Affect of Wet Granulation on the Properties of Ascorbic Acid and Caffeine Tablets: A Comparative Study

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Abstract

Ascorbic acid (81mg) and caffeine (65mg) tablets have been produced by using selected granules obtained through wet granulation method. By following the standard methods, comparative studies have been carried out on the tablet properties, i.e. tablet weight, thickness, hardness, friability, disintegration time, and dosage uniformity by weight variation. Before producing granules by using wet granulation, the flowability of dry blends in absence of the lubricant has been evaluated by using the standard methods. Granules have also been studied for their flowability to observe the improvement in this aspect.

Keywords: Ascorbic acid; Caffeine; Tablets; Tablet properties; Wet granulation.

1. Introduction

Tablets are the most preferred oral dosage form due to their advantages over other pharmaceutical dosage forms to formulators as well as physicians and patients [1]. They are manufactured through 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. The powder particle or granule sizes, types and amounts of excipients, compression forces, etc. can affect on tablet properties during manufacturing of tablets [2,3]. Therefore, these factors should be considered and maintained accordingly to produce tablets with specified properties. Tablet properties, such as tablet weight, thickness, hardness, disintegration time, dissolution rate, etc. can vary significantly by changing these factors. 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. Flowability, relevant to compressibility, of powders or granules, which is influenced by particle or granule sizes and distribution, results in variations in tablet properties. The powder or granule flowability can be measured by using the Carr's Index (CI) that is evaluated by the ratio of the difference between the tapped bulk density and the aerated bulk density to the tapped bulk density [4,5]. It can also be measured by using Hausner ratio (HR) which is evaluated by the ratio of the tapped bulk density to the aerated bulk density [6,7]. Though many factors are involved for the variation of tablet properties, and many studies have been performed on these aspects, clear cut data are still not available. 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 [8-10]. Many physiological and mental disturbances can be occurred due to its lacking in the human body [10]. On the other hand, caffeine (1,3,7-trimethylxanthine), which is one of the most frequently ingested pharmacologically active substance, is a central nervous system stimulant and is a natural alkaloid found in the leaves and seeds of many plants [11-13]. It increases alertness, boosts up energy and elevates mood of most of the peoples [14]. It is a common adjuvant for analgesic drugs such as paracetamol and acetylsalicylic acid [15]. The complex nature of ascorbic acid and caffeine is made them to choice as the model of study. In the present study, ascorbic acid and caffeine granules are produced by using wet granulation method. Without using the lubricant, the flowability of the dry blends is studied before producing the granules. Flowability of the mixture of selected granules is also studied by using standard methods after their production. Tablets are produced from selected granules to observe their properties, i.e. tablet weight, thickness, hardness, friability, disintegration and dosage uniformity by weight variation. Thus, a comparative study is carried out to get an obvious initiative of ascorbic acid and caffeine tablet properties.

2. Materials and methods

2.1. 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, magnesium stearate [MgSt (Bärlocher)] was used to lubricate the granules.

2.2. Methods

All methods were performed according to the Good Manufacturing Practices (GMP) [16]. The temperature, relative humidity and air pressure were maintained at 20°±2°C, ≈20% and >5 Pascal, respectively.

2.2.1. Granulation

The formulation ingredients, used for producing ascorbic acid and caffeine granules, are presented in **Table 1**. Except the lubricant (MgSt), 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. Flowability of ascorbic acid and caffeine dry blends (without lubricant), obtained by using the standard methods, are presented in **Table 2**. 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 10.8% and 11.0% for ascorbic acid and caffeine granules, respectively. 28ml and 21ml of deionised water were used as extra during the wet massing to reach the capillary stage of ascorbic acid and caffeine granulation, respectively. 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].

2.2.2. Lubrication

Granules of Mesh 14, 18, 30, 40 and 60 were mixed together properly and blended with 0.5% MgSt by using the twin shell V-blender for 3 minutes.

2.2.3. 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. 50g of the granule 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: 324 ± 10.5mg (warning limit: ± 3.0%, action limit: ± 5.0%), tablet hardness: 8 Strong-Cobb Units (SCU) ± 3.0% [warning limit: ± 2 SCU, action limit: ± 3 SCU] and tablet dimension: 9mm diameter (tablet thickness warning limit: ± 3.0%, action limit: ± 5.0%). Compression pressure was kept fixed (1.5 – 2.2 tons) for the whole period of the final tablet production. The lot of the produced tablets was collected in three bins at a time interval of 1.0 minute. To remove excess powder on the surface, the produced tablets were dedusted by using a deduster (KEY Industries, USA).

2.2.4. Sample collection

2.2.4.1. Tablet weight determination

From each of the three bins of ascorbic acid and caffeine tablets, 10 tablets were collected randomly to determine the tablet weight by using an electronic digital balance (Precisa Instruments Ltd., Switzerland; TIPT ID # WS04003).

2.2.4.2. Tablet thickness determination

From each bin of ascorbic acid and caffeine tablets, 10 tablets were collected randomly to determine the thickness by using Vernier calliper.

2.2.4.3. Tablet hardness determination

Eight tablets were taken randomly from each bin of ascorbic acid and caffeine tablets to test hardness by using a hardness tester (Pharma Test, Germany; TIPT ID # TE0901).

2.2.4.4. Tablet friability determination

The tablet friability [17] was evaluated as the percentage weight loss of 20 tablets, collected randomly from each bin of ascorbic acid and caffeine tablets. The tablets were weighed accurately by using the electronic digital balance (Precisa Instruments Ltd., Switzerland; TIPT ID # WS04003) and placed in a friability tester (Scepter, Canada; TIPT ID # QC95/008). After 100 rotations (25 rotations/min, for 4 min), the tablets were removed and reweighed accurately. The tablets were then dedusted, and the loss in weight caused by fracture or abrasion was recorded as percentage friability [(Final weight – Initial weight/ Initial weight) × 100]. The accepted percentage friability was kept as ≥ 1%.

2.2.4.5. Tablet disintegration time determination

Six tablets were collected randomly from each of the three bins of ascorbic acid and caffeine tablets to determine the disintegration time[18] by using a tablet disintegration tester (HAAKE W13, Vankel, USA; TIPT ID # 94001). One tablet was placed in each tube of the basket rack assembly and a disc was added on each tube. The rack was immersed in deionised water at 37±2ºC and the apparatus was operated at a frequency rate between 29 – 32 cycles per min. The time (min) to disintegrate and fall of the tablets through the screen was recorded. The acceptable tablet disintegration time for uncoated tablets was kept as 5 – 30 min.

2.2.4.6. Dosage uniformity determination by weight variation

Ten tablets were selected randomly from each of the three bins of ascorbic acid and caffeine tablets to determine the dosage uniformity by weight variation [19] by using the electronic digital balance (Precisa Instruments Ltd., Switzerland; TIPT ID # WS04003). The Standard Deviation (SD) and percentage Relative Standard Deviation (%RSD = [SD/Mean] × 100) were evaluated accordingly, and the accepted %RSD was kept as ≥ 2%.

3. Results and discussion

The CI and HR of ascorbic acid and caffeine dry blends (without lubricant) and granules are presented in **Table 2**.

Tablet weights (in mg), thickness (in mm) and hardness (in SCU) of ascorbic acid and caffeine tablets are presented in **Table 3**, **Table 4** and **Table 5**, respectively.

Friability (in %) and disintegration time (in min) of ascorbic acid and caffeine tablets are presented in **Table 6** and **Table 7**, respectively.

Along with % of active, mean of active weight, SD, and %RSD, **Table 8** represents the dosage uniformity by weight variation of ascorbic acid and caffeine tablets.

The CI and the HR are the indication of powder or granule flowability relevant to compressibility [4-7]. **Table 2** is the evident that flowability of powder blends of ascorbic acid and caffeine increases due to granulation and flowability of granules is better than the blends. Therefore, it is better to use granules rather than powder blends to produce the tablets. It is reported that flowability increases with the decrease in granule size, and tablet weight variation decreases with the decrease in granule size [20]. However, it may vary due to the variation in formulation. Particle size of starting materials may have an intense affect on the granule size [21], relevant to flowability and compressibility. The mixture of granules of Mesh 14, 18, 30, 40 and 60, which is used in the present study, is assumed having good flowability and compressibility to produce ascorbic acid and caffeine tablets within specification.

At a constant compression force, tablet weight variation may be an indication of changes in die fill. The weight variation, influencing the drug uniformity, can be controlled by using mixture of granules of different sizes. 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, the void space may not be occupied properly during die fill due to the large sizes, resulting in tablet weight variation. According to **Table 3**, the average ($\bar{x}$) tablet weight of Bin 1 of ascorbic acid tablets is higher than Bin 2 and Bin 3, and $\bar{x}$ for tablet weight of Bin 3 is higher than Bin 2. The $\bar{x}$ for tablet weight of Bin 3 of caffeine tablets is found to be lowest (**Table 3**). However, mean of average ($\bar{x}$-bar) of tablet weight for ascorbic acid tablets is lower mean than that of caffeine tablets (329.0mg and 329.1mg, respectively). It reveals that flowability, relevant to compressibility, of ascorbic acid granules may better than caffeine granules during filling the die cavity. The $\bar{x}$ for tablet thickness of ascorbic acid tablets is found as lower than that of caffeine tablets (**Table 4**), which is also supported by the $\bar{x}$-bar (4.856mm and 5.198mm, respectively). Moreover, $\bar{x}$ for tablet hardness of ascorbic acid tablets are found as lower than that of caffeine tablets (**Table 5**). The $\bar{x}$-bar for tablet hardness of ascorbic acid and caffeine tablets is evaluated as 8.8 SCU and 9.9 SCU, respectively). Due to the hydrophilic nature of ascorbic acid [8,10], it can generally be postulated that the hardness of ascorbic acid tablets would be high for the ease of bonding, such as H-bonding, during the compression process. The less hardness of ascorbic acid tablets may occur due to the use of MgSt as a lubricant, which is hydrophobic in nature, and is widely used as a lubricant in tablet production at concentrations between 0.25 – 5.0% [22]. Hydrophobic lubricants are more efficient than hydrophilic lubricants, which can also alter other physicochemical properties of tablets, such as hardness, disintegration time, etc. [23-25]. 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 [26]. However, proper amount of lubricant for compression and lubrication time should carefully be maintained. In general, tablet hardness is decreased for using increased concentration of lubricant, and therefore, this aspect may be controlled by using appropriate amount of lubricant and lubrication time.

Friability (%) of both of the ascorbic acid and caffeine tablets are found as acceptable, i.e > 1% (**Table 6**). However, $\bar{x}$ for friability of ascorbic acid tablets is supposed to be lower than that of caffeine tablets (**Table 6**), which is in consistence of the hydrophilic nature of ascorbic acid [8,10] that may impart the ease of formation of more bonding during the compression process, resulting in increase of friability.

The disintegration time for ascorbic acid tablets is lower than that of caffeine tablets (**Table 7**), which is in accordance with the water-solubility and moisture sensitivity of ascorbic acid. The $\bar{x}$-bar for disintegration time of ascorbic acid and caffeine tablets is found as 13.88 min and 17.7 min, respectively. The higher disintegration time of caffeine tablet may be an impact of the lubricant amount and/or lubrication time. Over lubrication may interfere with the bonding of particles or granules 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. However, it is reported that in combination, caffeine can increase the solubility of paracetamol [27].

Various factors, such as flowability, particle or granule size, relative compression force, types of tablet presses, etc. can be involved in tablet weight variation, relevant to do dosage uniformity. The SD for % active is found as higher for ascorbic acid than that of caffeine tablets (**Table 8**). However, %RSD for both of the ascorbic acid and caffeine tablets are found as acceptable, i.e. > 2% (**Table 8**).

4. Conclusion

Ascorbic acid (81mg) and caffeine (65mg) tablets, produced through wet granulation process, have been found as differ from each other in various properties. Based on the formulations used in the present study, it is found that flowability, relevant to compressibility, of granules is better than powder blends of ascorbic acid and caffeine tablet formulations without the lubrication. In order to produce tablets with specification, it is therefore, better to use granules produced by wet granulation rather than dry blends used to produce tablets through other methods, such as direct compression. The tablet weight and thickness variation for ascorbic acid tablets has found lower than caffeine tablets. In comparison with caffeine tablets, tablet hardness of ascorbic acid tablets has found lower. Both of the ascorbic acid and caffeine tablets has found possess acceptable friability, friability of ascorbic acid tablets has found lower than caffeine tablets. Tablet disintegration time for ascorbic acid tablets has found lower than caffeine tablets. Though %RSD for dosage uniformity by weight variation has been found as acceptable, both of the ascorbic acid and caffeine tablets are found as acceptable, SD for ascorbic acid tablets has found as higher than caffeine tablets. Due to the adverse affects on the tablet properties, the size of granules, types and concentrations of lubricants and compression forces, which may considerably related to one another, should, therefore, be controlled carefully during the tablet production to preserve the drug properties. The findings, presented in this paper, will be helpful to design further studies for the production of tablets with specificity to overcome disadvantages of conventional tablets.

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Table 1. Formulation ingredients used for producing ascorbic acid and caffeine granules.

Component	Origin	TIPT Lot	Ascorbic acid (81mg)	Caffeine (65mg)
Ascorbic acid	Honson Ingredients	13A0101	25.0%	–
Caffeine	Jilin Shulan Synthetic Pharmaceutical Co. Ltd.	13A0206	–	25%
Lactose Monohydrate (Flowlac 100)	Wyndale	07B0511	50.0%	50.0%
Microcrystaline Cellulose (MCC 102)	Mingtai Chemical Co. Ltd.	13B0402	18.0%	18.0%
Polyplasdone-XL	International Specialty Products, Inc.	00B0411	3.0%	3.0%
Plasdone K90	International Specialty Products, Inc.	05B0502	3.5%	3.5%
Magnesium stearate	Bärlocher	T99B0211	0.5%	0.5%

"–" Refers "not applicable.

Table 2. Flowability of ascorbic acid and caffeine dry blends (without lubricant) and granules.

Ingredients	Bulk volume (ml)	Tapped volume (ml)	Bulk density (g/ml)	Tapped density (g/ml)	Carr Index (CI%)		Hausner Ratio (HR)	
					CI%	Flowability	HR	Flowability
Dry blend (without lubricant)								
Ascorbic acid	35.3	27.3	0.53	0.69	30.2	Poor	1.3	Poor
Caffeine	33.2	25.9	0.51	0.65	27.5	Slightly poor	1.27	Poor
Granule mixture (Mesh 14, 18, 30, 40 and 60)								
Ascorbic acid	31.4	26.5	0.49	0.58	18.4	Fair	1.2	Good
Caffeine	34.3	30.0	0.55	0.63	14.5	Good	1.15	Good

Table 3. Tablet weight (in mg) for ascorbic acid and caffeine tablets.

Tablet no.	Ascorbic acid (81mg)			Caffeine (65mg)		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	327	323	330	333	320	326
2	333	325	332	324	333	323
3	330	330	330	333	331	326
4	331	325	329	331	333	331
5	332	324	325	327	329	329
6	331	328	324	328	333	333
7	333	331	326	332	327	332
8	326	333	330	331	331	328
9	330	333	333	328	329	329
10	328	330	328	325	330	328
$\bar{x}$	330.1	328.2	328.7	329.2	329.6	328.5

Table 4. Tablet thickness (in mm) for ascorbic acid and caffeine tablets.

Tablet no.	Ascorbic acid (81mg)			Caffeine (65mg)		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	4.86	4.71	4.82	5.32	5.12	5.03
2	4.89	4.80	4.87	5.28	5.17	5.14
3	4.89	4.82	4.91	5.26	5.11	5.13
4	4.85	4.82	4.91	5.26	5.13	5.16
5	4.88	4.74	4,93	5.28	5.22	5.18
6	4.90	4.76	4.82	5.26	5.14	5.21
7	4.93	4.71	4.81	5.26	5.21	5.22
8	5.00	4.96	4.82	5.31	5.20	5.19
9	4.80	4.93	4.90	5.30	5.23	5.01
10	4.90	4.88	4.86	5.22	5.23	5.15
$\bar{x}$	4.89	4.813	4.865	5.275	5.176	5.142

Table 5. Hardness (in SCU) for ascorbic acid and caffeine tablets.

Tablet no.	Ascorbic acid (81mg)			Caffeine (65mg)		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	7.1	10.1	10.9	9.5	8.5	8.5
2	7.1	9.7	7.4	10.0	10.2	9.4
3	7.2	9.1	9.8	10.6	9.6	9.7
4	8.3	10.0	9.9	10.1	10.3	10.3
5	8.2	9.8	9.1	10.9	10.2	9.9
6	8.3	9.1	9.5	9.6	11.0	10.0
7	9.4	7.1	9.1	9.8	9.2	10.3
8	8.2	7.9	7.9	10.1	9.6	9.8
$\bar{x}$	7.98	9.1	9.2	10.08	9.83	9.74

Table 6. Friability of ascorbic acid and caffeine tablets.

Bin no.	Ascorbic acid (81mg)				Caffeine (65mg)			
	Initial weight (g)	Final weight (g)	Weight loss (%)	$\bar{x}$	Initial weight (g)	Final weight (g)	Weight loss (%)	$\bar{x}$
1	6.666	6.654	0.18	0.115	6.587	6.570	0.26	0.22
2	6.635	6.634	0.015		6.517	6.501	0.25	
3	6.717	6.707	0.15		6.590	6.580	0.15	

Table 7. Disintegration time (in min) for ascorbic acid and caffeine tablets.

Tablet no.	Ascorbic acid (81mg)			Caffeine (65mg)		
	Bin 1	Bin 2	Bin 3	Bin 1	Bin 2	Bin 3
1	15.9	15.5	12.5	15.6	17.1	17.3
2	11.7	12.6	17.1	17.3	21.0	17.3
3	13.3	12.1	12.4	18.5	17.5	18.4
4	14.8	15.3	16.2	18.1	17.3	15.8
5	13.2	12.7	12.3	17.5	18.1	18.1
6	13.1	16.4	12.7	18.6	17.5	17.5
$\bar{x}$	13.67	14.1	13.87	17.6	18.1	17.4

Table 8. Dosage uniformity by weight variation of ascorbic acid and caffeine tablets.

Tablet no.	Tablet weight (mg)	Active weight (mg)	% of Active	Mean of Active weight	SD	%RSD
Ascorbic acid (81mg)						
1	332	83.0	102.5	81.58	0.88	1.08
2	328	82.0	101.2			
3	331	82.75	102.2			
4	327	81.75	100.9			
5	325	81.25	100.3			
6	327	81.75	100.9			
7	324	81.0	100.0			
8	326	81.5	100.6			
9	321	80.25	99.1			
10	322	80.5	99.4			
Caffeine (65mg)						
1	328	65.8	101.2	65.72	0.49	0.75
2	329	66.0	101.5			
3	324	65.0	100.0			
4	329	66.0	101.5			
5	329	66.0	101.5			
6	324	65.0	100.0			
7	332	66.6	101.5			
8	327	65.6	100.9			
9	326	65.4	100.6			
10	328	65.8	101.2			