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Design and evaluation of terbutaline sulphate immediate release tablets prepared by fluidized bed granulation technology

Sayani Bhattacharyya [1], Mohan RB[2]
[1]Department of Pharmaceutics, Krupanidhi college of Pharmacy, Bangalore
[2] Department of Pharmaceutics Oxford college of Pharmacy, Hongasandra, Bangalore.
Corresponding author : sayanibh@gmail.com

Abstract

Objective: The aim of the present study was to develop immediate release tablets of terbutaline sulphate by using fluidized bed granulation technology intended for fast action in the treatment of asthma.

Materials and methods: The process of granulation by fluidized bed granulation technology was used to prepare eight formulations (F1-F8) using various concentrations of binders PVP K-30, PVP K-90 and disintegrants microcrystalline cellulose, sodium starch glycolate.The granules were evaluated for preformulation parameters like bulk density, tapped density, Carr's compressibility index, and hausner ratio, angle of repose, loss on drying, and sieve analysis. The compressed tablets were evaluated for post compression parameters like thickness, hardness, weight variation, friability, disintegration, drug content, content uniformity and dissolution. The stability studies were performed for a period of 3 months at 30ºC/75%RH & 40ºC/75%RH.

Results: All the formulations disintegrated in less than 10 mins and released drug more than 90% in 15 mins. Formulations F4 and F8 were found to be the best formulations and was found to be stable in the varied environmental conditions.

Conclusion: It can be concluded that immediate release tablet of terbutaline sulphate prepared by fluidized bed granulation technique can yield a fast release tablet.

Key words: Terbutaline sulphate, Asthma, Fluidized bed granulator,Immediate release tablet.

Intrduction

Asthma is a chronic disease affecting airways, results in breathlessness, tight chest, wheezing and coughing. It causes reversible obstruction of airwaysdue to constriction and inflammation (1,2,3). Terbutaline Sulphate is a FDA approved anti-asthma drug in the class of beta-adrenergics and used in acute treatment of bronchial asthma. Following an oral administration of Terbutaline sulphate, the onset of action starts within 30 minutes with a peak effect shown at 120 to 180 mins and last for 4 hrs or longer (4,5).

The Fluidized bed granulation technology is apotential one-step automated process in a closed system used in formulation development to improve therapeutic efficacy by improving the porosity and thereby dissolution of drug(6). The complete process of mixing, granulation and drying of several ingredients in a closed condition reduces the problem of material handling and shortens process time compared to other granulation processes. This enclosed process, reduces the exposure of the potent drug to the environment and complies with the cGMP (7). From

the formulation perspective, this process improves flow and compression characteristics of the powder materials, reduces segregation of varied density powder ingredients and thereby maintains content uniformity. In this technology powders are made to fluidize in a controlled air pressure inside the chamber. A binder solution or suspension is sprayed onto the fluidized particles toform agglomerates and subjected to drying at optimized conditions of temperature and air pressure.This method produces highly dispersible granules with a characteristic porous structure that enhances wettability, disintegration time and drug release of the final product. Particle size of the granules can be controlled by adjusting the quantity and droplet size of binder (8,9,10).Many articles for terbutaline sulphate first release tablets have been published by conventional granulation methods of preparation, so the present study focuses on terbutaline sulphate immediate release tablets by fluidized bed granulation technique.

Materials

Terbutaline Sulphate was obtained as a gift sample from AstraZeneca Pharma India Ltd, Bangalore, India. Rest of the ingredients used were of analytical grade.

Methods

Preparation of Binder Solution: A solvent mixture of isopropyl alcohol and purified water in 2:1 ratio was prepared and binder (PVP K30 / PVP K90) was added slowly to this mixture under continuous stirring at 100 to 200 rpm until a clear solution was obtained.

Granulation and compression: Eight different formulations of 185 mg of terbutaline immediate release tablets were prepared by varying the composition of PVP K30 / PVP K90.All the intra granular materials as mentioned in Table 1(Terbutaline sulphate, maize starch and lactosemonohydrate) were sifted through 20 mesh ASTM sieve and charged into fluidized bed processor (Pam Glatt, Germany) and dry mixed for 20 minutes. The binder solution was sprayed through spraying nozzle (top spray) as atomized liquid droplets. After complete addition of binder solution, spraying was stopped and drying was carried out till loss on drying (LOD) of granules was not more than 3.0%. LOD was checked at 60°C for 20 minutes by using infra red (IR) moisture analysing balance (Mettler Lj16, India). The critical process parameters for fluid bed granulations were maintained for all the formulationsas mentioned in the Table 2.

The dried granules were loaded in to the double cone blender (Kalweka, India). Extra granular materials like micro crystalline cellulose (MCC) or sodium starch glycolate (SSG) and Maize starch were sifted separately through 20 mesh sieveand were loaded in to the double cone Blender and mixed for 20 minutes. Magnesium Stearate was sifted through 60 mesh ASTM sieve and added to the above granules and lubricated for 4 minutes in the blender. The lubricated granules were compressed in B-tooling compression machine (Lab press, India).

Pre compression study of the granules

Loss on Drying (LOD) : Drying was carried out at set inlet temperature of 40ºC to 50ºC. Drying was continued till the product temperature reached to 45ºC. 10 g of sample was collected from sample with drawing port of FBP and LOD was recorded by using Mettler Toledo IR moisture analysing balance at 60°C for 20 minutes(11).

Particle size analysis : A sample of 10 g powder was placed on the top sieve. The nest of sieve was fixed to the mechanical shaker apparatus and shaken for a certain period of time (20min).The powder remaining on each sieve was weighed(12)

Bulk Density: It is the ratio of totalmass of powder to the bulk volume of powder and was measured by Bulk Density Apparatus, Campbell electronics, India.

Tapped density: The powders were tapped for 10,100 and 500 times in the bulk density apparatus, Campbell electronics, India. Tapped density is calculated as the ratio of total mass of powder to the tapped volume of powder.

Compressibility Index : It is the ratio of tapped density to the bulk density. It is given by

Hausner Ratio = Tapped density / Bulk density

Evaluation of Tablet (13,14)

Hardness

Hardness or diametric crushing strengthis a force required to break a tablet across the diameter. This is an indication of tablets strength to with stand the shock during handling, packaging, and shipping. The Hardness of the prepared batches of tablets were measured by Stokes- Monsanto tester.

Friability

Friability of the tablets was tested in Roche friabilator. 10 tablets were weighed initially and rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and reweighed. The % friability was calculated using theformula.

F=(Winitial-Wfinal) *100/Winitial

Where F=% friability

Winitial= Initial weight of 10 tablets

Wfinal= Final weight of 10 tablets

Thickness

Tablet thickness was measured by verniercalipers.

Weight Variation of tablets

20 tablets were selected at random. The average weight was determined. The individual tablet weight was compared with the average weight of the 20 tablets.

Table 1: Formulation tables for terbulatine sulphate tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Terbutaline Sulphate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose Monohydrate (% w/w)	61.95	60.95	60.40	56.65	61.95	60.95	60.45	60.95
Starch maize (% w/w)	30.00	30.00	30.00	33.20	30.00	30.00	30.00	30.00
PVP K-30 (% w/w)	1.00	2.00	2.50	2.70	-	-	-	1.00
PVP K-90 (% w/w)	0	0	0	0	1.00	2.00	2.50	1.00
MCC (% w/w)	5.00	5.00	5.00	5.40		-	0	2.50
SSG (% w/w)	0	0	0	0	5.00	5.00	5.00	2.50
Magnesium Stearate(% w/w)	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	185	185	185	185	185	185	185	185

Table 2: Process parameters for fluid bed granulation

Parameter	Granulation stage	Drying stage
Spray rate (ml/ min)	10.00±2.00	-
Atomization air (bar pressure)	1.50±0.50	-
Air blow speed (CFM)	45.00±5.00	65.00±5.00
Inlet temperature(^{0}C)	45.00±5.00	65.00±5.00
Product temperature(^{0}C)	30.00±5.00	45.00±5.00
Exhaust temperature(^{0}C)	25.00±5.00	55.00±5.00

Uniformity of Drug Content

Mobile Phase was prepared by dissolving 4.13 – 4.33 g of 1-Hexane sulphonic acid sodium salt in 750 ml of 50 M Ammonium formate solution and added to 250 ml of methanol followed by filtration through 0.45µm membrane filter.

Drug content was determined byion-pair chromatography on a stainless steel column of 250mm x 4.6 mm packed with octadecylsilyl silica gel bonded to porous silica 5 µ, as stationary phase in HPLC and detected at 276nm. 1-hexane sulphonic acid sodium salt in ammonium formate and methanol was used as mobile phase. Sample solution was prepared by dissolving 10 tablets in a volumetric flask with the mobile phase. Drug content was calculated and compared with the response factors for the reference standards using HPLC Agilent 1100 and 1200 series.Drug content was calculated from determining concentration of drug by the following formula

Concentration of drug in samples (µg/L) =(Vs xCs) /V

whereVs = spiked volume (ml),
Cs = spiked concentration (µg/ml),
V = Sample volume.

Disintegration test

The disintegration time of tablet was measured in water (37^0C) USP disintegration test apparatus. Three trials for each formulation were performed.

Dissolution

The dissolution rate was determined in simulated gastric fluid without enzymes at 37^0C, using the USP apparatus - I rotating basket method using 900ml simulated gastric fluid without enzyme of pH 1.2 to silumate linear kinetics of absorption of terbutaline sulphate. Temperature of the dissolution medium was maintained at $37^0 \pm 0.5^0$C. Samples were withdrawn after every 5 minutes and filtered through 0.45 m filters and injected into HPLC. The percentage drug release was calculated by using HPLC Agilent 1100 and 1200 series.

The % release was calculated using the formula to find the drug content in course of time

Stability studies

The most satisfactory formulations of terbutaline sulphate were subjected to stability study. The stability study were carried out at two different conditions 30±2°C/75±5%RH and 40±2°C/75±5%RHfor three months. The samples were withdrawn periodically after each month and studied for physical characteristics,drug content, disintegration time and *in vitro* drug release. The data so obtained was compared with the initial data of the tablets.

Results and Discussion

Terbutaline Sulfate is a FDA approved anti-asthma drug. With oral administration of Terbutaline sulphate, the onset of action takes place within 30 minutes. In this study an attempt has been made to formulate aimmediate release tablet of terbutaline sulphate using fluidized bed granulation technique to promote rapid onset of action.The tablets were prepared using lactose monohydrate as diluent,starch maize as filler to keep the tablet weight 185mg constant. Microcrystalline cellulose, sodium starch glycolate were used as disintegrants, PVP K30 and PVP K 90 as binder, in a 2:1 mixture ofisopropyl alcohol and purified water as vehicle. The spray rate was optimized between 8-12 ml/min, atomization air pressure at1-2 bar, air blower speed at 40-50CFM, inlet temperature at 40-50^0C and exhaust temperature at 30-40^0C.Drying was achieved at air blower speed of 60-90 CFM, inlet temperature at 60-80^0Candexhaust temperatureat 60-90^0C.

Evaluation of precompression parameters

The prepared granules were studied for pre compression analysis as shown in table 3. Moisture is an important factor in compaction of blended powders into tablets. Residual moisture has impact in the flow and compression property of the granules. Tensile strength is generally low at low moisture content. Therefore,

LOD of granules (in-process) is an indicator of process end point and in the present study it was found to be low. LOD of the granules was found to be minimum within the range of 1.56-2.53%.

The preformulation study conducted on granules evaluation for flow property showed hausner's ratio below 1.14 and carr'sindex below 18.3. The hausner ratio and carr's index below 1.25 and 25 respectivelyproved the good flow properties of the powders(15). Control of particle size is essential in achieving good flow properties and proper mixing of granules and powders in tablet manufacturing. Particle size can affect a wide range of properties such as the flowability, uniformity in content, the solubility and surface area properties of a tablet formulation. The granules prepared by the fluid bed granulation technique were found to be of uniform granule size in the range of 250 to 400µm (range of sieve no 40-60) and more porous with good flow properties. The sieve analysis showed the granules were moderately coarse and the maximum retention was in sieve no 40 as shown in Figure 1.

Evaluation of post compression parameters

Tablet thickness was relatively constant for all the formulations. Tablet weight had some variations these variations may be attributed to the differences in bulk density in the formulations. However, all formulations were in agreement with the pharmacopoeial requirements regarding the uniformity of weight as shown in (Table 4)which showed less possibility of variations associated with the tablet press or the method of preparation (16). The hardness varied from 4.1±0.06 to 5.1±0.09 Kg/cm^2. Percentage Friability of all batches ranged from 0.16-0.45 % (within the limit <1%) which indicated the strength of the tablets to withstand mechanical stress during manufacturing and handling.

All the formulations were subjected to disintegration and drug release study. It revealed that all the formulations took less than 10 mins to disintegrate and released more than 90 % of drug in 15 mins as shown in table 5 and figure 2 and 3. The improvement of dissolution may be attributed to the enhancement of porosity and wettability of the granules.

Thereby thefluidised granulation process improved the flow and compression characteristics, reduce segregation, improve content uniformity and thus produced highly dispersible granules with a characteristic porous structure that enhanced wettability, disintegration time and drug release of the final product.

Comparing the disintegration and dissolution study among eight formulation, F4 andF8 with maximum dissolution profile were taken for further stability studies.

Stability study of the optimized formulations

F4 and F8 weretakenfor stability studies at varied conditions *i.e.,*is 30±2°C/65±5%RH. and40±2°C/75±5%RH for 3 months. No significant changes were seen in morphology, friability, drug content,

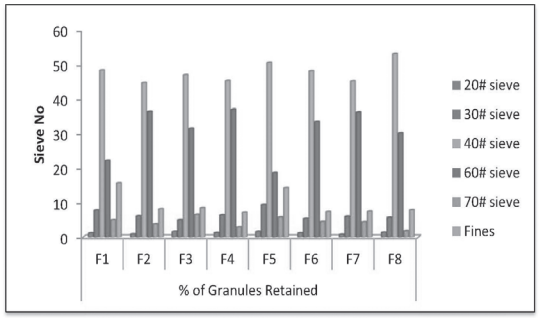

Figure 1: Sieve analysis of precompressed granules (F1-F8)

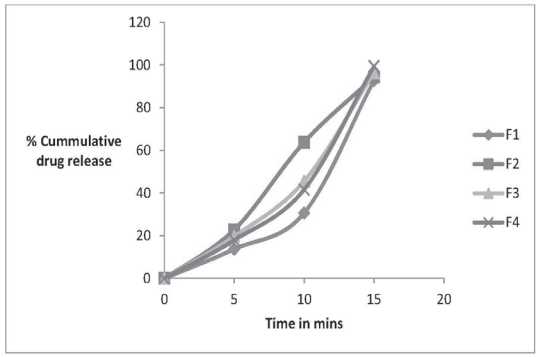

Figure 2: Drug release studies of formulations (F1-F4)

Table 3: Pre compression study

Formula	LOD	Bulk Density g/ml	Tapped Density g/ml	Carr's index	Hausner's ratio
F1	1. 56	0.59±0.01	0.67±0.01	12.16	1.13
F2	1.62	0.55±0.01	0.63±0.02	11.20	1.12
F3	1.73	0.55±0.01	0.61±0.01	9.80	1.10
F4	1.86	0.51±0.01	0.56±0.01	8.10	1.08
F5	2.20	0.54±0.01	0.65±0.01	16.90	1.20
F6	2.47	0.53±0.01	0.61±0.01	13.11	1.15
F7	2.53	0.50±0.01	0.60±0.01	16.60	1.20
F8	2.21	0.50±0.01	0.56±0.02	9.90	1.11

All values are mean ±Standard deviation (SD) and no of replicates (n)=3.

Table 4: Evaluation of terbulatine sulphate tablets

Formula	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Avg Weight (mg)	Drug Content (%)
F1	3.36±0.03	4.5±0.10	0.45±0.02	182.3±2.88	98.14±5.58
F2	3.33±0.07	4.2±0.06	0.30±0.06	183.82±3.06	98.01±5.16
F3	3.33±0.07	5.0±0.07	0.20±0.02	183.68±3.20	98.04±2.57
F4	3.35±0.02	4.1±0.10	0.26±0.02	184.54±3.00	99.59±2.28
F5	3.36±0.04	4.6±0.05	0.20±0.03	184.11±2.90	98.66±4.26
F6	3.34±0.06	5.1±0.09	0.19±0.05	184.24±2.77	100.82±3.92
F7	3.33±0.08	5.3±0.10	0.25±0.02	184.36±3.09	98.94±4.82
F8	3.21±0.05	4.5±0.05	0.16±0.03	182.8±2.96	99.05±2.94

All values are mean ±Standard deviation (SD) and no of replicates (n)=3.

Table 5: Disintegration and release study of terbulatine sulphate tablets

Formula	Disintegration (Min)	% Drug release at 15mins
F1	4.30±0.05	92.70±0.20
F2	3.35±0.09	94.40±0.50
F3	3.30±0.12	96.40±0.30
F4	3.25±0.10	99.40±0.30
F5	5.05±0.08	95.10±0.40
F6	7.50±0.11	95.60±0.30
F7	8.10±0.10	90.70±0.20
F8	4.40±0.07	97.00±0.40

All values are mean ±Standard deviation (SD) and no of replicates (n)=3.

Table 6: Stability study of formulations F4 and F8 at30±2°C/75±5%RH

Condition (30±2°C/75±5%RH)						
Formulations		**F4**			**F8**	
Time Period (month)	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Hardness (kg/cm^2)	4.2	4.2	4.2	4.5	4.5	4.7
Friability%	0.26	0.25	0.25	0.16	0.16	0.13
Disintegration time (min)	4.3	42.3	4.35	4.5	3.4	4.45
% Drug Content	99.2	99.4	99.6	98.2	98.1	97.4
% Drug Release at 15 min	99.5	99.1	99.4	97.6	97.1	96.3

Table 7: Stability study of formulations F4 and F8 at40±2°C/75±5%RH

Condition (40±2°C/75±5%RH)						
Formulations		**F4**			**F8**	
Time Period(months)	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Hardness (kg/cm^2)	4.2	4.2	4.2	4.5	4.5	4.7
Friability%	0.26	0.25	0.25	0.16	0.16	0.13
Disintegration time (min)	4.3	42.3	4.35	4.5	3.4	4.45
% Drug Content	99.2	99.4	99.6	98.2	98.1	97.4
% Drug Release at 15 min	99.5	99.1	99.4			

disintegration time, and % Drug release (Table 6, and 7) at the end of the study period. Hence, it was observed that the developed Terbutaline Sulphate tablets were stable and retained their potency after stability studies.

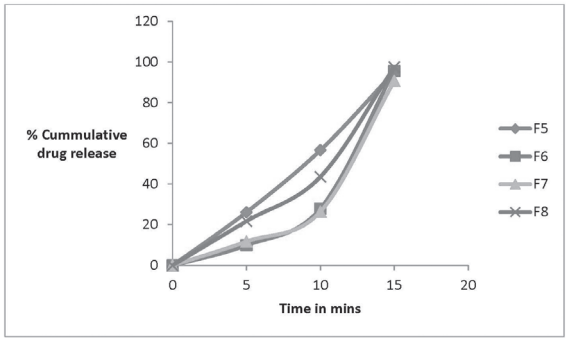

Figure 3: Drug release studies of formulations (F5-F8)

Conclusion

The granules prepared by the fluid bed granulation technique were found to have uniform granule size in the range of 250 to 400µm, and a porous nature with good flow properties. The tablets prepared from these granules were compressed without any chipping, capping and sticking. Formulated tablets had given satisfactorily result for various physico-chemical evaluations of tablets like tablet dimension, thickness, hardness, friability, weight variation, and drug content. Optimized formulations F4 and F8 revealed the stability of the formulations at varied temperature and humid conditions. So it can be concluded that an immediate release tablet of Terbutaline sulphate prepared by fluidized bed granulation technique can yield a fast release tablet compare to normal granulation technology.

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