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AFFECT OF GRANULE SIZES, TYPES AND CONCENTRATIONS OF LUBRICANTS AND COMPRESSION FORCES ON TABLET PROPERTIES

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ABSTRACT: By using five different sieve sizes of ascorbic acid granules, affects of granule sizes on tablet properties, i.e. tablet weight and hardness have been studied with standard methods. Affects of lubricant types and concentrations on tablet properties, i.e. tablet hardness and disintegration time have also been studied by using magnesium stearate and sodium stearyl fumarate as the lubricants for producing tablets from mixed sizes granules of ascorbic acid. Moreover, affects of high, moderate or medium and low compression forces on tablet hardness and disintegration time have been studied by using the mixed sizes granules of ascorbic acid. The result reveals that medium sized granules are better than smaller or larger granules to produce tablets within the specificity. Tablet weight variation has been found as higher during the production of tablets from smaller or larger granules. Production of tablets without lubricants has been complicated due to the difficulties in tablet ejection, resulting in picking, sticking, capping and cracking of tablets, higher tablet hardness and lower disintegration time. With increasing concentration of lubricants, tablet hardness has been found to be decreased, whereas disintegration time has been observed to be increased. The order of sensitivity of the granules has been found as 3% > 5% > 0.25% for magnesium stearate and 5% > 0.25 > 3% for sodium stearyl fumarate. Increased tablet hardness and disintegration time have been observed for the increase in compression forces.

INTRODUCTION: Due to the ease of manufacturing, convenience in administration, accurate dosing, stability, tamper-proofness and safety compared to other pharmaceutical dosage forms, tablets are the most popular and versatile solid dosage form in use nowadays[1]. The manufacturing of tablets is a complex multi-stage process under which the starting materials change their physical characteristics a number of times before the final dosage form is produced.

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Many factors, such as powder particle or granule sizes, types and amounts of excipients, compression forces, etc., can affect on tablet properties during manufacturing of tablets. Therefore, these factors should be considered to produce tablets with specified properties, such as tablet hardness, disintegration time, dissolution rate, etc. Three vital properties of powders or granules, e.g. free flowing, coherence to form compact and excellent compressibility, are necessary for making tablets with particular properties.

Flow ability, relevant to compressibility, of powders or granules, which is influenced by particle or granule sizes and distribution, results in variations in tablet properties. Sizes of particles or granules can often be expressed as a number which

corresponds to the mesh screen size of a sieve, and the powder or granule flow ability and compressibility, can be measured by using the Carr's Index that is evaluated by the ratio of the difference between the tapped bulk density and the aerated bulk density to the tapped bulk density[2]. It can also be measured by using Hausner ratio which evaluated by the ratio of the tapped bulk density to the aerated bulk density[3]. On the other hand, lubricants are one of the major types of excipient that are used to improving the quality and manufacturing efficiency of tablets[4], mainly due to their characteristics to improve fluidity (glidant property), filling properties, as well as to prevent powder adhesion (anti-adherent property) to punch faces, and minimize die-wall friction, reducing wear and tear of tablet press and tooling [5, 6].

They also can serve various therapeutic-enhancing purposes, such as facilitating drug absorption or solubility, or other pharmacokinetic considerations. Magnesium stearate [Mg $(C_{18}H_{35}O_2)_2$], which is hydrophobic in nature, is widely used as a lubricant in tablet production at concentrations between 0.25 – 5.0%[5]. Magnesium stearate (MgSt) is a fine, white, precipitated or milled, impalpable powder of low bulk density, and is found in many mixtures that are safe for human consumption[7].

It exists as "Plate-like" crystals (or lamellae) stacked together like a deck of cards[4]. On the other hand, sodium stearyl fumarate ($C_{22}H_{39}NaO_4$) is a water-soluble fine white powder of hydrophilic nature, and is used in the situations where other lubricants fail to provide tablets of adequate stability, hardness, content uniformity, disintegration and dissolution rate[8]. The sensitivity of material to mixing with a lubricant is expressed by lubricant sensitivity ratio, which can quantitatively measured as the ratio between difference in hardness of an unlubricated tablet and a lubricated tablet to the hardness of an unlubricated tablet[9]. Again, tablet properties can be varied for different types of tablet presses as they maintain various compression forces[10].

The force exerted on the powder or granule in the dies is, therefore, should be controlled to ensure that each tablet is perfectly formed within the specification. In general, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. Due to the adverse affects on the tablet properties, appropriate sizes of powder particles or granules, suitable lubricant at the right concentration and proper compression pressure should, therefore, be selected carefully during the tablet production to preserve the drug properties.

Though many studies have been performed on these aspects, the affect of these factors are still obscure, and therefore, extensive efforts are required to employ on it. Ascorbic acid, which is best known by its antioxidant activity and the free radical scavenging, is a poorly compressible water-soluble and moisture sensitive essential vitamin[11-13]. Many physiological and mental disturbances can be occurred due to its lacking in the human body[13].

This complex nature of ascorbic acid is made it to choice as a model of study. In the present study, ascorbic acid granules of five different sieve sizes of mesh 14, 18, 30, 40 and 60 have been used to observe the affect of granule sizes on tablet properties, e.g. tablet weight and hardness. MgSt and sodium stearyl fumarate have been used as lubricants at different concentrations to observe the lubricant types and concentrations on the tablet properties e.g. tablet hardness and disintegration time. Moreover, three different compression forces have been applied to find out the affect on tablet hardness and disintegration time.

MATERIALS AND METHODS:

Materials

All chemicals, used in the present study, were approved only for training purposes. Granules were produced by using Ascorbic Acid (Honson Ingredients; TIPT* Lot # 13A0101), Lactose Monohydrate (Flowlac 100 [Wyndale; TIPT Lot # 07B0511]), Microcrystaline Cellulose (MCC 101 [Mingtai Chemical Co. Ltd.; TIPT Lot # 12B0108]), Polyplasdone–XL (International Specialty Products, Inc.; TIPT Lot # 00B0411) and Plasdone K90 (International Specialty Products, Inc.; TIPT Lot # 05B0502) at 25%, 50% 18%, 3% and 3.5%, respectively. After granulation, MgSt (Bärlocher) and sodium stearyl fumarate (Pruv®, Rettenmaier) were used to lubricate the granules

Methods:

All methods were performed according to the Good Manufacturing Practices (GMP) [14]. The temperature, relative humidity and air pressure were maintained at 20°±2°C, 20% and >5 Pascal, respectively.

Granulation:

Except the lubricants (MgSt and Pruv®), all other ingredients were firstly dry blended by using a twin shell V-blender (The Patterson – Kelley Co. Inc., USA; TIPT ID # PE95002) for 20 minutes. 40% of the binder (Plasdone K90) was used in this blend. The resulting dry blend was then used for low shear wet granulation by using a Hobart Planetary Granulator (TIPT ID # PE9600). The calculated 60% void volume of the dry blend was used as the volume of deionised water to prepare binder solution with the rest of the 60% of the binder (Plasdone K90).

The concentration of the binder solution was calculated as 11.1%. 25ml deionised water was used as extra during the wet massing to reach the capillary stage. After reaching the capillary stage in the wet granulation, the granules were then passed through a Mesh 10 screen of Manesty Rotogram Granulator 184 TBS (Mark III, England; TIPT ID # PE00002). The screened granules were then transferred into a dryer (Gruenberg, Gruenberg Oven Co., Inc., USA; TIPT ID # PE94001), and dried until the moisture content was reached at 2 – 3%. The dry granules were sieved with a Ro-Tap shaker (W.S. TYLER, USA; TIPT ID # TE97001) and collected separately from mesh 14 (1410µm), 18 (1000µm), 30 (590µm), 40 (420µm) and 60 (250µm) (USA Standard Testing Sieve, A.S.T.M. E – 11 Specification, VWR Scientific, USA).

Lubrication:

100g granules of each size of Mesh 14, 18, 30, 40 and 60 were weighted and selected as five lots for testing the granule size affect on the tablet properties, e.g. tablet weight and hardness. 0.5% MgSt was blended separately with each of the five lots by using the twin shell V-blender for 3 minutes.

The rest of the dry granules were then properly mixed together, from which eight lots of 100g of each were selected to study the affect of MgSt and Pruv® at different level of concentrations on the tablet properties e.g. tablet hardness and disintegration time. Two of the eight lots of mixed dry granules were kept without mixing the lubricant (MgSt and/or Pruv®), and the rest of the six lots were blended separately with 0.25% MgSt, 0.25% Pruv®, 3% MgSt, 3% Pruv®, 5% MgSt and 5% Pruv® for 3 minutes.

Again, three lots of 100g of dry mixed granules were selected and blended separately with 0.5% MgSt for 3 minutes to study the affect of compression forces on tablet properties, e.g. hardness and disintegration time.

Compression:

A Stokes B2 round tablet press (Manesty Betapress, F.J. Stokes Corporation, USA; TIPT ID #PE9500) with 16 stations and 9mm round standard concave tooling was used for the compression process. 25g of the selected granules from each lot was used for set-up, i.e. manual run without feed frame, manual run with feed frame and automatic run with feed frame. Then, the final tablet production was carried out. During the final tablet production, the following tablet parameters were followed: tablet weight: 350 ± 10.5mg, tablet hardness: 8 Strong-Cobb Units (SCU) ± 3.0 % and tablet dimension: 9mm diameter. Each lot was divided into three bins.

Tablets were collected in each bin of the lot at a time interval of 1.0 minute. Compression pressure was kept fixed (1.5 – 2.2 tons) for the whole period of the final tablet production, except the final tablet production to study the affect of compression forces on tablet properties. During the tablet production to study the affect of compression forces on tablet properties, compression forces were changed from low (≈ 1 ton) to moderate or medium (≈ 2.5 tons), and moderate to high (≈ 4 – 4.2 tons). To remove excess powder on the surface, the produced tablets were dedusted by using a deduster (KEY Industries, USA).

Sample Collection

From each bin of the lots, 10, 8 and 6 tablets were collected randomly to determine the tablet weight, hardness and disintegration time, respectively.

RESULTS AND DISCUSSION:

Based on the Carr's Index and Hausner Ratio, the flowability of the granules of different sizes used in the present study is presented in **Table 1**.

TABLE 1. FLOWABILITY OF GRANULES WITH DIFFERENT SIZES.

Granule size	Bulk volume (ml)	Tapped volume (ml)	Bulk density (g/ml)	Tapped density (g/ml)	Carr Index (CI%)		Hausner Ratio (HR)	
					CI%	Flowability	HR	Flowability
14	33	31	0.54	0.57	5.26	Excellent	1.06	Good
18	30	27	0.48	0.54	11.11	Good	1.13	Good
30	32	29	0.65	0.71	8.45	Excellent	0.92	Good
40	31	28	0.57	0.63	9.52	Excellent	1.11	Good
60	30	25	0.57	0.69	17.39	Fair	0.83	Good

Tablet weights (in mg) for tablets produced at from different sizes of granules, and determined by using an electronic balance (Precisa Instruments Ltd., Switzerland; TIPT ID # WS04003), are presented in **Table 2**.

Tablet hardness (in SCU) for tablets produced with different sizes of granules, determined by using a hardness tester (Pharma Test, Germany; TIPT ID # TE0901), are presented in **Table 3**.

Tablet hardness (in SCU) for tablets produced by using different lubricant concentrations of MgSt and Pruv® are presented in **Table 4**. Tablet disintegration time (in Min.) Tablets produced by using different lubricant concentrations of MgSt and Pruv®, estimated by using a tablet disintegration tester (HAAKE W13, Vankel, USA; TIPT ID # 94001), are presented in **Table 5**. Lubricant sensitivity ratio, calculated by using the average ($\bar{x}$) tablet hardness of different lots for different lubricant concentrations, are presented in **Table 6**.

Table 7 and **Table 8** represent tablet hardness (in SCU) and disintegration time (in Min.) for tablets produced at different compression forces, respectively.

The Carr's Index and the Hausner ratio are the indication of powder or granule flowability relevant to compressibility [2, 3]. According to the Carr's Index **(Table 1)**, granules of mesh 14, 30 and 40 having excellent flowability, whereas granules of mesh 18 and 60 contain good and fair flowability, respectively. The Hausner ratio **(Table 1)** reveals that the granules of all mesh have good flowability. Therefore, all of them can be used to produce tablets with excellent, good or fair compressibility.

Affect of granule sizes:

At a constant compression force, tablet weight variation may be an indication of changes in die fill. According to **Table 2**, the mean of average ($\bar{x}$-bar) of tablet weight for the granules of lot 1 of mesh 40 is 349.9mg, which is close to the specificity (350 ± 10.5mg). The $\bar{x}$-bar of the tablet weight for the granules of lot 2 (mesh 18) and lot 3 (mesh 30) are found as 352.2mg and 348.8mg, respectively. Therefore, using medium size granules of mesh 18, 30 and 40 is supposed to be better for producing tablets with the specificity. The lowest and second lowest $\bar{x}$-bar for tablet weight are found for the granules of lot 5 (mesh 60) and lot 1 (mesh 14) [323.6mg and 335.8mg, respectively].

Therefore, production of tablets from granules of mesh 14 and 60 is supposed to rise in weight variation influencing the drug uniformity. However, it may be possible to overcome by controlling other factors or using the mixture of granules of different sizes. It is reported that flowability increases with the decrease in glanule size, and tablet weight variation decreases with the decrease in granule size15. However, it may vary due to the variation in formulation. Particle size of starting materials may have an intense affect on the granule size16.

It is assumed that granules of smaller sizes may give rise to strong electrostatic forces due to very great surface areas resulting in processing and/or inter-particle and/or inter-granule friction from movement, which may cause weight variation during tablet production. On the other hand, due to the greater mass, granules of larger sizes may flow better than granules of smaller sizes. However, in case of very large granules, such as granules of

mesh 60 used in the present study, the void space may not be occupied properly during die fill due to the large sizes, resulting in tablet weight variation. Some other factors may be involved in this case. It is obscure, and therefore, further studies are required to find out the proper explanation.

The closer to the specified tablet hardness (8 SCU ± 3.0 %) are found for lot 2 of mesh 18 ($\bar{x}$-bar = 7.7), lot 3 of mesh 30 ($\bar{x}$-bar = 7.68) and lot 4 of mesh 18 ($\bar{x}$-bar = 8.6) **[Table 3]**. Lot 5 (mesh 60) and lot 1 (mesh 14) show the lowest ($\bar{x}$-bar = 5.7) and the second lowest ($\bar{x}$-bar = 6.6) hardness (Table 3). Therefore, medium size granules, such as mesh 18, 30 and 40, are better to use for producing tablets within the specificity. However, tablet hardness increases with the increased granule size (e.g. mesh 14 - 40), and decreases again for the larger granule size (e.g. mesh 60) **[Table 3]**.

This may be due to an increase in the plastic deformation and fragmentation from the smaller to the larger granules during compaction with a resultant increase in the surface area of the fragmented granules/particles necessary for particle-particle bonding. Very smaller sized granules may not prone to further deformation and fragmentation due to the limited sizes. For very larger sized granules, plastic deformation and fragmentation, resulting into particle-particle bonding, may be concerned due to the presence of large void spaces, and more compression forces may be required to overcome it. However, it is difficult to explain and more efforts are necessary to find out the elucidation.

Affect of lubricant type and concentration:

Along with some other purposes, lubricants are mainly used to facilitate tablet ejection during compression process. Use of appropriate type and proper amount of lubricant during compression can minimize the tablet defects, relevant to the production of tablets within the specification. Without using lubricants, production of tablets within specification is not possible at all.

TABLE 2. TABLET WEIGHT (IN MG) FOR TABLETS PRODUCED WITH DIFFERENT SIZES OF GRANULES.

Tablet	Lot 1 (Mesh 14)			Lot 2 (Mesh 18)			Lot 3 (Mesh 30)			Lot 4 (Mesh 40)			Lot 5 (Mesh 60)		
no.	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	326	335	343	350	320	359	352	342	352	349	351	351	320	341	329
2	332	338	345	331	359	361	348	348	350	346	346	352	251	320	342
3	339	331	331	360	331	348	346	347	349	347	352	348	333	310	340
4	328	343	339	352	318	372	349	346	347	352	354	347	318	318	320
5	333	335	341	360	333	366	349	349	351	351	351	346	320	322	310
6	332	340	338	370	368	366	348	345	348	350	350	351	310	320	308
7	337	334	340	361	357	360	347	344	353	349	348	345	320	320	311
8	331	330	328	338	331	370	348	351	350	353	350	350	329	323	320
9	339	346	337	369	360	361	352	349	351	353	347	354	331	339	318
10	336	333	333	321	350	363	353	347	352	348	348	359	322	321	322
$\bar{x}$	333.3	336.6	337.5	351.2	342.7	362.6	349.2	346.8	350.3	349.8	349.7	350.3	325.4	323.4	322

TABLE 3. TABLET HARDNESS (IN SCU) FOR TABLETS PRODUCED WITH DIFFERENT SIZES OFGRANULES.

Tablet	Lot 1 (Mesh 14)			Lot 2 (Mesh 18)			Lot 3 (Mesh 30)			Lot 3 (Mesh 40)			Lot 5 (Mesh 60)		
no.	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	6.8	7.4	7.3	7.6	7.1	5.2	7.7	6.6	8.1	8.2	10.5	8.5	6.9	5.5	5.6
2	7.1	6.3	7.8	6.5	6.4	7.2	7.1	9.5	9.4	8.5	7.3	9.7	6.3	6.3	7.0
3	7.0	6.5	5.5	6.4	6.2	7.0	6.5	7.8	9.3	9.2	9.5	8.6	6.4	5.6	5.4
4	5.8	7.4	7.0	10.6	7.3	11.7	7.1	6.9	7.7	6.2	9.4	7.1	4.5	6.8	4.5
5	6.5	5.8	7.4	9.8	8.2	6.4	7.2	6.5	8.6	8.8	9.8	8.5	6.1	4.7	4.7
6	6.8	5.9	6.0	10.8	7.3	8.6	6.5	7.1	6.8	9.5	8.8	6.7	4.9	4.1	3.2
7	7.2	6.9	6.3	12.3	5.5	6.3	7.4	10.5	7.9	8.2	8.0	8.9	4.9	6.7	5.9
8	6.0	7.1	5.0	6.8	8.0	5.8	7.5	7.9	6.6	8.9	8.7	8.4	7.2	6.4	6.5
$\bar{x}$	6.65	6.66	6.5	8.9	7.0	7.3	7.1	7.9	8.1	8.4	9.0	8.3	5.9	5.8	5.4

A lot of noises are produced from the machineries during tablet production from granules without lubricant, i.e. MgSt and Pruv®. Tablet weight variation is taken place due to picking and sticking. Moreover, capping and cracking are occurred due to difficulties in tablet ejection. Lot 2 with 0.25% MgSt ($\bar{x}$-bar = 8.3) is found to produce tablets closer to the specific hardness (8 SCU ± 3.0 %), whereas tablet hardness for lot 7 with 3% Pruv® ($\bar{x}$-bar = 7.6) is found to be closer to the specificity

(Table 4). In general, tablet hardness is decreased for using increased concentration of lubricant.

TABLE 4. TABLET HARDNESS (IN SCU) FOR TABLETS WITH DIFFERENT LUBRICANT CONCENTRATION.

Tablet no.	MgSt) Bin 1	Bin 2	Bin 3	Lot 2 (0.25% MgSt) Bin 1	Bin 2	Bin 3	Lot 3 (3% MgSt) Bin 1	Bin 2	Bin 3	Lot 4 (5% MgSt) Bin 1	Bin 2	Bin 3
1	11.2	10.8	10.3	9.6	8.8	9.9	6.1	4.5	3.9	6.3	7.9	6.9
2	9.5	13.4	8.5	9.2	7.3	6.9	4.9	4.9	5.8	9.3	5.9	7.7
3	11.3	7.7	11.4	7.3	8.2	6.9	4.9	4.1	5.0	6.3	6.2	8.5
4	8.6	7.9	10.1	8.9	7.6	8.2	5.0	4.9	4.0	8.9	5.8	7.4
5	10.2	9.2	5.9	7.2	9.3	9.2	4.2	4.7	5.6	8.0	6.5	5.5
6	6.5	8.9	11.5	10.1	8.9	7.8	6.6	6.2	5.0	7.2	6.3	8.7
7	8.7	12.4	11.3	6.6	7.4	9.3	5.1	6.0	4.7	7.4	7.7	6.6
8	7.1	6.3	10.9	8.3	8.2	7.3	5.0	5.8	5.5	6.7	6.6	7.1
x̄	9.1375	9.575	9.9875	8.4	8.2125	8.188	5.225	5.1375	4.9375	7.5125	6.6125	7.3
	Pruv®)			Lot 6 (0.25% Pruv®)			Lot 7 (3% Pruv®)			Lot 8 (5% Pruv®)		
	Bin 1	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**
1	7.7	10.1	13.1	7.2	7.8	6.9	8.2	7.9	7.5	7.1	6.2	3.9
2	10.8	10.9	6.7	5.8	7.2	5.3	7.8	6.9	7.9	5.6	5.9	6.1
3	11.1	11.0	9.7	5.2	7.9	8.5	7.7	7.1	8.2	5.1	5.1	5.8
4	8.9	7.8	8.8	5.4	6.2	5.8	7.1	5.8	8.8	6.2	5.3	5.1
5	8.2	12.0	8.0	7.2	8.8	5.4	7.9	7.8	6.8	5.3	5.0	4.9
6	7.2	10.8	10.1	7.4	5.8	8.2	6.8	7.1	7.6	5.9	5.5	5.0
7	12.0	11.5	9.8	5.2	6.6	5.8	7.3	7.9	7.4	6.1	4.6	5.0
8	10.6	9.7	11.0	8.2	5.8	5.3	8.1	6.8	7.8	4.8	5.1	6.3
x̄	9.6	10.5	9.65	6.45	7.01	6.4	7.6	7.2	7.75	5.8	5.3	5.26

According to the U.S.P., the accepted tablet disintegration time is 5-30 minutes for uncoated tablets. Disintegration time for lot 3 (3% MgSt), lot 4 (5% MgSt), lot 7 (3% Pruv®) and lot 8 (5% Pruv®) is found as higher (x̄-bar = 37, 64.9, 48.3 and 68.2, respectively) than the accepted value, which is acceptable for lot 2 (0.25% MgSt; x̄-bar = 7.3) and lot 6 (0.25% Pruv®; x̄-bar = 8.1) **Table 5**. The tablet hardness is observed as the lowest for using 3% MgSt (x̄-bar =

TABLE 5. TABLET DISINTEGRATION TIME (IN MIN.) FOR TABLETS WITH DIFFERENT LUBRICANT CONCENTRATION.

Tablet no.	Lot 1 (0% MgSt) Bin 1	Bin 2	Bin 3	Lot 2 (0.25% MgSt) Bin 1	Bin 2	Bin 3	Lot 3 (3% MgSt) Bin 1	Bin 2	Bin 3	Lot 4 (5% MgSt) Bin 1	Bin 2	Bin 3
1	4.1	3.5	3.9	7.1	5.8	7.6	36	38	35	66	59	61
2	4.3	5.1	3.0	6.5	8.1	7.1	29	41	43	63	65	70
3	6.1	5.3	7.3	7.0	6.9	7.8	40	34	38	68	71	65
4	3.3	5.9	5.1	7.9	8.0	5.9	35	31	34	62	67	61
5	4.5	6.7	9.0	7.3	7.3	8.1	37	42	39	58	65	69
6	6.3	5.5	4.0	7.5	7.9	7.8	39	38	37	65	68	65
x̄	4.8	5.3	5.4	7.2	7.3	7.4	36	37.3	37.7	63.7	65.8	65.2
	Lot 5 (0% Pruv®)			Lot 6 (0.25% Pruv®)			Lot 7 (3% Pruv®)			Lot 8 (5% Pruv®)		
	Bin 1	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 1**	**Bin 2**	**Bin 3**
1	8.0	5.3	3.2	8.1	8.0	8.1	45	55	46	68	65	73
2	5.9	3.0	4.1	8.3	8.5	8.0	48	51	56	66	69	68
3	6.1	4.5	4.0	8.1	8.0	8.0	41	46	55	69	71	66
4	4.2	3.4	5.8	8.1	7.8	8.0	50	41	47	73	77	59
5	3.0	5.8	7.2	7.9	8.1	8.1	46	51	46	70	68	66
6	3.0	3.2	5.2	8.0	8.0	7.8	44	53	49	64	68	68
x̄	5.03	4.2	4.9	8.09	8.07	8.0	45.7	49.5	49.8	68.3	69.7	66.7

5.1) and 5% Pruv® (x̄-bar = 5.5), which is highest for using no MgSt or Pruv® **(Table 4)**. Though lubricant is not used, disintegration time for lot 1 (0% MgSt) is found to be acceptable (x̄-bar = 5.2), which is found lower than the acceptable value for lot 5 (x̄-bar = 4.7) **[Table 5]**. Amongst all, lot 8 (5% Pruv®) shows the highest disintegration time **(Table 5)**. It reveals that an increase in concentration of the lubricant, Pruv® gives more increase in disintegration time than MgSt **(Table 5)**. Therefore, 0.25% MgSt can be used generally as a lubricant to produce tablets closer to the

studied specification. 0.25% Pruv® can also be used to produce tablets closer to the studied specification, especially to the disintegration time. On the other hand, granules with 3% Pruv® could produce tablets with the hardness closer to the specification, but the disintegration time would be out of the specification. Lubrication of granules is a surface phenomenon.

It is stated in previous reports that hydrophobic lubricants are more efficient than hydrophilic lubricants, which can also alter other physicochemical properties of tablets, such as hardness, disintegration time, etc.17-19. These influences are explained by the formation of a hydrophobic film around host particles giving a molecular coverage which makes the interparticle bound formation more difficult. Thus, the lubrication process is a combination of factors involving lubricant material, formulation to be lubricated, and the mechanical process, which results in the final dosage form. Hydrophilic lubricants can be used in special requirement where hydrophobic lubricants cannot be used due to problems of compaction, lubrication, stability or for biopharmaceutical reasons[8]. However, proper amount of lubricant for compression and lubrication time should carefully be maintained. Over lubrication may interfere with the bonding of particles resulting in weak tablets.

Increase of the lubricant concentration in tablet formulation can create a barrier between tablet granules or particles and the disintegrating liquid of interest, resulting in an increase of disintegration time of the tablet. Extended release drug formulations have become very popular, which can overcame some of the disadvantages of tablets such as fluctuations of the drug concentration in the plasma and on the site of action, frequency of dosing, drug toxicity, costs, etc.20. Different type and concentration of lubricants may be applied to produce extended release drugs. However, extensive exertions are required to fulfill this intention.

The lubricant sensitivity ratio for 0.25% MgSt is calculated as lower than 5% MgSt, which is lower than 3% MgSt **(Table 6).** Therefore, the granules are supposed to be more sensitive to 3% and 5% MgSt than 0.25% MgSt. On the other hand, lubricant sensitivity ratio for 3% Pruv® is calculated as lower than 0.25% Pruv®, whereas lubricant sensitivity ratio of 5% Pruv® is higher than 0.25% Pruv® **(Table 6).** It reveals that the order of sensitivity of the granules is 5% Pruv® > 0.25% Pruv® > 3% Pruv®. Data on the comparative sensitivity of lubricants to a specific material, such as ascorbic acid granules, are still not adequate, and therefore, further studies are required in this aspect.

TABLE 6. LUBRICANT SENSITIVITY RATIO (LSR) FOR TABLETS WITH DIFFERENT LUBRICANT CONCENTRATION.

% Lubricant	LSR
0.25% MgSt	0.14
3% MgSt	0.47
5% MgSt	0.25
0.25% Pruv®	0.33
3% Pruv®	0.24
5% Pruv®	0.44

Affect of compression forces:

Tablet properties can be varied for different types of tablet presses as they maintain various compression forces. The force exerted on the powder/ granule in the dies is, therefore, should very carefully be controlled to ensure that each tablet is perfectly formed within the specification. Tablet hardness and disintegration time increase with an increase in compression force (**Table 7** and **Table 8**). It is in consistent with the findings of the affect of compression forces on Aspirin tablets[21]and Cefuroxime Axetil[22].

Lot 1 under low compression force (≈ 1 ton) having the lowest tablet hardness ($\bar{x}$-bar = 2.3) and the lowest disintegration time ($\bar{x}$-bar = 1.3), whereas lot 3 under high compression force (≈ 4 – 4.2 tons) having the highest tablet hardness ($\bar{x}$-bar = 25.4) and the highest disintegration time ($\bar{x}$-bar = 64.3) [**Table 7** and **Table 8**]. The calculated $\bar{x}$-bar for tablet hardness and disintegration time for lot 2 under moderate compression force (≈ 2.5 tons) are found as 12.5 and 36.7, respectively (**Table 7** and **Table 8**).

It reveals that compression force has a much greater affect on the disintegration time than on the hardness. The affect of compression forces may be

used to produce extended release drugs that provide continuous supply of small but therapeutic amounts of active compound after administration at rates sufficiently controlled[20].

TABLE 7. TABLET HARDNESS (IN SCU) FOR TABLETS PRODUCED AT DIFFERENT COMPRESSION FORCES (C.F.).

Tablet no.	Lot 1 (C.F.: Low ≈ 1 ton)			Lot 2 (C.F.: Moderate ≈ 2.5 tons)			Lot 3 (C.F.: High ≈ 4 – 4.2 tons)		
	Bin#1	Bin#2	Bin#3	Bin#1	Bin#2	Bin#3	Bin#1	Bin#2	Bin#3
1	2.5	1.9	2.0	12.4	12.7	13.0	28.1	25.4	25.7
2	2.2	2.2	1.9	11.8	10.2	14.1	26.9	28.0	26.2
3	2.5	2.4	2.3	12.6	11.8	12.0	22.9	20.7	26.8
4	2.3	2.4	2.2	12.5	14.2	10.8	25.1	26.9	22.4
5	2.6	2.4	2.1	13.0	13.4	13.0	23.3	24.8	26.0
6	2.7	2.6	2.3	13.1	11.5	13.0	22.6	28.5	26.4
7	2.5	1.9	2.4	13.1	12.4	12.6	27.1	23.6	27.2
8	2.6	2.0	2.4	12.4	12.3	12.5	25.4	25.7	22.5
$\bar{x}$	2.5	2.23	2.2	12.61	12.3	12.63	25.2	25.45	25.4

TABLE 8. TABLET DISINTEGRATION TIME (IN MIN.) FOR TABLETS PRODUCED AT DIFFERENT COMPRESSION FORCES (C.F.).

Tablet no.	Lot 1 (C.F.: Low ≈ 1 ton)			Lot 2 (C.F.: Moderate ≈ 2.5 tons)			Lot 3 (C.F.: High ≈ 4 tons)		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	1.35	1.3	1.28	35.5	38.2	35.0	61.0	65.0	67.15
2	1.27	1.25	1.3	34.15	40.0	43.0	69.0	60.0	66.0
3	1.35	1.33	1.3	36.35	34.1	38.15	66.0	68.0	62.0
4	1.3	1.38	1.4	35.3	31.3	34.1	61.25	68.0	63.35
5	1.37	1.29	1.28	37.5	35.3	39.05	60.0	65.1	61.0
6	1.4	1.26	1.35	39.0	38.0	37.0	62.0	68.1	65.0
$\bar{x}$	1.34	1.31	1.32	36.3	36.2	37.7	63.2	65.7	64.1

REFERENCES:

1. Ankit G, Ajay B, Kumar KM and Neetu K: Tablet coating techniques: Concepts and recent trends. International Research Journal of Pharmacy 2012; 3:50-58.
2. Satpute MM and Tour NS: Formulation and in vitro evaluation of fast dissolving tablets of metoprolol tartrate. Brazilian Journal of Pharmaceutical Sciences 2013; 49:783-792.
3. Stage 6 Harmonization <616> Bulk density and tapped density of powders, USP Official December 1, 2012 (http://www.usp.org/sites/default/files/usp pdf/EN/USPNF/revisions/m99375-bulk density and tapped density of powders.pdf).
4. Shadangi M, Seth S and Senapati D: Critical roles play of magnesium stearate in formulation development of a highly soluble drug metformin hydrochloride. International Journal of Pharmaceutical Sciences and Research 2012; 3:1188-1193.
5. Venkateswarlu K and Shanthi A: Formulation and evaluation of sustained release Glipizide matrix. IOSR Journal of Pharmacy and Biological Sciences 2012; 2:17-23.
6. Late SG, Yu Y-Y and Banga AK: Effects of disintegration promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. International Journal of Pharmaceutics 2009; 365:4-11.
7. Bastos MdeO, Friedrich RB and Beck RCR: Effects of filler-binders and lubricants on physicochemical properties of tablets obtained by direct compression: A 22 factorial design. Latin American Journal of Pharmacy 2008; 27:578-83.
8. Li J and Wu Y: Lubricants in pharmaceutical solid dosage forms. Lubricants 2014; 2:21-43.
9. Jagtap S, Amrita B, Rina M and Jain D. Development of directly compressible ascorbic acid tablet using novel excipients. Journal of Advanced Scientific Research 2012; 3: 15-24.
10. Harbir K, Gurpreet S, Rana AC and Seema S: Pharmaceutical tablets and tablet compression machines: a review. Novel Science International Journal of Pharmaceutical Science 2012; 1:529-536.
11. Apeji YE, Oyi AR and Musa H: Formulation and evaluation of ascorbic acid tablets by direct compression using microcrystalline starch as a direct compression excipient. International Journal of Health Research 2011; 4:111-106.
12. Heber D: PDR for Herbal Medicines. Thomson Healthcare, Montvale, Forth Edition 2007.
13. Iqbal K, Khan A and Muzaffar A: Biological significance of ascorbic acid (Vitamin C) in human health- a review. Pakistan Journal of Nutrition 2004; 3:5-13.
14. Health Products and Food Branch Inspectorate, Good Manufacturing Practices (GMP), Guidelines – 2009 Edition, Version 2 (GUI–0001). Health Canada, 2011.
15. Anand C, Vidyasagar G and Rajmane M: Optimization of granule size and disintegrants on formulation of rapid dispersible tablets of tolfenamic acid. Journal of Drug Delivery & Therapeutics 2013; 3:31-40.

16. Herting MG and Kleinebudde P: Roll compaction/dry granulation: effect of raw material particle size on granule and tablet properties. International Journal of Pharmaceutics 2007; 338:110-118.
17. Potnuri NR, Rao DG, Rao SA, Reddy GM and Reddy SS: Effects of binders, lubricants and fillers on drug release from diltiazem hydrochloide bi-layered matrix tablets obtained by direct compression and wet granulation technique. International Journal of Pharmacy 2012; 2:117-128.
18. Alderborn, G: Comprimidos e compressão. In: Aulton ME, editor. Delineamento de Formas Farmacêuticas. Artmed, Porto Alegre, 2005:401-43.
19. Ghayas S, Sheraz MA, Anjum F and Baig MT: Factors influencing the dissolution testing of drugs. Pakistan Journal of Health Research 2013; 1:1-11.
20. Aulton M. Aulton's pharmaceutics – The design and manufacture of medicines. Elsevier, Edinburgh, Third Edition 2007.
21. Nokhodchi A, Bolourtchian N and Farid Dj: Effects of hydrophilic excipients and compression pressure on physical properties and release behavior of aspirin-tableted microcapsules. Drug Development and Industrial Pharmacy 1999; 25:711-716.
22. Basavaraj NK, Shamrez AM, Veerendra KN and Manvi FV: Effect of compression pressure on dissolution and solid state characterization of Cefuroxime Axetil. Journal of Analytical & Bioanalytical Techniques 2010; 1:112. doi:10.4172/2155-9872.1000112.

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