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Research

Encountered granule flow in gemfibrozil tablet USP 600mg using novel technology

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Abstract

The aim of this study was to formulate solid dosage form of Gemfibrozil and the scope of the study to design of experiment for Gemfibrozil tablet using 600mg using Roll compaction method is to increase the flow of the blend which resolved the die filling problem during compression and useful for granule flow. Die fill problem is encountered in production batches if the flow of the blend is not optimum. The flow of the blend is related to the characteristics of granules..Gemfibrozil is a waxy, crystalline, hydrophobic material that results in prolongation of disintegration time during storage in stability studies. Because of the fluffy nature of API flow problem was also encountered. Product and process characteristics important to desired performance must be derived from combination of prior knowledge and experimental assessment during product development, which is required to achieve objectives of Quality by Design (QbD). From prior knowledge and experimental data, a multivariate model linking product and process measurements and desired attributes was constructed. Flow of Gemfibrozil blend was improved by addition of colloidal silicone dioxide, selecting microcrystalline cellulose of higher particle size and by producing granules of sufficient strength. Since the major portion of the tablet was Gemfibrozil, the role of particle characteristics was also investigated.

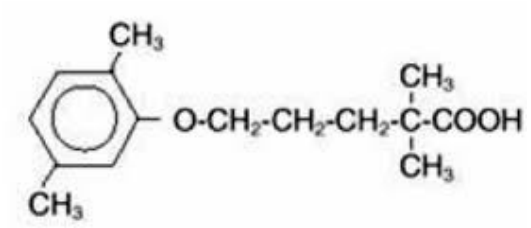
Keywords: Gemfibrozil, Granule flow, QbD, Hydrophobic material, Microcrystalline cellulose, roll compaction method

INTRODUCTION

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and very lowdensity lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol. While modest decreases in total

and low density lipoprotein (LDL) cholesterol may be observed with Gemfibrozil therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia often results in a rise in LDLcholesterol. LDL-cholesterol levels in Type IIb patients with elevations of both serumLDL-cholesterol and triglycerides are, in general, minimally affected by Gemfibrozil treatment; however, Gemfibrozil usually raises HDL-cholesterol significantly in this group. Gemfibrozil increases levels of high density lipoprotein (HDL) sub fractions HDL and HDL, as well as lipoproteins AI and AII. Epidemiological studies have shown thatboth low HDL-cholesterol and high LDL-cholesterol are independent risk factors for In the primary prevention component of the Helsinki Heart Study, in which 4081 male patients between the ages of 40 and 55 were studied in a randomized, double-blind, placebo-controlled fashion, gemfibrozil therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the gemfibrozil treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson types. The study involved subjects with serum non-HDL-cholesterol of over 200 mg/dL and no previous history of coronary heart disease. Over the five-year study period, the gemfibrozil group experienced a 1.4% absolute (34% relative) reduction in the rate of serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo, p=0.04 (see Table I). There was a 37% relative reduction in the rate of nonfatal myocardial infarction compared to placebo, equivalent to a treatment-related difference of 13.1 events per thousand persons. Deaths from any cause during the double-blind portion of the study totaled 44(2.2%) in the gemfibrozil randomization group and 43 (2.1%)in the placebo group.

Drug Profile: GEMFIBROZIL
Brand name: Lopid.



It is available as a brand-name drug and a generic drug. Gemfibrozil comes only in the form of a tablet you take by mouth.
Gemfibrozil is used to lower triglycerides, a type of fat in your bloodstream. Having very high levels of triglycerides raises your risk of pancreatitis (inflammation of the pancreas).
Empirical formula is C15 H22 O3
Molecular weight is 250.35

Therapeutic Category: Lipid Regulating agent
The; the solubility in water and acid is 0.0019% and in dilute base it is greater than 1%. T
The melting point is 58°–61° C. Gemfibrozil, USP is a white solid which is stable under ordinary conditions.
Granulation and compression Process:

Wet Granulation: This method commonly used if dose of drug is high along with poor flow property. This method also provides more uniform mixing so as to prevent blend uniformity related issues.

Dry Granulation: This method is used when the API used is heat and moisture sensitive. This method Improve tablet disintegration since it does not involve the use of water so it increases water-uptake ability of the disintegrates.

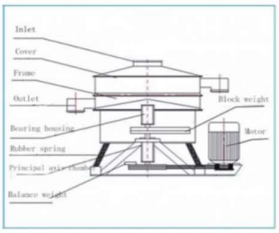
Direct Compression: This method involves fewest processing steps as compare to otherprocesses. It is also useful for moisture and heat sensitive APIs. API is having poor flow properties Hence wet granulation method was selected for further development.

Sr.No	Steps	Parameter
	Sifting	Milling speed Screen Size Mesh size
	Extra Granular Material	Mesh size
	Lubrication	Blend Speed

	Blend time
Roll compaction	Milling
	Screen
	Retention

MATERIALS AND METHODS

Vibrator sifter , Roll compactor, multimill, blender, compression, machine, metal detector, DE duster, stirrer, coating machine, blanace hardness tester, friability tester, DT apparatus



Mesh Used for sifter

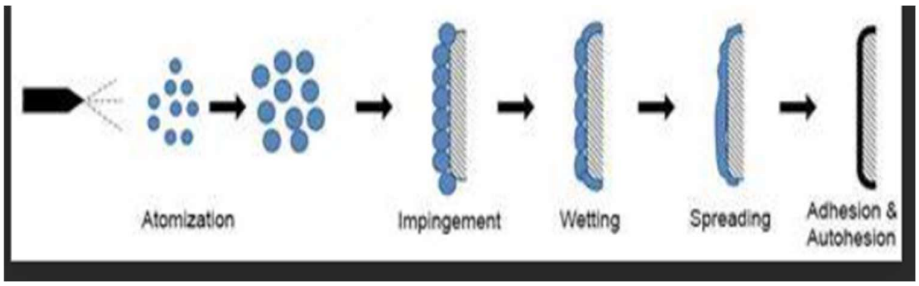
Roll compactor: Roller Compactors are used to force fine powders between two counter rotating rolls and presses the raw materials into a solid compact (flakes, sheets, strips). Roll Compacters are also called dry granulators.

Blender: The blender works on the principle of centrifugal forces principle in which the different shape vessels containing bulk drug granules revolve at some specific speed of constant RPM. And the process is called the blending of the granules.

Compression: Compress the lubricated granules in compression area using 51 station double rotary compression machine equipped.

Punch and dies: The basic principle behind the tablet compression machine is hydraulic pressure. This pressure is transmitted unreduced through the static fluid. Any externally applied pressure is transmitted via static fluid to all the directions in the same proportion. ... The tablet compression procedure that is used in different pharmaceutical companies is divided into four distinct stages. These are named as filling, metering, compression and ejection

Coating Machine: Coating the tablets



Tablet coating is the process where coating material is applied to the surface of the tablet to achieve the desired properties of dosage form over the uncoated variety. The advantages of coating are: improving taste, odor, and colour of the drug, improving ease of swallowing by the patient, improving product stability, To protect against the gastric environment, To improve mechanical resistance of the dosage form, Modifying release properties
Desining of the study: Design of the Drug product is Components of Drug Product, Manufacturing Process , Development Compatibility

Selection of Excipients

Microcrystalline cellulose is Microcrystalline Cellulose Ph. Eur :Colloidal silicon anhydrous,Glidant; Anticaking Agent; Emulsion Stabilizer; Suspending Agent; Thermal Stabilizer; Viscosity-Increasing Agent; Desiccant, and Solubility-Enhancer, Sodium Croscarmellose CalciumStearate

Manufacturing formula

During process development, the manufacturing steps and critical process parameters : The method of manufacture is Sifting,blending sifting blending,compaction, milling,sifting,pre lubrication compression, coating and packing

Material	**Function**	**Manufacturer**	**% per dosage form**	**Mg per solid dosage form**
Dry mixing				
Gemfibrozil USP	Active	Sigma-Aldrich	600	84
Microcrystalline Cellulose	Dilute	MINGTAI CHEMICAL	115.53	16.17
Methyl cellulose	Binder	SakshiChem Sciences Private Limited	100	14
Silica Colloidal anhydrous	Glidant	Deguss	3.50	0.490
Croscarmellose sodium	Disintegrate	SOLUTAB®	30.00	4.20
Calcium Stearate	Lubricant	Ferro Industry	2.0	0.28
Pre Lubrication /Lubrication				
Microcrystalline Cellulose	Dilute	MINGTAI CHEMICAL	40	5.60
Silica Colloidal anhydrous	Glidant	Deguss	4	0.56
Croscarmellose sodium	Disintegrate	SOLUTAB®	20	2.80
Calcium Stearate	Lubricant	Ferro Industry	5	.78
	Core weight		920.00	128.00
Coating				
Opadry White	Coating solution	Colorcon	20	3.36
Purified water	Solution			20.64
	Coated tablet		940	131.60
Material	**Function**	**Manufacturer**	**% per dosage form**	**Mg per solid dosage form**
Dry **mixing**				
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Calcium Stearate	Lubricant	Ferro Industry	2.0	0.28
Lubrication				
Microcrystalline Cellulose	Dilute	MINGTAI CHEMICAL	40	5.60
Silica Colloidal anhydrous	Glidant	Deguss	4	0.56
Croscarmellose sodium	Disintegrate	SOLUTAB®	20	2.80
Calcium Stearate	Lubricant	Ferro Industry	5	.78

Material	Function	Manufacturer	% per dosage form	Mg per solid dosage form
	Core weight		920.00	128.00
Coating				
Opadry White	Coating solution	Colorcon	20	3.36
Purified water	Solution			20.64
	Coated tablet		940	131.60

Manufacturing Process flow –parameter-Equipment

Sr.no	Steps	Parameter	Equipment used
	Raw material to be used in the manufacturing shall be procured from the approved vendor		
2	**Sifting**		
	Gemfibrozil USP	# 20	Sifter Verification of sieve integrity before and after use
	Microcrystalline Cellulose	# 20	
	Methyl cellulose	# 20	
	Silica Colloidal anhydrous	#10	
	Croscarmellose sodium	#10	
3	**Blending**		
	Gemfibrozil USP,Microcrystalline Cellulose ,Methyl cellulose,Silica Colloidal anhydrous ,Croscarmellose sodium	20 minutes in Blender at 50 RPM	Blender RPM and time
4	**Sifting**		
	calcium stearate through #30	# 30	Sifter Verification of sieve integrity before and after use
5	**Blending**	10 minutes in Blender at 50 RPM	Blender RPM and time
	Add sifted calcium stearate through #30 in blender		
6	**Roll Compaction**	Control the parameter	Roll Compactor Compaction Pressure i.e. compaction force per cm of roll width. Speed of feeding screws Roll Speed
	Compact above material in the roll compactor to increase the powder flow and retention		
7	**Multi** Mill		
	Milling and Sifting of the material Mill with 8.0 mm screen and sift the milled granules by 20 mesh Mill with 2.0 mm screen and sift the milled granules by 20 mesh	8.0 and 2.0 mm screen 20 mesh	Verification of sieve integrity before and after use
8	**Sifting**		Verification of sieve integrity before and after use
	Sift the granules through #80 mesh ,Compact granules should not be less than 75-80 % retain on # 80 mesh		
9	**Lubrication**		
	Lubricate the granules in blender for 10 minutes. Add Sift Silica Colloidal anhydrous, Croscarmellose sodium and blend for 5 minutes	**At 50RPM**	Blender RPM and time
10	**Compression**		
	Unload the blend and compressed on 40 station of compression Killen machine	Turret speed Punch and die In process parameter	Compression machine
11	Coating	Spray rate Weight gain	Coating Machine
	Mask the core tablet		

Sr.no	Steps	Parameter	Equipment used
		Atomization pressure	

RESULTS AND DISCUSSION

Before Compaction-Premixing results: Sample is withdrawal for the blend uniformity,Bulk density ,tapped density and water content

Sampling point	ABC112	ABC113	ABC114
1	98.4	99.2	100.6
2	97.8	97.7	98.1
3	99.6	98.0	99.3
4	98.5	100.1	98.7
5	99.6	98.3	100.4
6	98.2	96.5	96.4
7	97.0	97.6	100.7
8	96.2	99.3	98.9
9	99.7	100.4	97.0
10	98.4	96.6	98.1
Mean	98.1	98.4	98.8
SD	1.04	1.82	1.61
% RSD	1.05	1.76	1.64
Bulk Density (g/ml)	0.375	0.353	0.380
Tapped Density (g/ml)	0.523	0.519	0.537
Water by KF (% m/m)	1.4	1.3	1.3

After compaction milling results: sample is withdrawal,Bulk density ,tapped density and Particle size Analysis (#80 mesh)

Sampling point	ABC112	ABC113	ABC114
Bulk Density (g/ml)	0.475	0.553	0.580
Tapped Density (g/ml)	0.629	0.745	0.737
Particle size Analysis (#80 mesh)	75.13	76.19	72.18

Lubrication results: sample is withdrawal for the blend uniformity ,Bulk density ,tapped density and water content

Sampling point	ABC112	ABC113	ABC114
1	98.7	96.5	98.7
2	96.7	97.6	100.4
3	98.4	99.3	100.1
4	99.3	99.8	98.3
5	100.4	96.6	96.5
6	96.6	98.5	97.6
7	98.4	99.6	99.3
8	97.0	98.2	100.4
9	98.1	97.0	97.6
10	98.8	98.5	99.3
Mean	98.6	97.1	98.4
Minimum	96.7	96.5	96.5
Maximum	100.4	99.3	100.4
% RSD	0.94	1.15	1.21
Description	White to off white granules	White to off white granules	White to off white granules
Assay (%)	99.7	98.8	99.6
Water content % m/m	1.3	1.4	1.6
Bulk Density (g/ml)	0.478	0.560	0.601
Tapped Density (g/ml)	0.630	0.739	0.745

Sampling point	ABC112	ABC113	ABC114
Particle size Analysis (Retention)			
20# Mesh	19.36	18.25	17.45
30# Mesh	36.12	35.12	38.12
40# Mesh	53.32	49.86	51.23
60# Mesh	74.62	63.74	71.8
100# Mesh	76.61	67.38	77.2
120# Mesh	85.56	81.32	84.4

Compression : sample is withdrawal for the Weight variation, Thickness , Hardness, Friability, Disintegration time, Dissolution profiling, Uniformity of dosage, assay

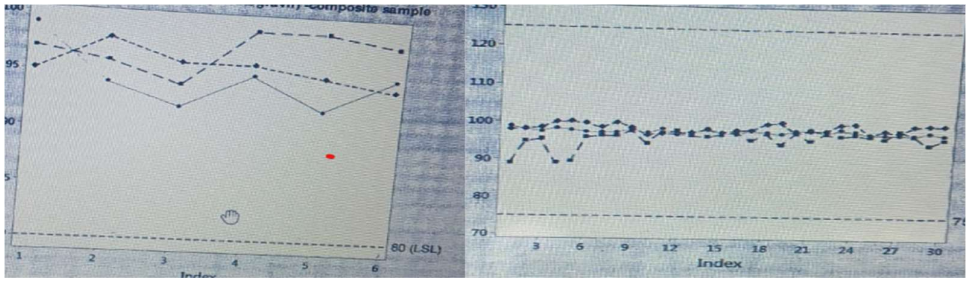
Test	ABC112				ABC113				ABC114			
Weight variation (mg)	909.3-927.5				917.6-936.2				9.13.2-929.8			
Thickness (mm)	6.40-6.52				6.40-6.66				6.94-7.12			
Hardness (N)	193-209				192-212				180-209			
Friability (%m/m)	0.1				0.1				0.1			
Disintegration time (minute)	4				5				4			
Dissolution profile	Min (%)	Max (%)	Mean	%RSD	Min (%)	Max (%)	Mean	%RSD	Min (%)	Max (%)	Mean	%RSD
10	92	94	93	1.18	91	94	93	1.36	93	97	97	0.125
20	94	100	97	2.54	95	97	96	0.78	95	97	98	0.90
30	97	100	99	1.02	97	98	98	0.42	97	99	98	0.77
45	100	101	101	1.02	98	99	99	0.55	98	100	99	0.78
Uniformity of dosage	93..2-95.3 Mean :94.2 % RSD :0.51				101.1-102.2 Mean :101.4 % RSD :0.31				100.6-101.4 Mean :101.0 % RSD :0.40			
Assay(%)	101.3				100.3				101.8			
Water content % m/m	1.9				2.4				3.6			

Coating: sample is withdrawal for the Weight variation, Thickness , Hardness, Friability, Disintegration time, Dissolution profiling, Uniformity of dosage, assay

Test	Standard	ABC112	ABC113	ABC114
Description	White to off white capsule shape tablet with break line on both the	White to off white capsule shape tablet with break line on both the side	White to off white capsule shape tablet with break line on both the side	White to off white capsule shape tablet with break line on both the side
Identification	The transitions minima spectra obtained from the sample shall be corresponded to transitions minima spectra obtained from the Gemfibrozil reference standard	The transitions minima spectra obtained from the sample is corresponded to transitions minima spectra obtained from the Gemfibrozil reference standard	The transitions minima spectra obtained from the sample is corresponded to transitions minima spectra obtained from the Gemfibrozil reference standard	The transitions minima spectra obtained from the sample is corresponded to transitions minima spectra obtained from the Gemfibrozil reference standard

Test	Standard	ABC112	ABC113	ABC114
Weight variation (mg)	8.924 g-9.746 g	910.3-927.5	917.6-936.2	9.13.2-929.8
Thickness (mm)	6.30 mm-7.28	6.40-6.52	6.40-6.66	6.94-7.12
Hardness (N)	NLT 160 N	193-209	192-212	180-209
Friability (%m/m)	NMT 1.0	0.1	0.1	0.1
Disintegration time (minute)	NMT 15 minutes	4	5	4
Dissolution by UV				
1	NLT 80% (Q) of label claimed – Gemfibrozil($C_{15}H_{22}O_3$) is dissolved in the 45 minutes	98.3	97.6	98.9
2		99.4	96.8	99.3
3		98.5	98.3	97.8
4		96.2	98.4	99.9
5		97.3	96.9	97.8
6		100.1	97.3	99.5
Uniformity of dosage	85-115 with RSD not more than 6.0%)	93.2-95.3 Mean :94.2 % RSD :0.51	101.1-102.2 Mean :101.4 % RSD :0.31	100.6-101.4 Mean :101.0 % RSD :0.40
Water content % m/m	NMT 4.0% m/m	2.9	2.1	2.6
Assay(%)	NLY 95.0 to NMT 105	99.6	100.6	99.4
Related Substance				
Impurity A	NMT 0.1%	Not Detected	Not Detected	Not Detected
Other Impurities	NMT 0.2%	0.10%	0.12%	0.11%
Total impurities	NMT 0.5%	0.12%	0.14%	0.10%

Dissolution by UV& Uniformity of dosage



3.3 Risk Assessment to Identify Variables Potentially Impacting Product Quality:

Critical Quality Attributes	Variables and Unit Operations					
	Particle size	Excipients	Dry Mix	Drying	Lubrication	Compression
Content Uniformity	L	L	L	L	L	H
Appearance	L	L	L	L	L	M
Hardness	L	M	L	M	L	M
Friability	L	M	L	M	L	M
Disintegration	L	M	L	L	L	M
Dissolution	H	L	L	L	L	M
Assay	L	L	L	L	L	M
Related Substances	L	L	L	L	L	L

L	Low Risk
M	Medium risk
H	High risk

CONCLUSION

The flow related problems during compression at commercial scale have been investigated. Generally it is difficult to compress the fluffy material because of its low bulk density. Gemfibrozil is alsoa material with low bulk density and low melting point. In present study, the flow related issue during compression was resolved by formulation development. Concerning statistical analysis related to QbD approach, it was shown that 32 full factorial experimental design and optimization technique can be successfully in the development of proper formulation of gemfibrozil without creating die fill problem and having sufficient granule strength. The microscopic characteristics are also important factor in this study because the API was approx. 80 % of the total tablet weight. In future the drugs having similar such characteristics (drug content more than 70 %, fluffy-low bulk density, low melting point) can be manufacture successfully on commercial scale by this approach.

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