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Article

Effects of granule particle size and lubricant concentration on tablet hardness containing large concentration of polymers

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The objective of this research work is to demonstrate the impact of granule size and lubricant concentration on the hardness of tablets in formulations containing higher concentration of polymers and to resolve the hardness issue during compression process. The work involves optimization of a milling process for size reduction of granules and blending process to achieve tablets of good hardness on compression. To optimize the granule size, different sized co-mill screens were used. The different concentration of lubricant were studied on different sized granules to check the effect on hardness of tablets and to obtained the desired hardness of tablets. Compression of lubricated blend in various concentration was performed using the gravity feeder and force feeder separately to check the impact on the over lubrication effect. This ultimately leads to less hardness tablets. Lubricated blends were evaluated by performing the Bulk Density, Tapped Density, Hausner ratio and compressibility index tests. Tablets were evaluated for the physical characteristics like weight variation, hardness, thickness and dissolution. It has been conclude that on using the optimum granules size and lubricant concentration in formulation, all the downstream problems can be resolved and this in turn helps in compression of tablets and also provides the good hardness to the tablets.

Keywords: Tablet hardness/effects. Granule size. Lubricant concentration. Polymer.

INTRODUCTION

Granule sizes play an important role in obtaining the hardness of tablets. Generally, as granules size increased, tablets were found to show increased weight variation, decreased hardness and increased friability. Whereas in reverse phase, granule size is very small, it leads to issues like sticking due to extra fine particles which enters in between the surface of punch and dies and form a thin film of it on inner surface of die. This finally prevents the compressed tablets to come out of the die i.e. issue of tablet ejection from the die.

Also in other way if the granule size is very small, the actual surface area will be more which in turn requires more lubricant concentration to cover completely. The effects obtained were largely dependent on the type and concentration of lubricant. Tablets containing talc as lubricant, shows decreased disintegration time with increased granule size. This represents need of optimum lubricant concentration for the compression of different granule size fractions (Jaiyeobaa, Oladiran, 1983).

The function of a lubricant in the product formulation is to prevent powder from sticking to the punches, dies and other metal components of the tablet press. A lubricant also facilitates the ejection of compacted tablets. Typically, lubricants account for a small percentage of the formula's content. It ranges from 0.25% to 2%. The most common lubricant in pharmaceutical formulations is magnesium stearate.

There are two common errors when processing lubricants. The first error is neglecting the pre-screening of lubricants to remove the lumpy, over-size particles. The second error is failing to blend the lubricant evenly into the product formulation. The lubricant must be able to contact with metal parts to work correctly. However, it is better to under-blend the lubricant than to over-blend it. Over-blending, will hide the lubricant within the other particles, rendering it useless.

Magnesium stearate, a metallic salt boundary

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lubricant, is probably the most commonly used lubricant for pharmaceutical tableting. It is relatively inexpensive and provides high lubrication.

MATERIAL AND METHODS

Material

All the raw materials, Nicergoline (Teva Pharmaceutical Industries), Lactose Monohydrate {Pharmatose 200M} (DFE Pharma, Netherlands), Microcrystalline cellulose {Avicel PH 101} (FMC Biopolymer, Philadelphia), Povidone {PVP K-30}(BASF Corporation, Germany), Xanthan Gum {Xanthural 75} (CP Kelco, Atalanta USA), Methocel K100 LVCR (Dow Chemicals, Michigan, United States), Lactose Monohydrate {Flowlac 100} (Molkerei Meggle Wasserburg Gmbh), Magnesium stearate (Peter Greven, Netherlands) used in the formulation are of Ph. Eur. grade.

The quadro co-mill (Model: U5, Ganson-Quadro), Blender (Model: GMP, Saral), Compression machine 16 station (Model: 102i, Fette compacting, Germany), Compression tooling size of 14X7 mm (Parle Elizabeth tools), Hardness tester (Dr. Schleuniger), Thickness tester (Vernier calliper of Mitutoyo) and Friability apparatus (Electrolab) were used for the processing of blend and compressing into tablets.

Method

Wet granulation, Drying and Milling process

The wet granulation method was used for powder blend using high speed mixer granulator with spraying gun and peristaltic pump for binder-water-solution addition. Drying is carried out in Retsch dryer at Research and Development.

The dried granules were taken from the same batch in equal proportion of 2.0 kg each. Then milling of dried granules were done using the Quadro co-mill with 24C (Condidur hole with hole size of 610 microns), 32R (Round hole with hole size of 813 microns) and 40G (Grater hole with hole size of 1016 microns) screen. After that blending was done using the double cone blender in R&D scale batch and multidirectional blender in Pilot scale batch. The milling speed was kept constant. It was 1500 rpm, for all the screen size.

Physical properties of powder blend

Particle size distribution

Sieve analysis for particle size distribution (Fayed, Otten, 1997; Hlinak *et al.,* 2006; Shekunov *et al.,* 2006) of milled granules was performed using electromagnetic sieve shaker (Make: Electrolab, Model: EMS-8) with 100g material for 5 min at power 5 starting with the larger sieve on top from 20# to 120# sieve. Each sieve along with the retained particles was weighed individually after shaking. The test was completed when the weight on the test sieves did not changed by more than 5% of the previous weight (Teixeira, 2009).

Bulk density and Tapped density

Bulk and tapped density of milled granules were performed using the density tester (Make: Electrolab, USP- method 1) using a 250 ml graduated glass cylinder. Approximately 200 ml of powder was carefully filled into the tared glass cylinder ensuring a flat top surface. The maximum bulk volume was noted.

Tapped density was performed at 500, 750 and 1250 taps to get the constant reading. The results are the mean of three replicates (USP, 2007a). Loose bulk density (LBD) and Tapped Bulk density (TBD) have been calculated using as the following equations (Baddam, Bandela, 2013; Carr, 1965).

LBD = Weight of the granules /Untapped Volume of the packing

TBD = Weight of the granules /Tapped Volume of the packing.

Hausner ratio (Hausner , 1967) = Tapped density / Bulk density

Carr's Index = (Tapped density – Bulk density) x 100 / Tapped density

Blending and lubrication

Milled granules were blended with extragranular materials for 10 min at 20 rpm and finally lubricated with magnesium stearate (0.93% of total theoretical weight of tablet). It was previously sifted through 60# sieve in 6 litre capacity double cone blender for 5 min at 20 rpm. The particle size distribution was measured for lubricated granules.

Tablet compression

Compression using Gravity & Force Feeder

The lubricated blend was compressed using both gravity feeder (Table III) and force feeder (Table IV) to check the impact on hardness. Compression done at different turret speed to check the impact of speed on physical parameters of the tablets and the parameters were recorded. Sufficient hardness of tablets around 14-22 kp is required to proceed for coating as next step.

Compression of blend into tablets with lesser concentration of lubricant:

Milled granules with 24C screen were divided into four equal parts of 2.0 kg each and blended separately with extragranular materials for 10 minutes at 20 rpm and finally it was lubricated. For lubrication, magnesium stearate was used in different concentration. These were 0.23%, 0.47%, 0.70% and 0.93% of total tablet weight (previously sifted through 60# sieve) in 6 litre capacity double cone blender for 5 minutes at 20 rpm. The blend was compressed and physical parameters of the tablets were recorded.

RESULT AND DISCUSSION

Optimization of milling process

In initial trials of formulation development, the 40G screen was selected for milling of dried granules. The granules obtained from the milling through 40G screen consists of heavier granules along with small portion of fines. Upon pre-lubrication with the extragranular material (comprising 30% hydrophilic, less dense, fine powder polymers), leads to the segregation of larger granules from the final lubricated blend. This was due to difference in the bulk density of granules and powder during the compression. This was in turn due to vibration in machine and hopper.

To avoid this segregation issue of granules, finer size screen of 32R and 24C was selected for milling process as a part of optimization. It was observed that the retains over 40# sieve is less for 24C screen granules in comparison to 32R & 40G screen. It can be clearly seen in the Table III. Also the time required for milling process is less in case of 24C & 40G screen in comparison with the 32R screen. (Table II) This in turn depicted the milling process efficiency and cost effectiveness, as the unmilled granules obtained after milling are less. The results are the mean of three replicates (Teixeira, 2009) (Table III).

Powder characterization

The physical characteristics like Hausner ratio and Carr's compressibility index shows the fair to passable flow of blend**.**

TABLE I - Unit formula composition

Sr. No.	Ingredients	%/tab			
	Trial Number	A	B	C	D
Intragranular Materials					
1	Nicergoline	6.98	6.98	6.98	6.98
2	Lactose Monohydrate (Pharmatose 200M)	7.44	7.44	7.44	7.44
3	Microcrystalline Cellulose (Avicel 101)	9.07	9.30	9.53	9.77
4	PVPK-30	8.14	8.14	8.14	8.14
5	Methocel K100 LVCR	20.93	20.93	20.93	20.93
6	Xanthan Gum (Xantural 75)	6.98	6.98	6.98	6.98
7	Purified Water	q. s.	q. s.	q. s.	q. s.
Extragranular Materials					
8	Methocel K100 LVCR	30.23	30.23	30.23	30.23
9	Lactose Monohydrate (Flowlac 100)	9.30	9.30	9.30	9.30
10	Magnesium Stearate	0.93	0.70	0.47	0.23
		100.0	**100.0**	**100.0**	**100.0**

TABLE II - Milling parameters

Parameters	Co-mill speed (rpm)	Milling time (min)	Unmilled portion remained after milling (g)
24C Screen	1500	25	97.0
32R Screen	1500	34	121.0
40G Screen	1500	22	75.0

TABLE III - Particle size distribution data (Cumulative % weight retained)

# Sieve	Milled Granules			Lubricated Granules		
	(24C screen)	(32R screen)	(40G screen)	(24C screen)	(32R screen)	(40G screen)
20	00.14	00.19	00.90	00.21	00.21	00.90
40	11.24	19.69	23.76	11.02	15.56	19.40
60	17.04	29.83	36.94	14.09	40.05	28.28
80	62.30	74.71	56.46	70.54	74.13	43.68
100	72.98	85.84	68.70	77.94	86.01	62.54
120	76.88	88.12	77.12	80.07	91.48	76.62
140	83.84	95.12	85.66	86.06	93.46	83.36
Fine collector	100.48	100.41	100.16	100.66	100.17	100.08
BD g/mL$	**00.386**	**00.404**	**00.412**	**00.416**	**00.387**	**00.478**
TD g/mL$	**00.483**	**00.531**	**00.564**	**00.547**	**00.531**	**00.693**
Carr's Index$	**20.00**	**24.00**	**27.00**	**24.00**	**27.12**	**31.00**
Hausner Ratio$	**01.25**	**01.32**	**01.37**	**01.32**	**01.37**	**01.45**

*Limit: Fair: 1.19-1.25 (Hausner ratio) & 16-20 (Carr's index), Passable: 1.26-1.34 (Hausner ratio) & 21-25 (Carr's index) & Poor: 1.35-1.45 (Hausner ratio) & 26-31 (Carr's Index), (General Chapter, 1174 USP, 2007b). $: Values are mean of three replicate testing.

TABLE IV - Compression data form trial no T1A (using gravity feeder) of 24C screen milled granules

S. No.	Wt. Variation (mg) @10 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg)@ 15 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)
1	436.00	20.60	05.56	436.00	16.20	05.58	436.00	16.40	05.59
2	433.00	21.70	05.52	433.00	17.30	05.60	433.00	16.20	05.60
3	435.00	22.00	05.54	432.00	16.40	05.62	432.00	15.00	05.61
4	430.00	20.90	05.56	436.00	17.20	05.58	434.00	15.900	05.60
5	433.00	21.20	05.57	432.00	16.30	05.60	436.00	16.20	05.59
6	437.00	20.60	05.60	436.00	15.90	05.62	433.00	16.80	05.58
7	433.00	19.70	05.62	433.00	16.40	05.59	429.00	15.60	05.60
8	429.00	20.30	05.59	434.00	16.70	05.58	433.00	15.70	05.56
9	433.00	20.70	05.57	436.00	16.90	05.60	430.00	16.60	05.57
10	436.00	20.60	05.53	434.00	17.20	05.62	431.00	16.30	05.60
11	432.00	21.30	-	434.00	16.40	-	433.00	16.70	-
12	434.00	20.30	-	436.00	15.70	-	436.00	15.90	-
13	433.00	20.70	-	437.00	16.20	-	432.00	16.30	-
14	433.00	21.20	-	434.00	15.30	-	431.00	16.40	-
15	436.00	21.60	-	434.00	16.40	-	434.00	16.30	-
16	430.00	20.30	-	437.00	15.20	-	434.00	15.90	-
17	432.00	20.60	-	433.00	16.40	-	436.00	16.30	-
18	436.00	20.40	-	430.00	15.30	-	432.00	16.40	-
19	437.00	21.20	-	432.00	16.20	-	433.00	15.70	-
20	433.00	21.40	-	430.00	16.70	-	436.00	16.30	-
Min	**429.00**	**19.70**	**05.52**	**430.00**	**15.20**	**05.58**	**429.00**	**15.60**	**05.56**
Max	**437.00**	**22.00**	**05.620**	**437.00**	**17.30**	**05.62**	**436.00**	**16.80**	**05.61**

Bulk density of 24C passed milled granules indicates that the blend is fluffier in comparison with the granules of 32R & 40G screen milled granules. Also the Carr's index and Hausner ratio indicates the fair flow of granules with compare to 32R & 40G screen milled granules, which is having poor flow. (Table III)

Blending and lubrication

Blending and lubrication time was optimized and fixed to 10 min and 5 min respectively. The magnesium stearate concentration's effect on blending and compression has been studied. And it has been found that the higher concentration i.e. 0.93% of total tablet weight is much higher. This is leading to decrease in hardness of tablets. It has also formed hydrophobic layer over the granules and finally have reduced the compactability between the granules. This ultimately has led to less hardness than the desired. (Table VII)

The study of granules with lubricant concentration of 0.23%, 0.47% and 0.70% of total tablet weight was performed. It has been observed that the concentration 0.47% has produced tablets with very good hardness with minimal ejection force and good aesthetic look. The tablets were shining. It indicates the optimum lubrication. Whereas the concentration of 0.23% has also produced the tablets with good hardness but with the increased ejection force. It has also produced sound during tablet ejection due to inefficient lubrication. (Table I)

Tablets produced with the lubricant concentration of 0.70% are up to the desired hardness with lesser ejection value. However the hardness obtained was lesser than that of 0.47% lubricant containing granules. Tablet had good aesthetic value and surface shining.

TABLE V - Compression of data for trial no T1B (using force feeder) of 24C screen milled granules

S. No.	Wt. Variation (mg) @10 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @15 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)
1	433.00	17.30	05.58	433.00	15.60	05.57	431.00	14.60	5.54
2	437.00	16.30	05.60	433.00	15.90	05.60	430.00	14.30	5.56
3	434.00	17.20	05.62	430.00	16.20	05.61	429.00	14.90	5.57
4	436.00	15.20	05.61	434.00	15.90	05.57	432.00	13.70	5.60
5	437.00	17.70	05.65	433.00	15.70	05.56	434.00	14.60	5.61
6	435.00	17.80	05.54	434.00	15.60	05.58	434.00	13.70	5.65
7	438.00	16.60	05.56	432.00	15.20	05.58	431.00	14.70	5.60
8	433.00	17.50	05.57	434.00	14.40	05.60	434.00	14.70	5.58
9	436.00	17.90	05.60	433.00	14.70	05.62	430.00	14.40	5.54
10	435.00	17.40	05.61	432.00	15.60	05.61	430.00	14.70	5.56
11	437.00	16.80	05.57	436.00	15.30	05.61	433.00	14.70	5.57
12	437.00	17.00	05.56	432.00	15.70	05.57	432.00	15.00	5.56
13	436.00	17.40	05.58	433.00	16.00	05.56	435.00	16.20	5.58
14	435.00	16.90	05.57	430.00	15.30	05.58	429.00	14.20	5.57
15	435.00	17.20	05.61	431.00	15.60	05.57	433.00	14.60	5.61
16	434.00	17.70	5.65	432.00	15.60	5.61	430.00	14.40	5.54
17	437.00	16.50	5.60	433.00	14.90	5.60	429.00	14.40	5.59
18	431.00	16.90	5.58	432.00	15.70	5.58	431.00	15.20	5.53
19	432.00	17.20	5.54	433.00	16.30	5.54	432.00	15.60	5.56
20	433.00	17.80	5.57	436.00	15.90	5.56	430.00	14.60	5.57
Min	**431.00**	**15.20**	**5.54**	**430.00**	**14.40**	**5.54**	**429.00**	**13.70**	**5.53**
Max	**438.00**	**17.90**	**5.65**	**436.00**	**16.30**	**5.62**	**435.00**	**16.20**	**5.65**

TABLE VI - Compression data for trial no T2 and T3 (using force feeder) of 32R & 40G screen milled granules.

	Trial No: T2 (with Force Feeder) - 32R passed granules			Trial No: T3 (with Force Feeder) – 40G passed granules					
S. No.	Wt. Variation (mg) @10 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @15 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)
1	430.00	15.40	5.64	432.00	15.50	05.69	432.00	15.60	05.60
2	435.00	16.60	5.68	429.00	15.40	05.66	434.00	16.00	05.58
3	431.00	15.90	5.67	428.00	15.40	05.67	432.00	16.00	05.56
4	437.00	16.50	5.70	428.00	15.70	05.66	436.00	15.90	05.61
5	435.00	16.40	5.67	429.00	15.30	05.69	434.00	15.50	05.56
6	436.00	16.100	5.64	427.00	15.40	05.67	432.00	15.90	05.58
7	436.00	16.50	5.66	431.00	15.90	05.64	433.00	15.70	05.60
8	431.00	15.20	5.64	429.00	15.10	05.68	431.00	15.70	05.61
9	433.00	15.50	5.67	429.00	15.40	05.64	434.00	15.90	05.58
10	435.00	16.30	5.64	432.00	15.80	05.66	434.00	15.40	05.56
11	431.00	15.20	-	427.00	15.40	-	432.00	16.00	-
12	432.00	14.90	-	430.00	15.00	-	433.00	15.40	-
13	430.00	15.60	-	430.00	15.40	-	432.00	16.10	-
14	428.00	15.70	-	429.00	15.00	-	434.00	16.50	-
15	429.00	16.20	-	432.00	15.30	-	433.00	15.90	-
16	431.00	15.90	-	426.00	15.80	-	435.00	15.60	-
17	432.00	15.50	-	429.00	14.90	-	432.00	15.60	-
18	435.00	15.30	-	430.00	15.60	-	436.00	15.20	-
19	433.00	15.80	-	429.00	15.40	-	429.00	16.00	-
20	431.00	16.00	-	429.00	15.60	-	432.00	15.70	-
Min	**428.00**	**14.90**	**5.64**	**426.00**	**14.90**	**5.64**	**429.00**	**15.20**	**5.56**
Max	**437.00**	**16.60**	**5.70**	**432.00**	**15.90**	**5.69**	**436.00**	**16.50**	**5.61**

Above said trial depicts that the 0.47% lubricant concentration has been optimal concentration for the formulation and this has been capable of producing the tablets with desired hardness and all physical value. (Table VII).

To counter check the effect of lubricant it had been decided to study the impact of force feeder on tablet hardness. All he blend with different concentration had been compressed using both the gravity feeder and force feeder respectively and it had been observed that the tablets produced using the gravity feeder had the better hardness whereas the tablets produced with force feeder had lesser hardness. Also the hardness is going on reducing with the time in case of blend having the lubricant concentration of 0.93%. Here granules were mixed inside the force feeder area. The feeder speed had been kept at lowest possible speed to prevent the over lubrication however it had not been supported.

It has also been observed that, the tablets observed for 5-10 min of compression have good hardness and this hardness has decreased with time.

CONCLUSION

Granule size is very much important to obtain the desired hardness of tablets. It has been established from the above experiments and have found that the 24C milled granules is capable of producing the good tablet hardness in comparison to the 32R & 40G screen milled granules. Maintained optimized granule size have helped

TABLE VII - Compression data for trial no T4A, T4B, T4C & T4D (using force feeder) of 24C screen milled granules

	Trial No: T4 (with Force Feeder) – 24C screen milled granules											
	T4A (0.23 % Mg. Stearate)			T4B (0.47 % Mg. Stearate)			T4C (0.70 % Mg. Stearate)			T4D (0.93 % Mg. Stearate)		
S. No.	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)	Wt. Variation (mg) @20 rpm	Hardness (kp)	Thickness (mm)
1	428	25.60	05.49	430	26.70	05.49	430	21.9	05.51	426	16.10	05.50
2	427	27.10	05.47	428	26.60	05.48	428	20.1	05.50	428	16.30	05.49
3	430	25.30	05.50	426	27.00	05.49	426	22.4	05.48	427	16.30	05.47
4	431	24.90	05.49	427	25.10	05.47	431	21.7	05.49	430	16.10	05.48
5	430	25.60	05.48	430	24.70	05.47	430	22.5	05.47	428	16.70	05.51
6	428	24.80	05.48	428	25.30	05.48	430	20.7	05.48	426	16.30	05.50
7	426	26.10	05.49	429	25.60	05.51	428	21.6	05.49	428	15.90	05.51
8	427	25.30	05.47	426	23.90	05.50	426	20.9	05.48	426	15.60	05.50
9	430	25.80	05.52	430	24.70	05.48	428	21.2	05.49	428	15.00	05.49
10	428	24.90	05.51	428	24.90	05.49	427	21.9	05.47	427	15.30	05.48
11	429	26.10	05.49	427	25.10	05.47	430	21.0	05.50	430	15.90	05.49
12	430	26.00	05.48	430	24.70	05.48	428	21.9	05.49	428	15.70	05.47
13	428	27.10	05.51	428	24.90	05.51	426	20.6	05.48	426	15.60	05.48
14	426	26.10	05.49	427	25.60	05.50	428	21.4	05.48	428	16.20	05.51
15	431	26.50	05.52	431	26.00	05.49	426	20.5	05.49	431	15.90	05.50
16	430	26.10	05.48	430	25.70	05.48	428	21.6	05.47	433	15.70	05.49
17	428	25.80	05.47	428	25.10	05.50	431	21.6	05.50	427	14.90	05.48
18	426	25.90	05.52	431	26.10	05.51	433	20.6	05.51	430	15.40	05.50
19	430	24.90	05.51	429	26.50	05.50	429	21.6	05.50	431	15.80	05.49
20	428	24.50	05.50	428	25.80	05.51	427	21.2	05.52	430	15.90	05.50
Min	**426**	**24.50**	**05.47**	**427**	**23.90**	**05.47**	**426**	**20.1**	**05.47**	**426**	**14.90**	**05.47**
Max	**431**	**27.10**	**05.52**	**431**	**27.00**	**05.51**	**433**	**22.5**	**05.52**	**433**	**16.70**	**05.51**
Avg	**429**	**25.70**	**05.49**	**429**	**25.50**	**05.49**	**429**	**21.3**	**05.49**	**428**	**15.80**	**05.49**

Wt. = weight

in prevention of segregation of granules and also helped in reducing the weight variation and other downstream issues during compression.

The optimum concentration of lubricant in the formulation plays an important role to get the optimum tablets hardness of around 18 kp. Due to its hydrophobicity nature, it has formed a layer around the granules. This has prevented the granules to compact-tightly mass. Ultimately this has led to less hard tablets production. So, selection of lubricant concentration for the formulation is very much important for good hardness and aesthetic look is required. This ultimately requires supporting the coating process, as this is next step. This also withstands tablets from attrition and jerk during the coating process for longer time.

Those tablets have not get optimum tablet hardness of about 18 kp, lead to abrasion at the tablet surface and finally the tablets produced with rough surface. The optimum concentration of lubricant also affects the tablet hardness when we are using the force feeder for mixing again and again. This leads to over lubrication.

Hence, it has been concluded that on using the optimum granules size and lubricant concentration in formulation, all the downstream problems can be resolved

and this in turn helps in compression of tablets and also provide the good hardness to the tablets.

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