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OPTIMIZATION OF VARIOUS PROCESS PARAMETERS FOR FORMULATION OF MODEL ANTI-HYPERLIPIDEMIC DRUG BY USING DRY GRANULATION METHOD

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Keywords:

Tablet, Anti- Hyperlipidemic, *In-vitro*, Granulation

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ABSTRACT: The Tablet manufacturing process is a complex process, influenced by several process variables The aim of this study was to optimize blending; roller compaction and tablets compression processes using design space approach for a model Anti- Hyperlipidemic drug Fluvastatin. 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 which includes Blending time, Roller force, Compression force and machine speed which were recognized as critical process parameters and were evaluated. A scale up batch is taken to evaluate and optimize the parameters. Critical quality attributes like Blend uniformity, granules parameters, flow behavior, tablet appearance, impact on tablet physical parameters and *in-vitro* drug dissolution release profile is evaluated to optimize the parameters. The data & test results of blend, granules and tablets at various in-process phases were complied with the specified limits and finished product sample analysis results found to be complying within specifications. This study and results obtained assures that the manufacturing process is reproducible, robust and will yield consistent product, which meets specification.

INTRODUCTION: Quality by Design (QbD):

Recently proposed quality-by-design (QbD) regulatory initiative of pharmaceutical product and process development has encouraged researchers in pharmaceutical industry to reach the "desired state" of drug manufacturing in 21st century. Main goal of this approach is to gain a comprehensive understanding of their manufacturing processes, with an accurate estimation of their robustness and reliability.

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The emphasis has changed from the need to demonstrate that the product will consistently meet relatively tight specifications to a new situation of being able to demonstrate that the product is controlled within a broader "design space" (DS). The design space (DS) concept is introduced as "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality."

Using this approach, it is essential to define relationship between critical formulation/process parameters and critical quality attributes (such as granule characteristics and tablet properties. A simplified quality assurance diagram under the QbD for drug product development is schematically represented in **Fig. 1**.[1, 2]

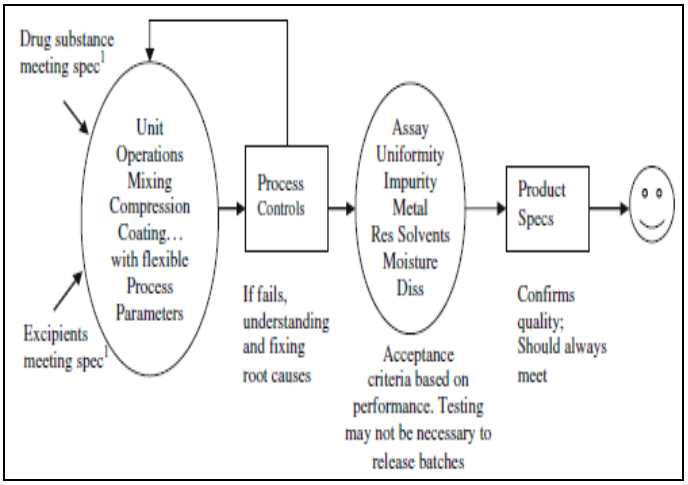


TABLE 1: A SIMPLIFIED QUALITY ASSURANCE DIAGRAM UNDER THE QBD FOR GENERIC DRUGS [2]

Process Optimisation:

The development and commercial release of a globally marketed pharmaceutical drug product necessarily begins in the realm of the very small. Drug discovery may focus on the molecular level, and early formulation may deal with only gram quantities of material. It is at the early formulation stage, however, that a tentative sequence of physico chemical operations is initially

Proposed and developed to transform the raw materials into a drug product with the desired quality attributes (e.g., potency, dissolution, etc.) At this early stage, these experimental operations are carried out in bench top or small pilot-scale equipment, and the process knowledge in the form of raw data obtained from these experiments is specific to that scale. Process optimization is the practice by which process knowledge is developed and formulated in such a way that it can be applied effectively to guide equipment selection process parameters, process conditions, and process control strategies, irrespective of scale.[3, 4]

An HPMC based extended release tablet formulation of a model anti-Hyperlipidemic drug is developed by dry granulation process. The manufacturing stages involve sifting, blending, blend lubrication, roller compaction, compression and coating.

The aim of our study was to define the design space of Blending operation, dry granulation and tablet compression process. In the first part, the assessment of process and formulation factors (critical material and process parameters) and their influence on critical quality attributes of intermediate and finished product was performed. Dry granulation parameters and compression force were varied, in order to develop new design space, evaluating their influence on tablets characteristics.

MATERIALS AND METHODS:

Materials:

Materials used in the presented study for the granulation and tableting experiments were: Fluvastatin sodium (TEVA API India limited.), Glyceryl behenate (Compritol 888 ATO, Gattefosse), Pregelatinized Starch (Starch 1500 - Colorcon), Hypromellose (Methocel K100LV CR - Colorcon), Hypromellose (Methocel K15MCR - Colorcon), Potassium Hydrogen Carbonate (Merck KgaA Germany), Magnesium Stearate (Peter Graven) and Opadry Yellow 81W42236 (Colorcon)

Manufacturing procedure:

Matrix tablets were prepared by dry granulation method with the formula optimized composition as given in **Table 1**.

TABLE 1: FINAL FORMULA COMPOSITION TO BE PROCESS OPTIMSED FOR

Sl.no	Name of the Raw Material	mg/tablet
	Core Tablets	
1	Fluvastatin sodium	84.28
2	Glyceryl Behenate	50.00
3	Pregelatinized Starch	81.72
4	Hypromellose (Grade A)	34.00
5	Hypromellose(Grade B)	32.00
6	Potassium Hydrogen Carbonate	13.00
7	Magnesium Stearate	5.00
	Core Tablet weight	300.0
	Coating agent	
8	Opadry Yellow	3.00
9	Purified Water	NA
	Coated Tablet weight	303.0

The manufacturing procedure for tablet production is as follows: Fluvastatin Sodium and other excipients except Magnesium Stearate were initially passed through 20# sieve. The sifted material is blended for suitable time interval in a lab scale bin blender. The blended material is lubricated with Magnesium Stearate sifted through #40 sieve for 5 minutes. The lubricated blend is compacted in Alexanderwerk WP200 roller compactor at suitable parameters to arrive at

desired granular material. The obtained granules were lubricated with extra granular Magnesium Stearate for 5 minutes and resulting granules were evaluated for the flow properties. Tablets were compressed using 10.0 mm round shaped punches on KORSCH XM-12 compression machine. As per the process optimization plan different critical process parameters were evaluated and studied for their effect on critical quality attributes or quality target product profile (QTPP) of products.

The details of equipments used for various manufacturing process and their capacities areas listed in **Table 2.**

TABLE 2: LIST OF EQUIPMENT UTILIZED FOR BATCH MANUFACTURING

Manufacturing Stage	Equipment used	Capacity	Manufacturer, Model No
Dispensing	Dispensing Booth	Not Applicable	March-Aire , 3300DFB
Sifting	Vibrosifter	Not Applicable	Jiangsu Gui Bao, ZS 350
Blending	Bin blender	10L,30L,50L and 100L	Zhejiang Canaan, HSD 100
Blend lubrication	Bin blender	10L,30L,50L and 100L	Zhejiang Canaan, HSD 100
Roller compaction	Alexanderwerk WP200	200 Kg/ hour	WP200
Granules lubrication	Bin blender	10L,30L,50L and 100L	Zhejiang Canaan, HSD 100
Compression	KORSCH XM 12 Compression machine	6 station Single layer and bi-layer Max speed: 60rpm	KORSCH XM 12
Coating	Glatt GMPC II	Glatt GMPC II	9L, 56L

Based on scientific understanding and prior knowledge, a risk assessment of the potential impact of the unit operations on the drug product CQAs was completed. **Table 3** shows the result of the risk assessment and identifies the unit operations which require further investigation to determine the appropriate control strategy.

TABLE 3: RISK MATRIX FOR DRUG PRODUCT CQAS FOR EACH UNIT OPERATION

	Unit operation				
DP CQAs	Blending	Blend Lubrication	Roller compaction	Granules lubrication	Compression
Appearance	Low	Low	Low	Low	High
Identity	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	High
Content uniformity	High	High	High	High	High
Dissolution	Low	Low	High	Low	High

Process Optimization – Blending and Blend Lubrication Unit Operation:

The manufacturing process uses a blending step followed by roller compaction to obtain granules for compression. The blend includes approximately 26% active and 74% excipients, which is mostly Glyceryl behenate and Pregelatinized Starch. Despite the presence of roller compaction and granules blending step (lubrication) later in the process train, this processing step was deemed critical because development studies indicated that material insufficiently blended or lubricated at this stage ultimately leads to unacceptable content uniformity of the finished drug product and roller sticking tendency during compaction respectively. Blending process was done for 12 minutes at 12 rpm with intermittent sampling was done at 4 minutes, 8 minutes and 12 minutes. The 12 minutes blended material is lubricated for 5 minutes at 12 rpm with intermittent sampling at 3 minutes and 5 minutes. Details is as listed in **Table 4.**

TABLE 4: PROCESS PARAMETERS FOR BLENDING AND BLEND LUBRICATION BATCH SIZE – 40, 000 TABLETS, 12.0 KG

	Blending			Blend Lubrication	
Batch No Machine RPM	Trial 1 12 RPM	Trial 2 12 RPM	Trial 3 12 RPM	Trial 1 12 RPM	Trial 2 12 RPM
Blending time (minutes)	4 minutes	8 minutes	12 minutes	3 minutes	5 minutes
Total Revolution	48 revolutions	96 revolutions	144 revolutions	36 revolutions	60 revolutions

The sampled materials are analyzed for individual blend content uniformity as per the approved method and evaluated for blend content uniformity at various blending time intervals.

Process Optimization – Roller compaction unit operation: [5, 6]

The purpose of the roller compaction and milling stages is to produce granulated product that is suitable for subsequent blending and compression. The initial blend is transferred to the roller compactor where a screw-feeder drives it between two rollers, which compact the material. The compacted ribbon is then broken up and passes through a rotating impellor screen mill. Critical process parameter for roller compaction process is Roller force, roller gap, roller speed and mill screen size. The parameters under evaluation are Roller force, roller gap and roller speed. A design experiment of 2 Level Factorial design with 1 center point is applied to evaluate the roller compaction parameters on critical quality attributes of drug product. The compacted granules are lubricated and compressed into tablets at pre-determined parameters. The factors and range for roller compaction parameter studied is as in **Table 5.**

TABLE 5: FACTOR STUDIED (CRITICAL PROCESS PARAMETERS)

Factor	Name	Units	Minimum	Maximum
Factor 1	Roller Force	Bar	30	50
Factor 2	Roller Speed	mm	3	9
Factor 3	Roller Gap	rpm	2	4

TABLE 6: DOE RUN DETAILS, BATCH SIZE – 40, 000 TABLETS, 12.0 KG

Trial 1 Lubricated Blend										
Run	Units	1	2	3	4	5	6	7	8	9
A: Force	KN/cm	30	50	30	50	40	50	30	50	30
B: Gap	mm	4	4	2	4	3	2	2	2	4
C: Speed	rpm	3	3	3	9	6	9	9	3	9

For tracking and understanding the granules are coded as Trial **1-A** to Trail **1-I.** The impact of these parameters on Critical Quality Attributes of Drug Products and Intermediates like Bulk density, Tapped density, PSD #60 meshes Cum. % retained and tablet dissolution profile is studied.

Process Optimization – Granulation Lubrication Unit Operation:

Following the roller compaction and milling, the milled granulation is blended with extragranular excipients in a third blending operation. The granules are mixed with 1.0% magnesium stearate (as lubricant). Based on the development data, the blending parameter targets listed in **Table 7** are acceptable for the proposed commercial scale lubrication blending process. Because studies have shown that wide variations in both blending time and blender fill volume have negligible impact on any CQA, this unit operation is considered robust and has no critical process parameters.

TABLE 7: PROCESS PARAMETERS FOR GRANULES LUBRICATION
Batch Size – 40, 000 Tablets, 12.0 kg

	Granules Lubrication
Batch No	Trial 1
Machine RPM	12 RPM
Blending time (minutes)	5 minutes
Total Revolution	60 revolutions

The sampled materials are analyzed for individual blend content uniformity as per the approved method and evaluated for blend content uniformity at various blending time intervals. No further optimisation is being done for this unit operation.

Compression process parameters: [7, 8]

During compression of the tablet, Compression Force (Pre-Compression and Main Compression) and machine speed should be optimized. Compression parameters for compression force and speed stud study are shown in **Table 8** and **9** respectively. Tablets of these batches were evaluated for Thickness, Weight variation, Friability and dissolution study.

TABLE 8: COMPRESSION FORCE STUDY

Batch Size – 40, 000 Tablets, 12.0 kg

Parameter	Optimization batch			
	High compression force	Target compression force	Low compression force	Without pre-compression force
Pre-compression force (Kn)	8.5	3.2	1.4	0.2
Main compression force (Kn)	36.1	23.1	17.3	13
Dosing (mm)	5.1	4.9	5.1	5.1
Machine RPM	15	15	12	12

TABLE 9: COMPRESSION MACHINE SPEED STUDY

Parameter	Optimization batch		
	High speed – 40 RPM	Target speed - 20 RPM	Low speed - 10 RPM
Main compression force (Kn)	23.1	23.1	23.1
Dosing (mm)	4.9	4.9	4.9
Machine RPM	40	20	10

RESULTS AND DISCUSSION:

Process Optimization – Blending and Blend Lubrication Unit Operation:

For batch No coded as Trail 1, blend uniformity data at blending stage and blend lubrication stage is tabulated in **Table 9** and graphical representation of % RSD with mixing time is shown in Figure 2 and 3. From the results we can say that % RSD is less than 4.0% at all time intervals. At blending stage with increase in blending time from 4 minutes to 12 minutes the % RSD is minimum and content uniformity is improved. Also with blend lubrication the % RSD reduced to less than 2.0% at 5 minutes blend lubrication time. So finally 12 minutes of blending time and five minutes of blend lubrication time was finalized.

TABLE 10: BLEND UNIFORMITY DATA AT BLENDING AND BLEND LUBRICATION STAGE

Fluvastatin ER Tablets 80 mg – Trail 1					
Sample	Blending stage			Blend Lubrication	
	4 minutes	8 minutes	12 minutes	3 minutes	5 minutes
	% drug content (Fluvastatin)				
A	95.8	94.2	101.1	96.0	97.1
B	99.9	101.2	99.3	103.5	99.8
C	105.5	99.7	100.7	103.0	98.8
D	96.9	98.3	101.5	99.0	100.8
E	96.6	98.8	100.0	97.2	101.3
F	96.8	101.8	100.2	102.2	98.7
G	101.7	100.3	100.9	95.6	100.3
H	98.0	100.7	103.0	98.7	101.0
I	97.6	101.8	104.0	101.3	102.2
J	99.4	98.6	100.4	99.2	98.5
Minimum	95.8	94.2	99.3	95.6	97.1
Maximum	105.5	101.8	104.0	103.5	102.2
Mean	98.8	99.5	101.1	99.57	99.9
%RSD	2.99	2.28	1.39	2.85	1.57

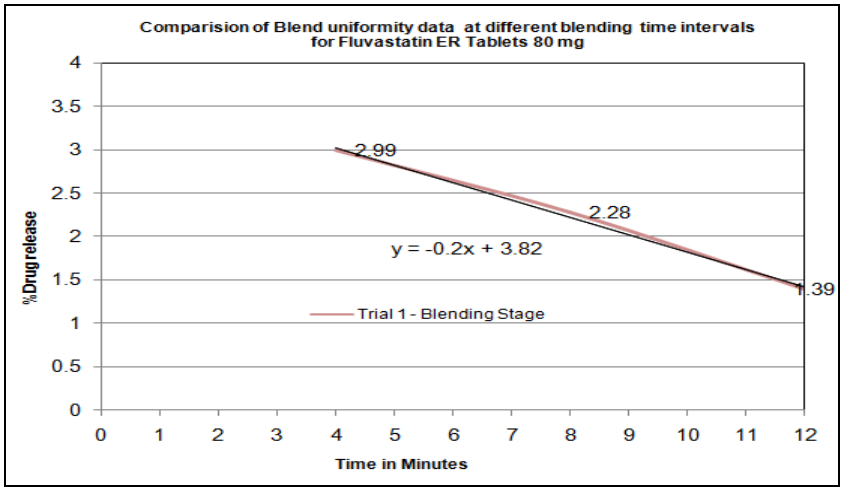


FIG.2: COMPARISON OF BLEND UNIFORMITY DATA AT DIFFERENT BLENDING TIME INTERVALS FOR FLUVASTATIN ER TABLETS 80 MG

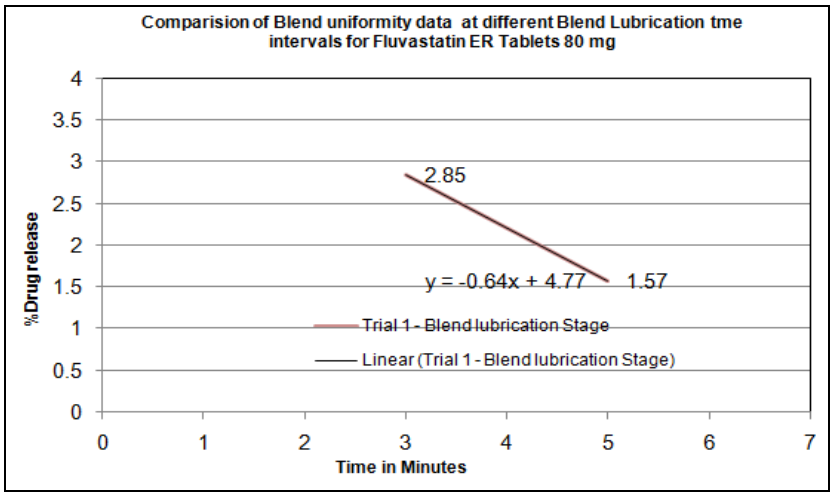


FIG.3: COMPARISON OF BLEND UNIFORMITY DATA AT DIFFERENT BLEND LUBRICATION TIME INTERVALS FOR FLUVASTATIN ER TABLETS 80 MG

Process Optimization – Roller compaction unit operation:

The trial batch In-process data for granules parameter and Dissolution profile for tablets at various time points is collated in tabular form. The analysed results, statistical data, Tablet parameters and dissolution profile are tabulated in **Table 10 – 13**. The statistical summary for the Design of experiments factorial model is tabulated in **Table10.** The contour plot, Pareto chart and Overlay plot for effect of model on evaluated parameters is as in **Fig. 4** and **5**.

TABLE 11: DOE RUN DETAILS AND OBSERVATIONS

STD No	Run	A: Force	B: Gap	C: Speed	Bulk Density	PSD #60 mesh Cum. % retained	Dissolution water 2 hr	Dissolution water 4 hr	Dissolution water 6 hr	Dissolution water 8 hr
	Unit	BAR	mm	RPM	g/mL	%	%	%	%	%
3	1	30	4	3	0.491	39.68	18	45	71	95
4	2	50	4	3	0.554	68.74	20	46	73	96
1	3	30	2	3	0.509	53.76	18	43	69	92
8	4	50	4	9	0.551	64.94	19	45	72	93
9	5	40	3	6	0.544	62.16	18	45	72	92
6	6	50	2	9	0.583	66.63	21	46	74	94
5	7	30	2	9	0.5	54.94	17	37	64	91
2	8	50	2	3	0.552	72.2	21	46	74	97
7	9	30	4	9	0.488	44.59	16	39	67	95

TABLE 12: DOE SUMMARY: STATISTICAL ANALYSIS

ANOVA Analysis	Bulk density		PSD #60 mesh Retained		Dissolution 2 hour		Dissolution 4 hour		Dissolution 6 hour		Dissolution 8 hour	
	p-values	Signal. Response effect	p-values	Signal. Response effect	p-values	Signal. Response effect	p-values	Signal. Response effect	p-values	Signal. Response effect	p-values	Signal. Response effect
Model	0.006	Yes	0.006	Yes	0.008	Yes	0.081	NA	0.059	NA	0.339	NA
Roller Force	0.001	Yes	0.001	Yes	0.002	Yes	0.035	yes	0.019	yes	0.2492	No
Roller Gap	0.13	No	0.061	No	0.082	No	0.648	No	0.745	No	0.3904	No
Roller Speed	0.639	No	0.801	No	0.082	No	0.099	No	0.157	No	0.2492	No

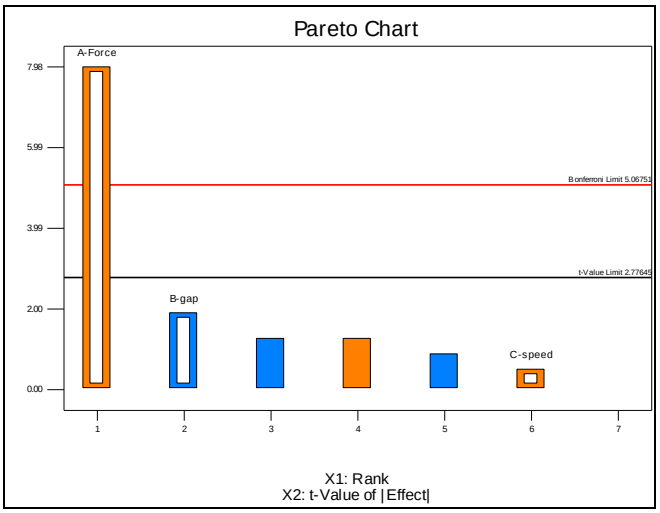
TABLE 13: TABLET PHYSICAL PARAMETERS FOR TABLETS COMPRESSED USING GRANULES COMPACTED AT DIFFERENT PARAMETERS

Parameter	Trial 1- A	Trial 1-B	Trial 1-C	Trial 1-D	Trial 1-E	Trial 1-F	Trial 1-G	Trial 1-H	Trial 1-I
Individual weight(mg)	299 - 306	306 - 313	299 - 308	300 - 305	295 - 306	291 - 306	298 - 305	298 - 308	299 – 304
Thickness(mm)	4.11 - 4.20	4.14 - 4.25	4.10 - 4.20	4.08 - 4.12	4.14 - 4.22	4.14 - 4.24	4.15 - 4.24	4.18 - 4.26	4.18 -4.24
Hardness(N)	52 - 61	52 - 68	60 - 65	52 - 65	55 - 64	39 - 50	52 - 64	50 - 64	51 – 62
Friability (1%)	Nil	Nil	Nil	Nil	Nil	nil	nil	Nil	Nil
Flow Properties	Good	Good	Good	Good	Good	Good	Good	Good	Good

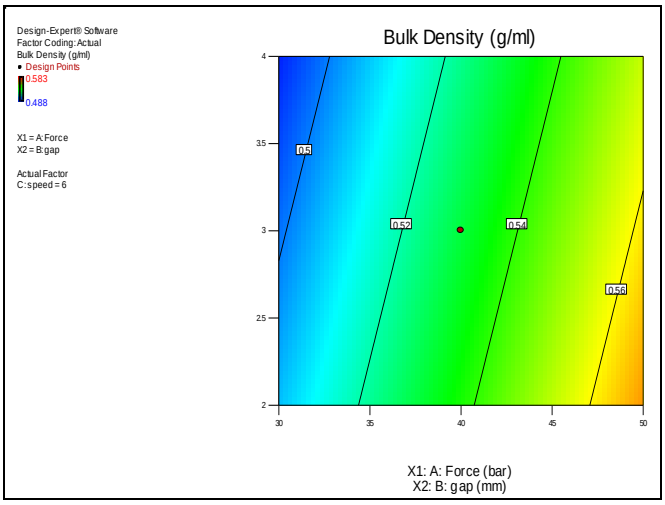
Table 11 shows the tablet physical testing results of tablets prepared using different granules using roller compaction granulation parameter. Data show goods similarity between different roller compaction parameter. The results also show that the speed at which the roller compactor equipment was operated at did not influence tablet crushing strength values.

TABLE 14: TABLET DISSOLUTION PROFILE FOR TABLETS COMPRESSED USING GRANULES COMPACTED AT DIFFERENT PARAMETERS

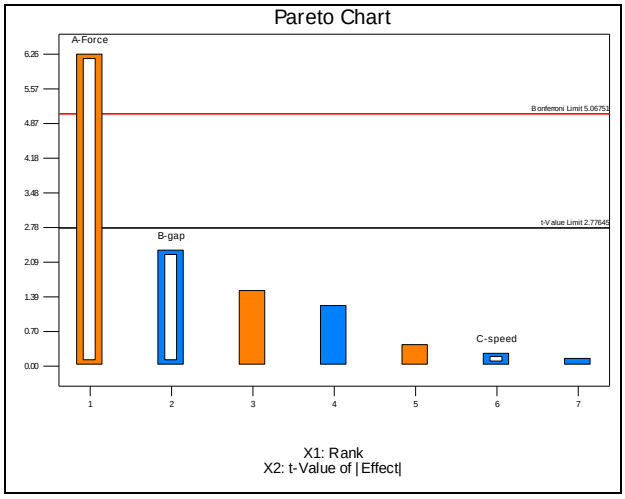
Dissolution Profile in Water at 50 rpm	Tablet dissolution Profile for tablets compressed using granules compacted at different parameters								
	Trial 1- A	Trial 1-B	Trial 1-C	Trial 1-D	Trial 1-E	Trial 1-F	Trial 1-G	Trial 1-H	Trial 1-I
Time point in Hours	Condition – Water, 1000 ml, USPI-I(Basket), Sampling at 2 Hours, 4 hours, 6 hours and 8 hours								
2 Hours	18	20	18	19	18	21	17	21	16
4 Hours	45	46	43	45	45	46	37	46	39
6 Hours	71	73	69	72	72	74	64	74	67
8 Hours	95	96	92	93	92	94	91	97	95



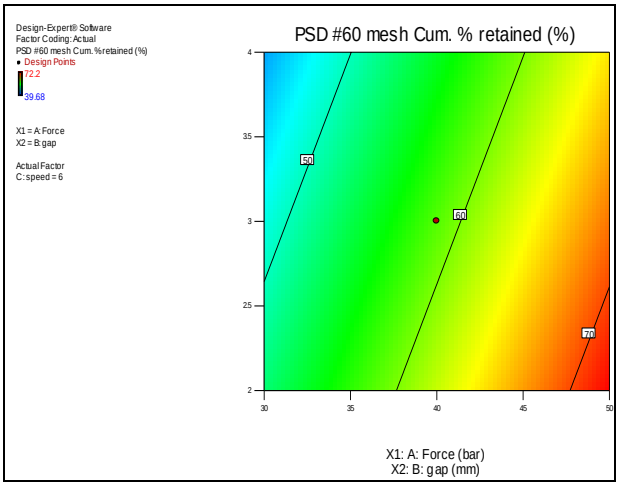
Pareto Chart for effect on Bulk density



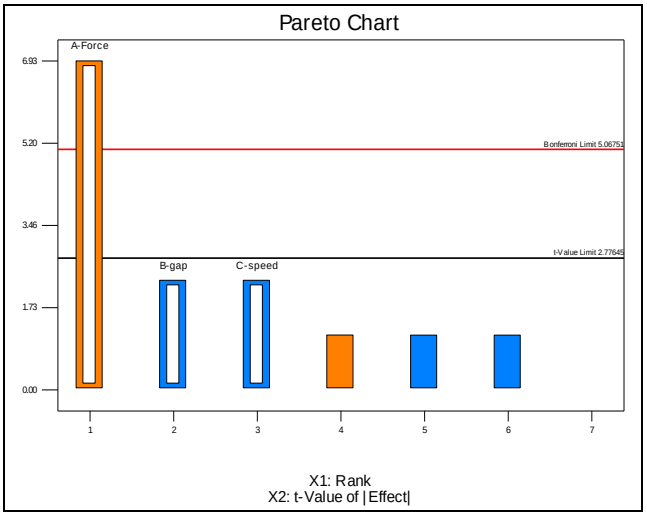
Contour plot for roll pressure and roller gap versus bulk density of granules



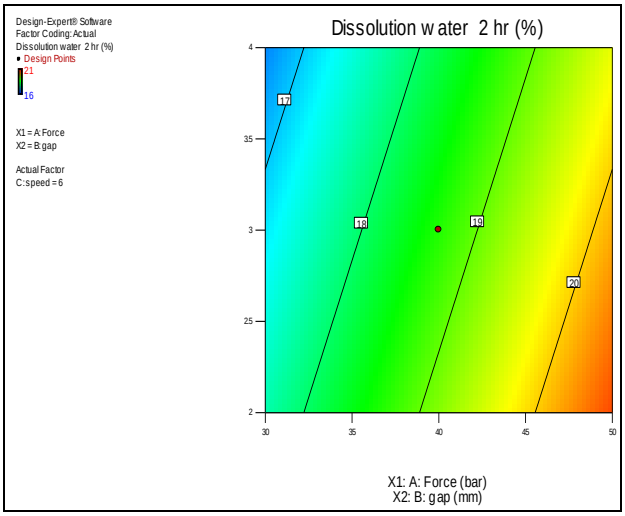
Pareto Chart for effect on PSD #60 Mesh Cum. % Retained of granules12593



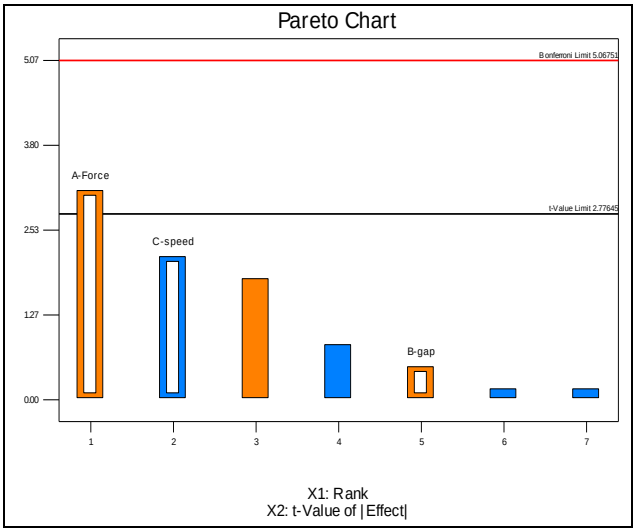
Contour plot for roll pressure and roller gap versus PSD #60 Mesh Cum. % Retained of granules



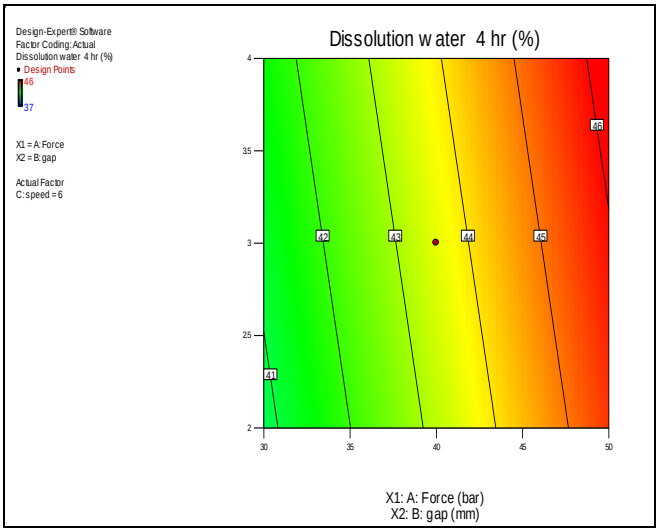
Pareto Chart for effect on Dissolution in water at 2 Hour



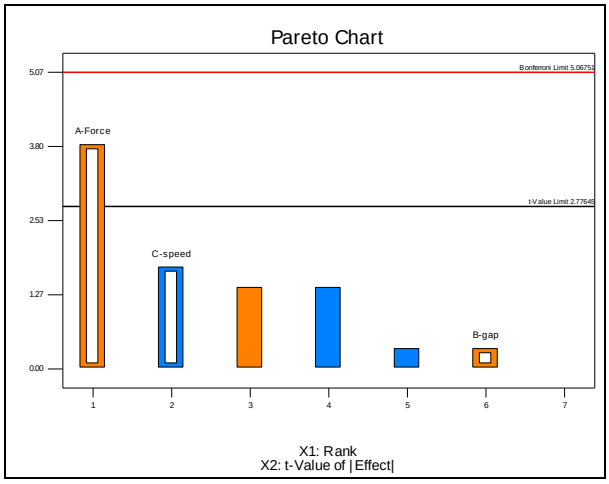
Contour plot for roll pressure and roller gap versus Dissolution in dissolution at 2 Hour



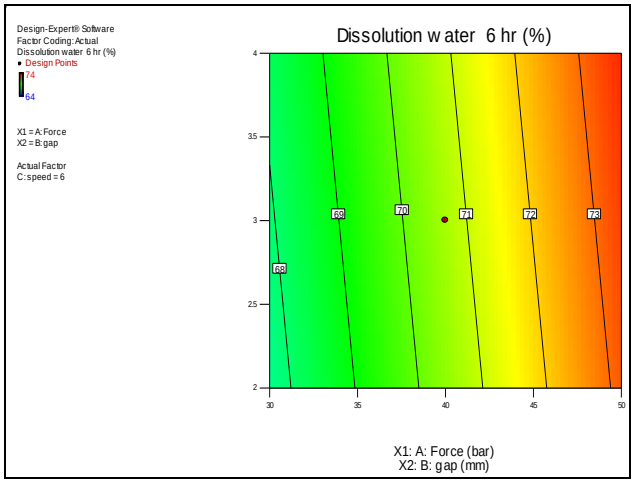
Pareto Chart for effect on Dissolution in water at 4 Hour



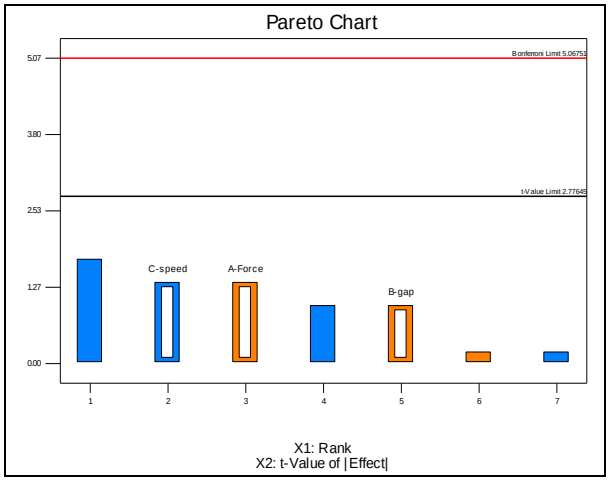
Contour plot for roll pressure and roller gap versus Dissolution in dissolution at 4 Hour.



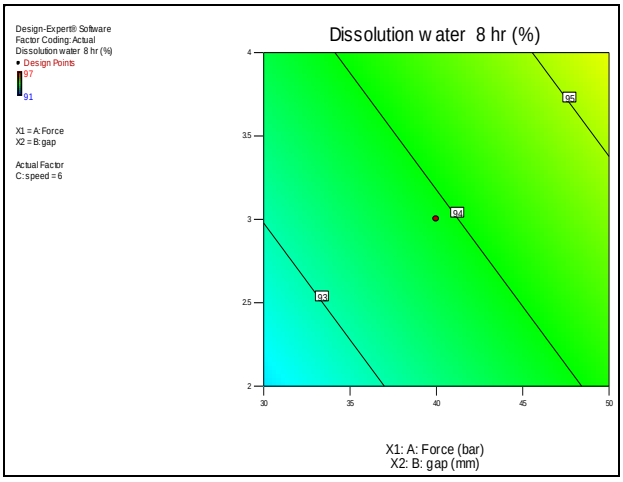
Pareto Chart for effect on Dissolution in water at 6 Hour



Contour plot for roll pressure and roller gap versus Dissolution in dissolution at 6 Hour

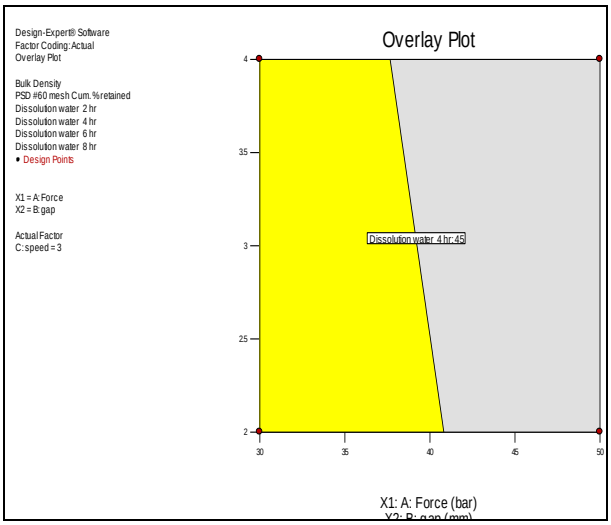


Pareto Chart for effect on Dissolution in water at 8 Hour

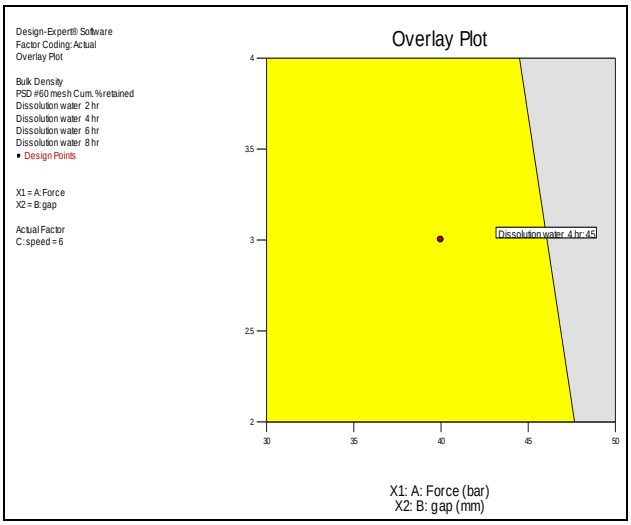


Contour plot for roll pressure and roller gap versus Dissolution in dissolution at 8 Hour

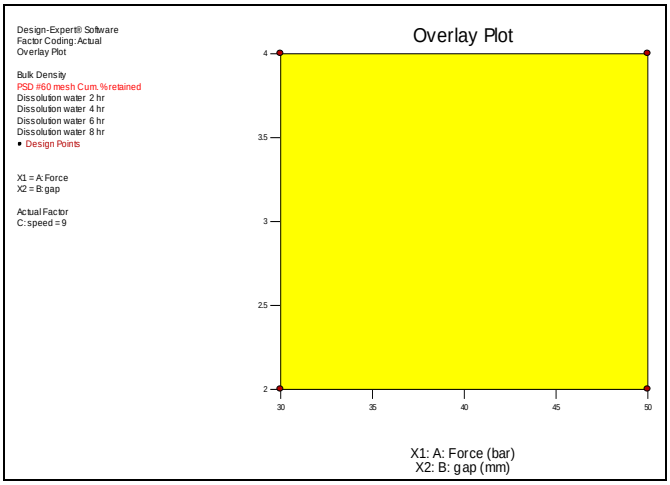
FIG.4: THE CONTOUR PLOT AND PARETO CHART FOR EFFECT OF MODEL ON EVALUATED PARAMETERS



Multiple Responses Overlay Plot at Roller Sped = 3 rpm



Multiple Responses Overlay Plot at Roller Sped = 6 rpm



Multiple Responses Overlay Plot at Roller Sped = 9 rpm

FIG.5: THE MULTIPLE RESPONSES OVERLAY PLOT AT DIFFERENT ROLLER SPED (3 RPM, 6 RPM AND 9 RPM)

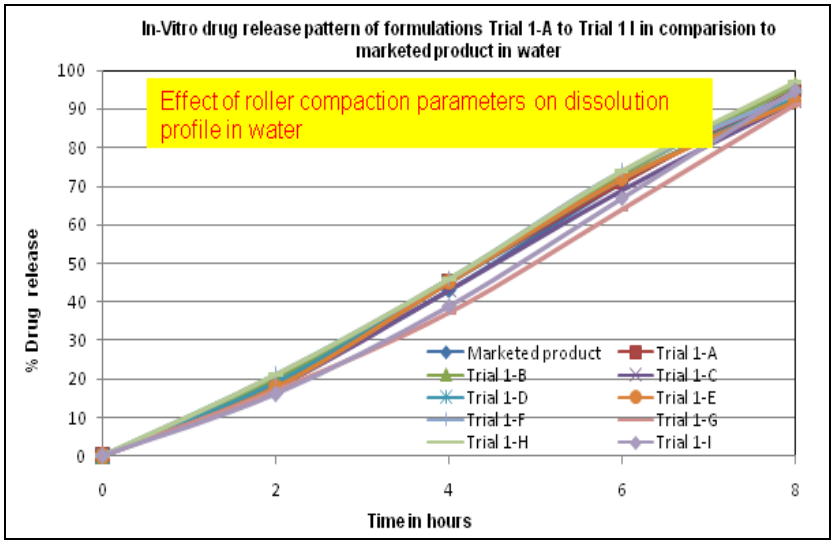


FIG.6: *IN-VITRO* DRUG RELEASE PATTERN OF FORMULATIONS TRIAL 1-A TO TRIAL 1 I IN COMPARISON TO MARKETED PRODUCT IN WATER

For all the 9 different granules the granules bulk density and particle size distribution was evaluated and found to be satisfactory. There was no flow problem during compression nor tablet sticking tendency during compression.

Roller pressure is the significant factor affecting all product attributes tested, but the operating range tested is within the design space (30 – 50 Bar). Roller gap may effect on the product attributes but not significant. Therefore the design space is what the operating range tested (2 - 4 mm). Roller speed was determined not to be critical process parameters. Therefore the design space is what the operating range tested (3 - 9 rpm). However the design space (overlay plot) indicates that at roller RPM of 9, the process gives a satisfactory properties for the granules. At 3 and 6 rpm the Dissolution at 4 hours is on the higher side out of the specification limit. Further studies to be continued to optimize the process or to identify the acceptable dissolution release profile.

1.1 Process Optimization – Compression unit operation:

Post compression parameters such as thickness, hardness, friability, weight variation are given in following **Table 14**. As shown in **Fig.7**, there was no effect on dissolution profile of tablet produced at different compression force. There was no capping or sticking defects for the compressed tablets at different compression force. Therefore

the evaluated main-compression range of 36 – 13 Kn is suitable to achieve tablets of desired quality attributes. Also with minimal pre-compression force of 0.2 Kn the binding of tablets were still reasonably good, as depicted in tablet parameters.

TABLE 14: TABLET PHYSICAL PARAMETERS FOR TABLETS COMPRESSED AT DIFFERENT COMPRESSION PARAMETER

Parameter	Compression force study			
	High compression force	Target compression force	Low compression force	Without pre-compression force
Individual weight(mg)	296 - 306	297 - 300	295 - 302	305 - 308
Thickness(mm)	4.06 - 4.15	4.07 - 4.13	4.10 - 4.14	4.27 - 4.36
Hardness(N)	55 - 65	54 - 64	54 - 60	43 - 56
Friability (1%)	Nil	nil	nil	Nil
Flow Properties	Good	Good	Good	Good

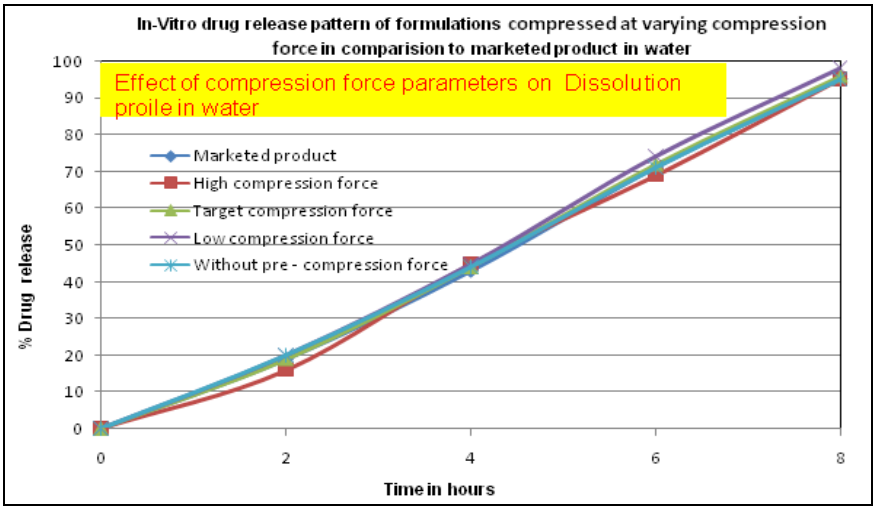


FIG.7: *IN-VITRO* DRUG RELEASE PATTERN OF FORMULATIONS COMPRESSED AT VARYING COMPRESSION FORCE IN COMPARISON TO MARKETED PRODUCT IN WATER

CONCLUSION: Tablet manufacturing by Dry granulation using roller compaction process is a widely used manufacturing process for poorly soluble drug having low bulk density. In manufacturing process, there are many factors which may affect final product. In this study all these critical process parameters were identified and optimized. Blending time and lubrication time in blender was also optimized. During roller compaction process the critical parameters were optimized using 3 factorial design with zero blocks. Roller compaction force is identified as the critical parameter affecting granules properties. During compression process, there was Tablet hardness which may affect release profile of drug. These parameters were also optimized. Finally its of the opinion that all the process parameters for formulation of Fluvastatin ER Tablets 80 mg by using Dry Granulation process were optimized to make the process a robust and reproducible in scale up manufacturing.

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REFERENCES:

1. EMA, 2014. Human Regulatory, Quality by Design, Guidance Documents. Accessed on 2016.06.13
2. Edina Pallagi, Rita Ambrus, Piroska Szabó-Révész, Ildikó Csóka. Adaptation of the quality by design concept in early pharmaceutical development of an intranasal Nanosized formulation. International Journal of Pharmaceutics. 2015; 491:384 – 392.
3. B. Venkateswara Reddy, K. Navaneetha, K. Venkata Ramana Reddy. International Journal of Pharmacy and Pharmaceutical Sciences.2014; 6(4):312 – 317.
4. Gurpreet Kaur, D.B. Sridhar, Manoj Gera. Optimization of Roll Compaction/Dry Granulation Process for Poorly

Flowable Antiviral Formulation. Am. J. PharmTech Res. 2012; 2(4): 544 – 557.
5. Milad Khorasani et al., Process optimization of dry granulation based tableting line: Extracting physical material characteristics from granules, ribbons and tablets using near-IR (NIR) spectroscopic measurement
6. Richard Hwang, Robert M. Noack. Application of design of experiments to pharmaceutical formulation development; 2(1): 58 – 65.
7. Stephanie Sutton. Optimizing Tableting Processes with Quality by Design. Pharmaceutical Technology. 2012; 36(5).
8. Ales Belic, Igor Skrjanc, Damjana Zupancic Bozic, Franc Vrecer. Tableting process optimisation with the application of fuzzy models. International Journal of Pharmaceutics. 2010; 389(1-2): 86-93.

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