressure to reduce manufacturing cost, while still maintaining strict purity standards and highest level of quality control[3, 4, 5]**.**

In the present study an attempt was made to develop co-processed excipient containing Lactose and Microcrystalline cellulose using spray drying technique. An Experimental Box-behnken design was applied to optimise processing parameters of spray dryer[6]**.**

MATERIALS

Microcrystalline Cellulose was obtained from Blue Cross Lab. Ltd., Nasik and Lactose was obtained from Loba chemie, Mumbai. Labultima LU 222 Lab spray dryer was used for spray drying process.

METHODS

Selection of feed suspension for optimization of spray drying parameters

Aqueous dispersion C1-C9 (table-1) of lactose and microcrystalline cellulose were prepared in distilled water with 10 % w/w solid content. The feed suspension was spray dried according to the process condition shown in table-2.

Evaluation of co-processed excipients[7, 8]

Percentage compressibility or Carr's index

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

$$Carr's\ index\ (\%) = \frac{tapped\ \ density - poured\ \ density}{tapped\ \ density}\ x\ 100$$

Hausner's ratio

Hausner's ratio was calculated using the formula,

$$Hausner's\ ratio = \frac{tapped\ \ density}{poured\ \ density}$$

Angle of repose

Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula,

$$\tan\theta = \frac{2h}{D}$$

Where, h and D are height and diameter of the pile respectively.

Moisture content

Moisture content was determined at 0% relative humidity created with calcium carbonate in desicator. The sample was kept in desicator and observed the weight loss, percent moisture content was calculated using following formula;

$$\text{Percent moisture content} = \frac{\text{Initial weight-final weight}}{\text{Final weight}} \times 100$$

Percent spray dried yield

Percent spray dried yield was determined by using following formula;

$$\%\ \text{Spray dried yield} = \frac{W2}{W1} \times 100$$

Where,

W2= weight of sample after spray drying

W1=weight of sample before spray drying

Scanning Electron Microscopy Study[9, 10]

To study the surface morphology of the spray dried product using SEM. The spray dried products were coated under argon atmosphere with gold/palladium and examined under scanning electron microscope.

Differential Scanning Calorimetry (DSC)[9, 10]

Thermal behaviour of drug and polymers were studied by differential scanning Calorimetry. Accurately weighed samples 5 mg were hermetically sealed in flat bottom aluminium Standard 40 µl pan and heated from 50 to 300^{0}C at a rate of 10^{0}C/min. under an atmosphere of nitrogen. Melting endotherms of drug, polymer and optimized formulation were determined in the same way. Thermograms were normalized and rescaled as needed before overlapping. An empty aluminium pan was used as reference.

Experimental design

An experimental design was applied in the present research work. The experimental trials were taken for all 17 combinations. The inlet temperature, atomization pressure and feed rate were selected as independent variables at two levels. The % spray dried yield (Y1), % moisture content (Y2) and percent compressibility (Y3) were selected as dependent variables[6].

Levels selection of parameters of spray dryer

The level of independent factors was selected on the basis of preliminary trials.

Dependent factors (response)

- Y1:percent spray dried yield
- Y2:percent moisture content
- Y3:compressibility index

The details of levels of independent factors and the actual design as shown in table-3 and table- 4.

Searches for Optimum Processing Parameters[6]

The optimization of the processing parameters of spray dryer was done on the basis of the results obtained in the above parameters and required % spray dried yield, moisture content and compressibility.

Validation of Optimum Formulations

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the spray dryer. The process was optimized for the dependent (response) variables Y1, Y2 and Y3. The optimum batch was selected based on the criteria of attaining the maximum value of percent spray dried yield, minimum value of percent moisture content and minimum compressibility index[6].

RESULT AND DISCUSSION

Evaluation of spray dried co-processed excipients stage-1 (C1-C9)

The prepared co-processed excipient evaluated for compressibility index, moisture content, angle of repose, Hausner ratio and percentage yield (Table-5).The bulk and tapped density were determined on three batches for each formulation, the highest densities 0.5984 and 0.7335 gm/cc respectively being obtained with formulation C8. Higher the percentage spray dried yield obtained from the trial C8 this means less deposition of product inside the drying chamber.

The high Hausner ratio, which measures the interparticulate friction, indicating greater cohesion between particles. High Carr's index reveals a tendency of powders to form bridges. These results suggest that the spray dried co-processed excipient obtained from trial C8 to have good flow property this is due to large particle size and less interparticulate cohesiveness. It was also found that the co-processed excipient (C1-C4) has poor flow property, low spray dried percentage yield and more moisture content therefore these co-excipient was not suitable for direct compression method.

The preliminary trials were conducted using 10 % w/v solid content feed suspension of different ratio of lactose and microcrystalline cellulose and spray dried according to set processing parameters of spray dryer. The results of evaluation of co-processed excipient suggest that the co-excipient has good compressibility, less moisture content and good spray dried yield; however trial P5 shows comparable

good results this is due to same proportion of lactose and MCC. Moreover from the preliminary study it was found that the inlet temperature of spray dryer may affect on moisture content of co-excipient therefore this factor is also decided for experimental design in further study.

Optimization data analysis

The general form of the MLRA model is represented in the Equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

Where Y is the dependent variable; b_0 is the arithmetic average of all the quantitative outcomes of 17 runs. b_1, b_2, b_{12} are the estimated coefficients computed from the observed experimental response values of Y and X_1 and X_2 are the coded levels of the independent variables. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity the actual design layout given in table- 6.

Full and Reduced Model assessment for the dependent variables

The ranges of responses Y_1, Y2 and Y3 were 13.18-34.23, 1.13-2.98 and 13.95-34.23 respectively. All the responses were fitted to various models using Design- Expert software. It was observed that the best-fitted models were quadratic. The values of R^2, adjusted R^2, predicted R^2, SD and %CV are given in table-7, along with the regression equation generated for each response.

Full Model for Y1 (% yield)

Full model equation:

$$\%yield = +13.92 + 7.33*X1 - 0.75*X2 + 2.17*X3 - 1.36*X1*X2 - 0.33*X1*X3 - 0.89*X2*X3 + 8.28*X1^2 + 1.96*X2^2 + 2.34*X3^2$$

It was observed that the independent variable viz. X1(inlet temperature), X3 (feed rate) had a positive effect on percentage spray dried yield, but X2 (atomization pressure) had negative effect. The interactive terms of all the factors shows negative effect of spray dried yield. The quadratic terms of all the factors shows the positive effect on the spray dried yield. (Table-8)

In the table p values for response Y1 (spray dried yield) represent that the quadratic contribution, (X1) and (X3) is significant model term and the quadratic contribution (X2) is no significant model term. From the figure of the response curve of Y1 , it is observed that as the inlet temperature and feed rate of the system increases from -1(80°c)level, 0(100°c) ,+1(120°c) and -1(5 rpm),0(7.5 rpm),+1(10 rpm) respectively the spray dried yield increases significantly on the other hand the atomization pressure increases from level -1(2), 0(3) and +1(4) the spray dried yield decreases significantly as shown in fig-1.

Full Model for Y2 (% moisture content):

Full model equation

$$\%\ moisture\ content = +2.28 - 0.53*X1 + 0.12*X2 + 0.24*X3 - 0.043*X1*X2 + 0.22*X1*X3 + 0.092*X2*X3 - 0.21*X1^2 - 0.24*X2^2 + 0.20*X3^2$$

It was observed that the independent variable viz. X2(atomization pressure) and X3 (feed rate) had a positive effect on percentage moisture content, but X1(inlet temperature) had negative effect. The interactive terms of X1X2 shows negative effect on moisture content and the interactive term of X1X3 and X2X3 shows positive effect on moisture content the quadratic terms of X3 factors shows the positive effect on the moisture content and X1 and X2 shows negative effect on moisture content. The

Model F-value of 11.89 implies the model is significant. There is only a 0.18% chance that a "Model F-Value" this large could occur due to noise (Table-9). In the table p values Y2 (percent moisture content) represent that quadratic contribution, (X1) and (X3) is significant model term and the quadratic contribution (X2) is no significant model term. From the figure of the response curve of Y2, it is observed that as the atomization pressure and feed rate of the system increases from -1(2) level, 0(3), +1(4) and -1(5), 0(7.5), +1(10) respectively the moisture content increases significantly on the other hand the inlet temperature increases from -1(80), 0(100) and +1(120) the moisture content decreases significantly as shown in fig-1.

Full Model for Y3 (% Carr's index)

Full model equation

Carr's index = +30.67-0.86*X1+8.14*X2+2.23*X3-0.098*X1*X2-2.77*X1*X3+1.69*X2*X3-3.45*$X1^2$-3.03*$X2^2$-6.26*$X3^2$

It was observed that the independent variable viz. X2(atomization pressure) and X3 (feed rate) had a positive effect on percentage Carr's index, but X1(inlet temperature) had negative effect. The interactive terms of X1X2 and X1X3 shows negative effect on percent Carr's index and the interactive term X2X3 shows positive effect on percent Carr's index, all the quadratic terms factors shows the negative effect on the percent Carr's index (table-10).

In the table p values Y3 (percent Carr's index) represent that quadratic contribution, (X2) and (X3) is significant model term and the quadratic contribution (X1) is no significant model term. From the figure of the response curve of Y3 , it is observed that as the atomization pressure and feed rate of the system increases from -1(2)level, 0(3) ,+1(4) and -1(5),0(7.5),+1(10) respectively the percent Carr's index increases significantly on the other hand the inlet temperature increases from -1(80), 0(100) and +1(120) percent Carr's index decreases significantly as shown in fig-1.

Searches for Optimum Processing Parameters

The optimized batch (O_1) was having the composition containing inlet temperature (120°C), atomization pressure (2 bar) and feed rate (5.01 rpm) which showed a good desired results. The optimized batch (O_1) was identified to provide desired values for % spray dried yield (33.19), % moisture content (1.058) and the compressibility index (11.27) ,the details of solution for optimized batch is given in table-11.

Validations of optimum formulations

The illustrates the comparison between the observed and predicted values of the responses Y1, Y2 and Y3 for the entire batch presented. It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental values, as prediction error was found to vary between 7.98% and 0.011%. For this reason it can be concluded that the equations describe adequately the influence of the selected independent variables on the responses under study. This indicates that the optimization technique was appropriate for optimizing the processing parameters of spray dryer. The linear correlation plots drawn between the predicted and experimental values for all the batches are shown in Figure, which demonstrated high values of R^2 (0.986,0.9386 and 0.9619). Thus, the low magnitudes of error as well as the values of R^2 in the present investigation prove the high prognostic ability of the optimization technique by factorial design as shown in fig-2.

Scanning Electron Microscopy Study (SEM)

SEM study showing surface features of the co-processed excipient **.**The trial number T16 was subjected for SEM study because of its comparatively high percent spray dried yield, good flow properties and less moisture content as shown in fig-3.

It's confirmed that the co-processed excipient prepared by spray drying method has spherical particle shape, smooth surface and less agglomeration

DSC analysis

DSC analysis of spray dried product T16 neither sharp endothermic nor exothermic peak was observed, suggesting that the complex of co-processed excipient is amorphous in nature. As shown in fig-4.

CONCLUSION

It was concluded that the spray drying method is suitable for the preparation of directly compressible co-processed excipient. This new technique will save the time and possible cost for the development of tablet dosage forms. This co-processed excipient will be useful to drug having low flow property and compressibility.

ACKNOWLEDGEMENT

I express my sincere thanks to SAIF, Kochin, Kerala, SSDJ College of Pharmacy for providing facilities for this work and MGV College of Pharmacy, Panchavati, Nasik for providing SEM analysis and DSC analysis for prepared formulation. Also I express my thanks to all my friends.

Table- 1: Composition of feed suspension for co-processed excipients (C1-C9)

Sr. No.	Excipient	Trial no.								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1	Lactose	-	10	5	4	6	6.5	7.5	8.5	9.5
2	Microcrystalline cellulose	10	-	5	6	4	3.5	2.5	1.5	0.5

All quantity in grams

Table-2: Process conditions of spray dryer during spray drying of preliminary trials

Sr. No.	Process parameters	Conditions
1	Inlet drying air temperature	120°c
2	Outlet drying air temperature	80°c
3	Feed rate	8 rpm
4	Atomisation pressure	2 bar
5	Aspiration speed	80 mmWC
6	Feed concentration (% solid content)	10%

Table-3: Translation of the coded levels in actual units

Coded level	Independent factors		
	Inlet temperature (°c) X1	**Atomization pressure (bar) X2**	**Feed rate (rpm) X3**
Lower level (-1)	80	2	5
High level (+1)	120	4	10

Table-4: Experimental design applied for optimizations of processing parameters of spray dryer using Box -behnken design:

Run	Factor 1 A-Inlet temperature (°C)	Factor 2 B-Atomization pressure (bar)	Factor 3 C-Feed rate (rpm)
1	100	3	7.5
2	120	3	10
3	100	4	5
4	100	3	7.5
5	120	4	7.5
6	100	4	10
7	100	3	7.5
8	100	2	5
9	80	3	5
10	80	4	7.5
11	80	3	10
12	80	2	7.5
13	100	3	7.5
14	100	2	10
15	120	2	7.5
16	100	3	7.5
17	120	3	5

Table-5: Evaluation of spray dried co-processed excipients stage-1 (C1-C9)

Trial No.	% yield	Bulk density (gm/cc)*	Tapped density (gm/cc) *	Carr's index (%)	Hausner ratio	Angle of repose (θ) *	Moisture Content (%) *
C1	09.45	0.4683 ±0.06	0.6534±0.08	28.32	1.39	31.89 ±0.06	3.45 ±0.19
C2	11.13	0.5674 ±0.12	0.7412±0.14	23.44	1.30	29.54 ±0.13	2.89 ±0.24
C3	16.34	0.3425 ±0.09	0.4998±0.21	21.47	1.25	23.56 ±0.89	2.23 ±0.19
C4	14.78	0.5647 ±0.63	0.7334±0.07	23.00	1.29	30.87 ±0.07	3.14 ±0.24
C5	24.88	0.4123 ±0.05	0.5127±0.07	19.58	1.24	21.89 ±0.04	1.42 ±0.08
C6	17.34	0.3456 ±0.18	0.4588±0.09	24.76	1.32	25.44 ±0.09	2.23 ±0.28
C7	21.34	0.4877 ±0.07	0.6301±0.06	22.59	1.29	22.56 ±0.78	2.01 ±0.07
C8	34.45	0.5984 ±0.04	0.7335±0.05	18.41	1.25	19.12 ±0.08	1.19 ±0.09
C9	26.89	0.5156 ±0.17	0.6477±0.18	20.39	1.26	24.89 ±0.14	1.89 ±0.19

*The values represent mean ± SD, n = 3.

Table-6*:* Layout of Actual Design

Run	Factor 1 X1-Inlet temp. (°C)	Factor 2 X2-Atomization pressure (bar)	Factor 3 X3-Feed rate (rpm)	Response 1 % yield Y1	Response 2 Moisture content (%) Y2	Response 3 Compressibility index (%) Y3
1	100	3	7.5	13.63	2.23	30.12
2	120	3	10	34.23	2.15	18.18
3	100	4	5	15.45	1.98	24.15
4	100	3	7.5	13.18	2.35	31.15
5	120	4	7.5	28.63	1.59	34.23
6	100	4	10	18.95	2.53	31.95
7	100	3	7.5	14.78	2.19	29.58
8	100	2	5	15.70	2.13	14.18
9	80	3	5	14.18	2.83	18.19
10	80	4	7.5	18.68	2.52	33.34
11	80	3	10	18.24	2.98	28.23
12	80	2	7.5	16.95	1.98	13.95
13	100	3	7.5	14.33	2.22	30.83
14	100	2	10	22.75	2.31	15.23
15	120	2	7.5	32.33	1.22	15.23
16	100	3	7.5	13.66	2.41	31.68
17	120	3	5	31.48	1.13	19.21

Table-7: Summary of results of regression analysis for responses Y1, Y2 and Y3

Models	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Response (Y_1) Quadratic	0.9860	0.9680	0.8032	1.30	6.55
Response (Y_2) Quadratic	0.9386	0.8597	0.1525	0.18	8.50
Response (Y3) Quadratic	0.9619	0.9128	0.4327	2.25	9.14

Table-8: Analysis of variance for response Y_1 (% spray dried yield).

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significance
Model	831.05	9	92.34	54.70	0.0001	S
X1-inlet temp.	429.54	1	429.54	254.46	0.0001	S
X2Atomization pressure	4.53	1	4.53	2.68	0.1454	NS
X3- feed rate	37.67	1	37.67	22.32	0.0021	S
Residual	11.82	7	1.69	-	-	-
Cor Total	842.87	16	-	-	-	-

*S indicates significant #NS indicates non-significant

Table-9*:* Analysis of variance for response Y1 (percent moisture content)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significance
Model	3.62	9	0.4	11.89	0.0018	S
X1-inlet temp.	2.23	1	2.23	65.86	<0.0001	S
X2-Atomization	0.12	1	0.12	3.55	0.1015	NS
X3- feed rate	0.45	1	0.45	13.35	0.0081	S
Residual	0.24	7	0.034	-	-	-
Cor Total	3.85	16	-	-	-	-

*S indicates significant #NS indicates non-significant

Table-10: Analysis of variance for response Y3 (percent Carr's index)

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	Significance
Model	896.94	9	99.66	19.62	0.0004	S
X1-inlet temp.	5.88	1	5.88	1.16	0.3176	NS
X2-Atomization	529.43	1	529.43	104.21	<0.0001	S
X3- feed rate	39.87	1	39.87	7.85	0.0265	S
Residual	35.56	7	5.08	-	-	-
Cor Total	932.50	16	-	-	-	-

*S indicates significant #NS indicates non-significant

Table-11: Details of Solution for optimized batch and evaluation of optimized batch

Sr. No.	Parameters	Solution for optimized batch	Optimized batch O1
1	Inlet temperature	120 ºc	120º c
2	Atomization pressure	2 bar	2 bar
3	Feed rate	5.01 rpm	5.01 rpm
4	% spray dried yield	33.19	32.89
5	% moisture content	1.058	1.049
6	Carr's index	11.27	12.01
7	Desirability	0.983	-

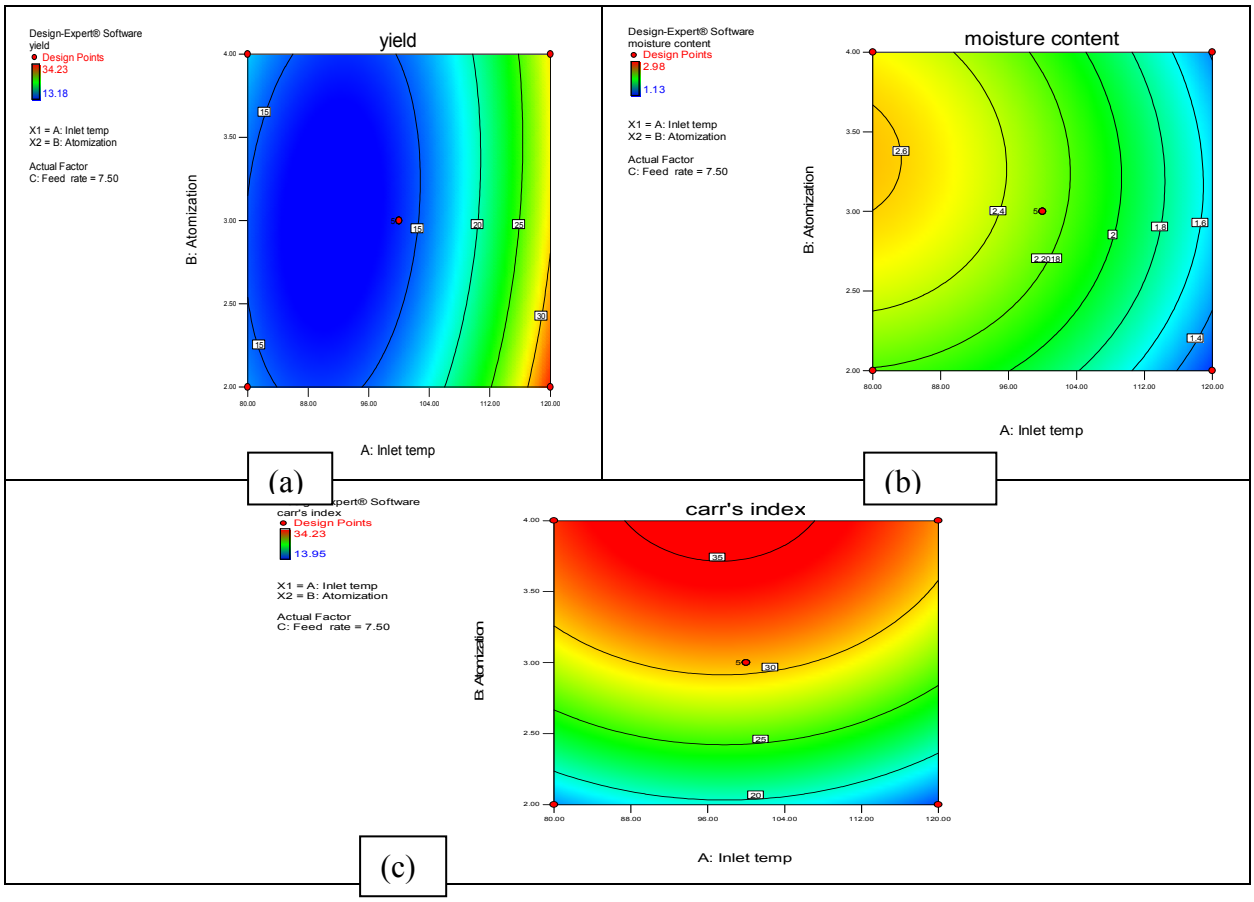

Fig.1: Contour plot for a-Y1, b-Y2 and c-Y3.

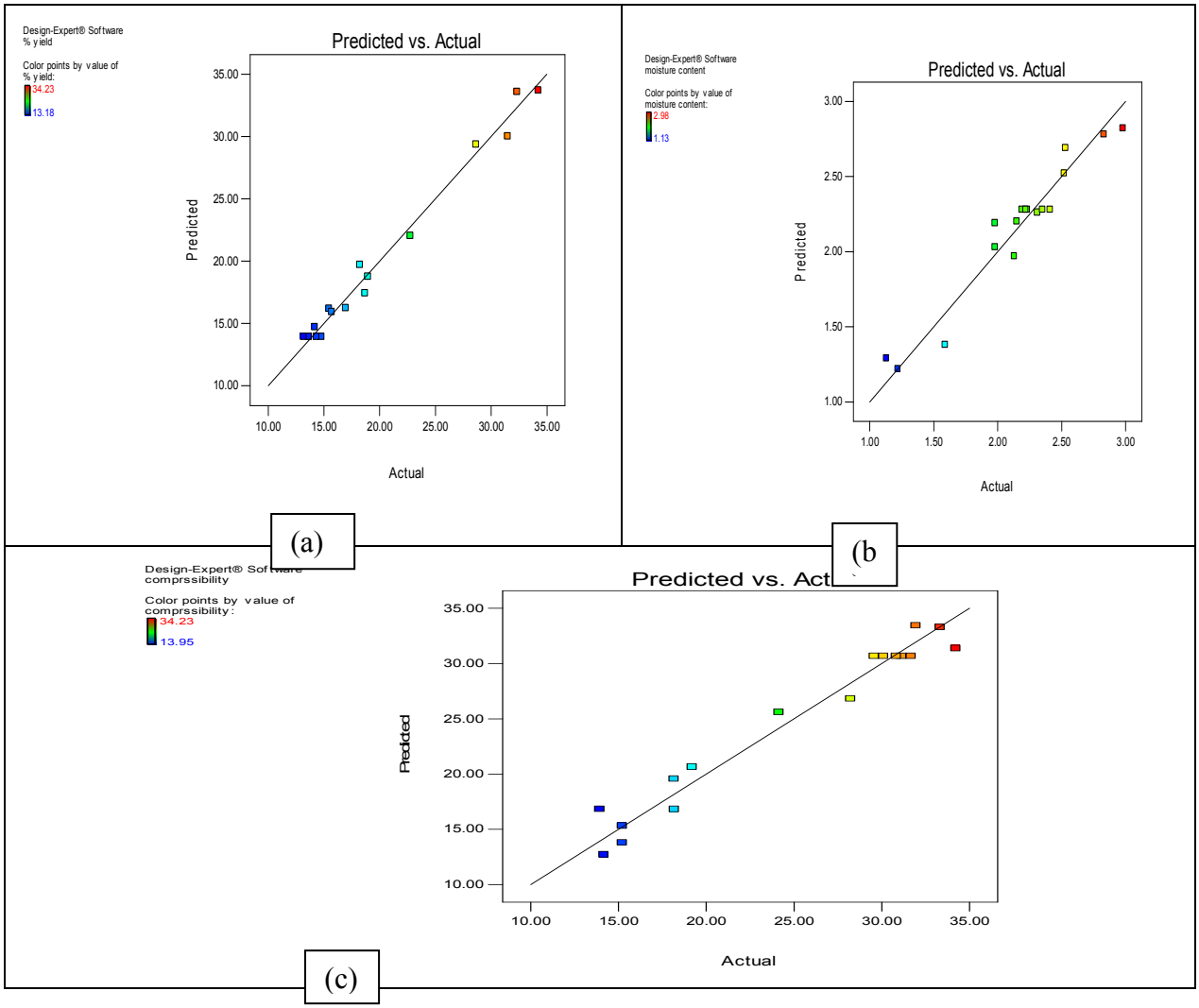

Fig. 2: Comparison between observed and predicted value of response a-Y1, b-Y2, c-Y3.

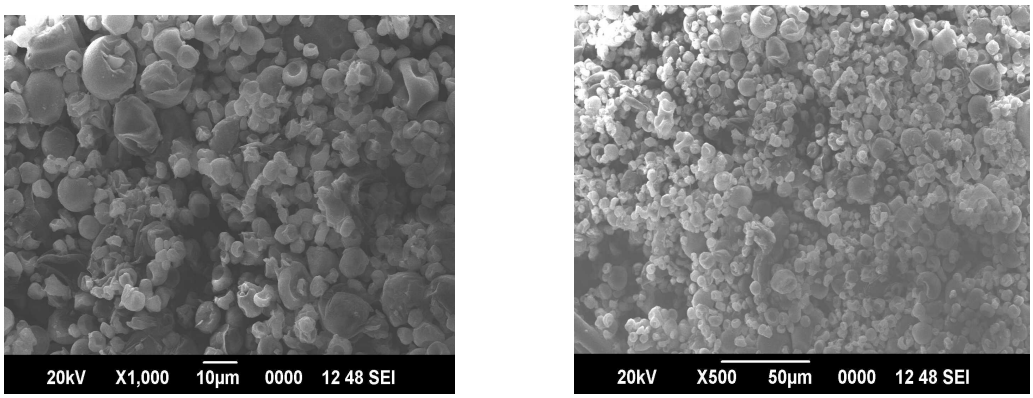

Fig.3: SEM image of optimized batch T16 co-excipient.

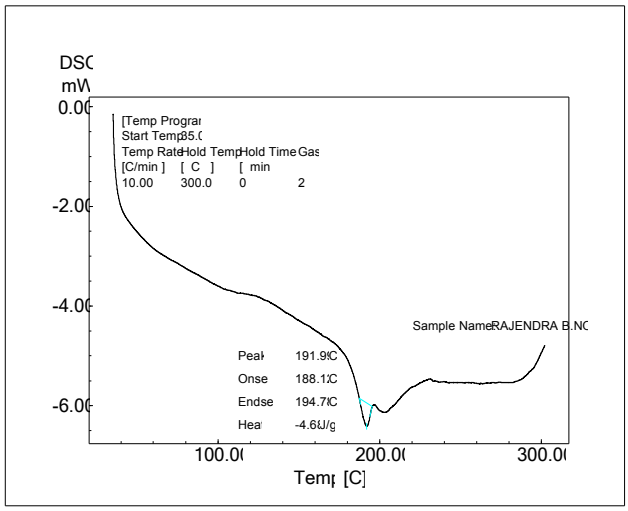

Fig.4: DSC curve for optimized formula

REFERENCES

1. Sumit Saha, Aliasgar F Shahiwala. Multifunctional co-processed excipients for improved tabletting performance' Expert opin. Drug delivery, 2009, 6(2):197-208.
2. Bolhuis, GK, and Chowhan ZT, Materials for direct compression, pharmaceutical powder compaction technology, vol-7, Marcel Dekker, USA, 1996, 419-499.
3. Gohel MC, Jogani PD. An investigation of the direct compression characteristics of co-processed lactose microcrystalline cellulose using statistical design, Pharm.Technol, 1999, 54-62.
4. Gohel MC. A review of co-processed directly compressible excipients, J. Pharm.Pharmaceutics. Sci., 2005, 8(1): 76-93.
5. Gohel MC. A review of co-processed directly compressible excipients' , J.pharm.Pharmaceut.Sci., 2005,8 (1):76-93.
6. Bolton S, Bon C. In: Pharmaceutical Statistics; Practical and Clinical Application. Vol. 80. 4th edition. New York, Basel and Hong Kong, Marcel Dekker, Inc., 2004, 265-288, 506-537.
7. Lachman L, Liberman HA, Kanig JL, Eds, Philadelphia. Preformulation, In: Theory and practice of industrial pharmacy; 3rd Ed. Lea and Febiger, 1986, 171-195.
8. USP 31/NF26.The United States Pharmacopoeial Convention, Rockville, MD, 2008, 231, 268-269.
9. Gonnissen Y, Remon JP, Vernaet C. Development of directly compressible powders via co-spray drying, Eua. J. Pharm. Biopharm., 2007, 67, 220-226.
10. Gonnisen Y, E.verhoeven, E.peeters. Co-processing via spray drying as a formulation platform to improve the compactability of various drugs Eur.J.Pharm. Biopharm., 2008, 69: 320-334.

***Corresponding Author**: *Mr.Rajendra K.Surawase,*
Lecturer,
Loknete Dr. J.D. Pawar College of Pharmacy,
Manur, Kalwan, Nasik-423501
Email ID: rajendra.surawase@gmail.com