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Optimization of Various Process Parameters for Formulation of Hypolipidemic Agent by Using Fluid Bed Technology

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ABSTRACT

The fluidized granulation process is a complex process, influenced by several process variables. In the present study, active factors related to fluid-bed granulation of ezetimibe was identified and studied. In the present study, various process parameters affecting product were studied. During the formulation of tablet, granulation, drying, blending and compression steps were involved. During each processes there are several factors which may affect product quality. So the main objective of present work was to identify various parameters and optimize the parameter for formulation of better product. Each batch was taken for each parameter by taking higher, optimum and lower range of value and each process was studied and evaluated for particular property. Granules were evaluated for blend uniformity analysis and moisture content while tablets were evaluated for average weight, disintegration time and in-vitro dissolution study.

Keywords: Fluid bed granulation, Povidone, Agglomeration, Blend uniformity analysis

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INTRODUCTION

The fluid-bed method of wet granulation is well known in the pharmaceutical and other industries as a one-step, enclosed operation. Because several ingredients can be mixed, granulated, and dried in the same vessel, the technique reduces material handling and shortens process times compared with other wet granulation processes. In addition to granulation for tableting, the fluid-bed top-spray method produces highly dispersible granules with a characteristic porous structure that enhances wettability. Fluidized bed granulation drying has established itself as a thermal treatment process for granular solids because of the intense mass and heat transfer ratios and because of the connecting of the process stages of drying, shaping and homogenization and also grading in the case of a continuous mode of operation [1, 6, 14]. Initially liquid products, such as solid solutions, solid suspensions or solid melts are converted into free-flowing, low-dust, granular solids. The liquid to be granulated is usually sprayed with a jet into a fluidized bed composed of solid particles, whereby a portion of the liquid forms a precipitate on the particles [8, 9]. The spraying in can occur in the fluidized bed from the top down, from the bottom up or sideways with a jet submerged in a chosen position. The solvent evaporates in the hot, unsaturated fluidizing gas and the remaining solid matter grows in layers on the particle surface (granulation or layered growth). Growth through agglomeration of the fluidized bed particles with each other also occurs, if, after the drying of liquid bridges, solid bridges arise. This is accomplished through the deliberate addition of a soluble binder [1, 2]. The rate of granule growth by agglomeration is proportional to the collision frequency between the particles present in the granulator, and the fraction of collisions that are successful, i.e. the fraction of collisions that lead to coalesce rather than rebound [5, 7]. In the present study, each processes parameters were studied and evaluated for different properties. The optimized parameters were identified and applied for formulation of ezetimibe tablet.

MATERIALS AND METHODS

Materials

Ezetimibe(Lupin Ltd.), Sodium Lauryl Sulphate(Merck), Povidone(S.D. Fine chemicals), Lactose Monohydrate(DMV Fonterra), Magnesium Stearate (Laser Chemicals) were used in the present study.

Methods

Calibration curve of drug

Preparation of 0.45% SLS in 0.05M acetate buffer pH 4.5

Dissolve 68 gram of sodium acetate trihydrate in 9 litres of purified water and adjust pH with glacial acetic acid and make volume up to 10 litres with purified water and mix, add 45g of SLS and dissolve it.

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Standard preparation

Transfer accurately weighed quantity of about 40 mg of drug working standard to 100ml volumetric flask. Add about 70ml of acetonitrile and sonicate to dissolve. Make volume up to mark with acetonitrile and mix. Dilute 5 ml of this solution with dissolution medium and mix. Absorbance value is shown in table no.1. Calibration curve is shown in fig.1.

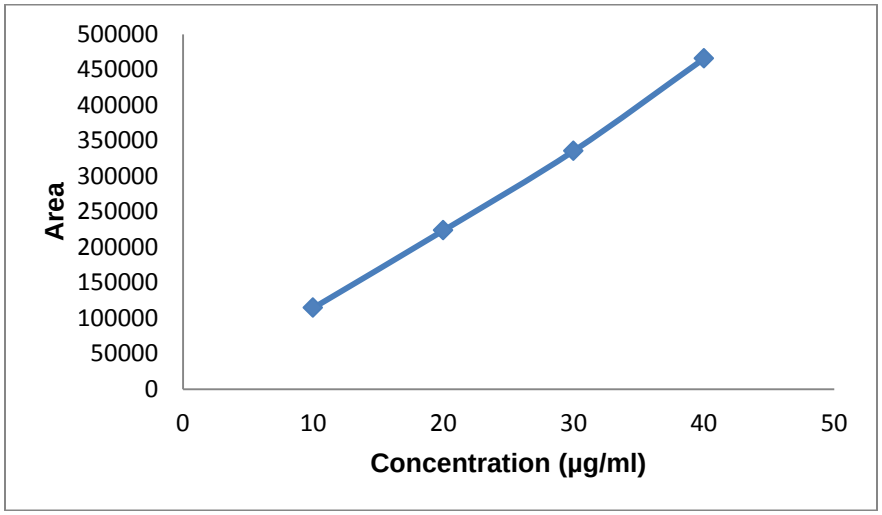

Fig.1: Calibration curve of drug

Table No.1: Calibration curve value for drug

Concentration (µg/ml)	Area
10	114421
20	223579
30	335642
40	465631

Procedure for formulation of ezetimibe tablet

Weigh accurately all the ingredients as shown in table no.2. Sift Lactose monohydrate, Sodium Lauryl sulphate and Drug through 40 mesh sieve. Transfer the sifted materials in FBP bowl. Add Povidone into the sufficient quantity of purified water with continuous stirring. Spray the binder solution through 1.0 mm nozzle on to the material retained in FBP bowl. Continuously observe the process parameters and record it at regular interval. Dry the granules at 60°C till moisture contents come below 2%. Sift the dried granules through 30 mesh sieve. Add Magnesium stearate (40#passed) in sifted granules and mix it properly in a polybag [10, 11]. Compress the blend on rotary compression machine containing 8.0×4.0mm 'D' tooling punches. Various process parameters studied are depicted in table no.3.

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Table No.2: Composition of Ezetimibe tablet

Sr. No.	Ingredients	Quantity (mg/tablet)
1	Ezetimibe	10
2	Lactose Monohydrate	81.75
3	Sodium Lauryl Sulphate	2.25
4	Povidone	5.0
5	Magnesium Stearate	1.0
6	Total Weight (mg)	100

Table No. 3: Various Process and Parameters to be studied

Process	Parameters
Granulation	Inlet air temperature Product temperature Spray pump RPM Spray rate Atomization air pressure
Blending Compression	Lubrication time Hardness Machine Speed

Granulation process parameters

Fluid bed granulation was carried out for formulation of ezetimibe tablet. Different batches were carried out at various granulation process parameters as shown in table no.4. Granules of these different batches were evaluated physically and notice the results.

Table No.4: Granulation process parameters for various batches

Sr. No.	In process parameters	T1	T2	T3	T4	T5	T6	T7	T8	T9
1	Inlet air temperature*	45	75	50	50	50	50	50	50	50
2	Product temperature	40	70	45	45	45	45	45	45	45
3	Exhaust temperature	40	40	40	40	40	40	40	40	40
4	Flap (%)	15	15	15	5	25	15	15	15	15
5	Inlet RH	10	10	10	10	10	10	10	10	10
6	Spray pump RPM	5	5	5	5	5	2	8	5	5
7	Spray rate (gm/minute)	5	5	5	5	5	2	8	5	5
8	Atomization air pressure(Kg/Cm^2)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.6	1.4

*: All temperatures are in °C

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Drying process parameter

Granules prepared were dried at different temperature for same period of time and then granules were evaluated for moisture content. Different batches were carried out at different temperature shown in table no.5.

Table No.5: Drying Process Parameter

Batch No.	T10	T11	T12
Drying Temperature	45	60	75
Drying time (minutes)	30	30	30
Machine	FBD*	FBD	FBD

*: Fluid Bed Dryer

Blending process parameters

For lubrication of dried granules, blending is necessary. For that purpose it is necessary to optimize blending time in blender. Because higher and lower blending time may affect tablet properties. Blending process parameters for lubricated blend is shown in table no.6. After various lubrication times, each batch blend is evaluated for blend uniformity analysis.

Table No.6: Blending process parameters for lubricated blend

Batch No.	T13	T14	T15
Machine RPM	18	18	18
Blending time (minutes)	1	3	5

Compression process parameters

During compression of the tablet, hardness and machine speed should be optimized. Compression parameters are shown in table no.7 for different batches. Tablets of these batches were evaluated for Thickness, Weight variation, Friability, Disintegration time and dissolution study.

Table No.7: Compression parameters

Batch No.	T16	T17	T18	T19	T20
Hardness	4.0-5.0	4.0-5.0	4.0-5.0	2.0-3.0	6.0-7.0
Machine RPM	15	35	25	25	25

Evaluation parameters

Evaluation of granules

Blend uniformity analysis (%)

Weigh accurately 100mg of blend and transfer it into 100ml volumetric flask. Add 70ml of diluent (Mixture of Water and Acetonitrile in ratio of 40:60). Shake the flask for 15 minutes. Make up the volume upto the mark with diluent. Filter the solution through 0.45µm Millipore filter [3, 4]. Inject the sample and record the chromatogram and measure the response of analyte peak. Blend uniformity analysis was carried out for the T8, T9 and T10 batches granules.

Table No.8: Blend uniformity analysis data for T13, T14 and T15.

Sr. No.	T13	T14	T15
1	97.7	102.6	101.2
2	109.1	101.9	102.0
3	102.0	102.4	101.7
4	102.5	103.4	102.4
5	102.3	100.7	102.0
6	99.54	101.8	104.5
7	103.2	101.0	102.9
8	103.8	102.5	99.7
9	101.7	101.7	103.4
10	98.9	102.2	104.4
Average	102.1	102.0	102.4

Moisture content (%LOD)

Moisture content of dried granules were determined by using Halogen Moisture Analyser (Mettler Toledo) and recorded.

Evaluation of tablet [12, 13]

Hardness

The hardness of the tablets was tested for 10 tablets by pharma hardness tester (Pharma Test, Germany) and average hardness was being taken and compared with that of standard one.

Friability

Friability test was performed in accordance with USP (Electroleb friabilator, Mumbai) 5 tablets were selected randomly, their individual weight was taken and then kept in the friabilator and rotated for 4 min at a speed of 25 rpm the tablets were taken out and any loose

dust from them was removed, the weight was registered and friability was calculated as a percentage weight loss.

Disintegration time

The disintegration of the tablets was tested in a disintegration tester (Pharma Test, Germany), six tablets were put in to a basket that was raised and lowered in a beaker containing preheated water at 37°C. The disintegration test was calculated as the mean value and as the range.

In-vitro dissolution studies

The release rate of tablets (n=6) were determined according to U.S. Pharmacopoeia using the Dissolution Testing Apparatus 2 (Electrolab, India) fitted with paddles. The dissolution test was performed using 900 ml of 0.45% SLS, 0.05M Acetate buffer, pH4.5, 900ml, 37±0.5°C and 50 rpm. A 5 ml sample was withdrawn from the dissolution apparatus at predetermine time interval, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µm membrane filter and diluted to a suitable concentration with dissolution medium. Area of this solution was measured by using HPLC (Shimadzu).

RESULTS AND DISCUSSION:

Granulation process

As shown in batch no.T1 and T2, there was no any effect of higher inlet temperature on granules but at lower inlet temperature, time required for the drying of granules was greater. Due to continuous spray of granulating solution from nozzle, after some period of time there was generation of wet mass in bowl due to improper drying and less inlet temperature. So we cannot run instrument continuously at lower inlet air temperature. In batch no. T4, the granules were not lifted up sufficiently because of lower flap. Due to this fluidization was not done properly and ultimately decreased granulation efficiency. For the batch T5, there was too higher flap, due to this granules forcefully strike below the upper side of container cloth and stick there. So the flap of 15% was optimized which show proper fluidization. In the case of batch T6, there was spray dried droplets found. This was due to lower spray rate of the coating solution. Lower spray rate cause decrease the solution to air volume ratio in the two fluid atomizers. Volume and force of the air remain same but decrease in solution volume. Hence finer droplets created. At the same drying rate finer droplets cause spray drying of atomized droplets result. In the case of batch T7, there was increased spray rate cause from 5 gm/min to 8 gm/min. The time required was less. So this set of parameter was superior. When spray rate of 10gm/min was tried, than there was a formation of wet lumps in FBP bowl. So spray rate should not be excess that make a wet lumps. In the case of batch T8, at this pressure droplet size of granulating solution atomized from the nozzle was larger. Non uniform distribution of granulating solution was seen. There was excessive wetting of granules and granules could not lift properly. Nozzle chock up was due to wet quenching. In the case of batch T9, there was

spray drying of atomized droplets due to fine droplets. Atomization air pressure of 1.0(Kg/Cm^2) was found to be satisfactory and show proper atomization.

Drying Process

In batch T10, drying temperature was less and due to this when moisture content was analysed, it was found to be 2.69% after 30 minutes of drying while in batch T11 and T12, it was found to be 1.55% and 1.27% after 30 minutes. Hence drying temperature should be optimum to reduce drying time.

Blending process

For batch no.T13, T14 and T15, blend uniformity data was shown in table no.8. From the results we can say that lubrication time for 1 minute shows minimum value and maximum value of 97.7 and 109.1, which depicts so much variation in blend uniformity. While 3 minutes lubrication time results show best results. Average value was found to be 102.0 for 3 minutes lubrication time. Five minutes lubrication time also show variation in ten sets and average value was found to be 102.4. So finally three minutes lubrication time was finalised.

Compression process

In batch no. T16, machine RPM was lower. As shown in table no.8, there was no effect on dissolution profile of tablet produced at lower machine speed. But when machine speed was higher, weight variation was seen due to improper die filling. So machine speed of 25 RPM was optimized. In batch T19, hardness was 2.0-3.0 kP due to this disintegration time was faster. Tablet may break easily during transport. In batch T20, higher hardness was there, due to this disintegration time get increased. Dissolution profiles of these batches are shown in table no.9. Physical evaluation of these batches tablets are shown in table no.10.

Table No.9: Dissolution profile of different batches

Time	T16	T17	T18	T19	T20
5	41.1	42.8	43.1	40.7	42.1
10	52.4	54.9	56.2	51.9	52.1
15	63.4	65.2	64.7	62.4	60.2
20	72.9	74.9	73.9	72.4	73.4
30	81.7	82.3	83.4	81.0	84.7
45	87.8	89.7	90.2	88.3	92.5
60	94.2	94.8	95.7	92.5	94.7

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Table No.10: Physical evaluation of tablets

Batch No.	Hardness (kP)	Average weight (mg)	Friability (%)	Disintegration Time (Seconds)
T16	4.2-4.9	100.5	0.09	175
T17	4.1-5.0	101.4	0.06	170
T18	4.3-4.8	100.5	0.04	170
T19	2.1-3.0	100.4	0.81	150
T20	6.1-7.0	101.1	Nil	210

CONCLUSION

Fluid bed granulation is a widely used granulation technique for poorly soluble drug having low dose. In FBP, there are so many factors which may affect final product. In this study all these parameters were identified and optimized. It is necessary to optimize process parameters to repeat the formulation. Drying temperature and lubrication time in blender was also optimized. During compression process, there was machine speed and hardness which may affect release profile of drug. These parameters were also optimized. Finally we can say that all the process parameters for formulation of ezetimibe by using FBP were optimized.

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