Comparison of Various Fillers on the Physical Properties of Compounded Tablets

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Abstract

Compounded tablets are solid dosage forms that contain active pharmaceutical ingredients that are usually formulated with suitable pharmaceutical excipients. Fillers are inert ingredients used as bulking agents that can affect the physical properties of the final compounded tablet. The objective of this study was designed to compare various types of fillers on the physical properties of compounded tablets. The fillers used in this study were starch, lactose monohydrate, microcrystalline cellulose, GranuLac 200, SorboLac 400, and CombiLac. The wet-granulation method was used to compound the tablets, and the physical characterization of the compounded tablets was evaluated for their weight variation, hardness, thickness, friability, and disintegration. Formulation 2a, which incorporated 50 mg of *A. muricata* extract and 200 mg of starch as a filler, was chosen as the most optimum formulation as it produced the best physical characterization test results when compared to other formulations. Formulation 2a disintegrated within the specified time limit of 7.41 minutes while having the desired hardness and friability of 5.52 kg and 0.67%, respectively. Moreover, it produced a uniform weight and thickness. Formulations 1, 2, and 7 possessed promising properties, suggesting its potential for compounding tablets containing *A. muricata* extract as a tablet supplement. These findings warrant further thorough investigations.

Keywords: Compounded Tablets, Bulk Density (BD), Tapped Density (TD).

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INTRODUCTION

Herbal supplements are available in a variety of dosage forms, with tablets having the most potential when compared to other dosage forms since they are more compact, lighter, less expensive, and easier to pack, carry, and store. The physical properties of pharmaceutical powders are critical in the pharmaceutical industry[1] due to the fact that products must achieve optimum powder flow to obtain end products with the following: acceptable content uniformity, weight variation, and physical consistency.[2] Various methods are recommended and are widely used in industrial applications for determining the flow properties of powders, including[2]: measuring the angle of repose, bulk density (BD), tapped density (TD), Carr's index (CI), and Hausner ratio (HR).

Following the completion of the manufacturing process, final product quality-control (FPQC) tests (i.e., weight variation, friability, hardness, thickness, disintegration tests) for pharmaceutical compounded tablets are performed in

accordance with U.S Pharmacopeia [3] specifications to determine whether the quality parameters are within the acceptable limits. [4]

Fillers (or diluents) are pharmaceutical ingredients that are not pharmacologically active are essential in tablet preparations. Fillers consist of heterogeneous groups of substances intended to constitute the necessary amount of the tablet when the drug dosage itself is insufficient to generate the bulk. The range of fillers in a pharmaceutical formulation may differ from 5% to 80%.[5] As one of the most well-known excipients, starch is a classic excipient that is utilized in a variety of pharmaceutical formulations. Depending on the implementation, certain starches can be employed as disintegrants, fillers, or binders.[6] As a diluent, starch is used to promote appropriate mixing processes in manufacturing operations, especially by the wet-granulation process.[7] Besides starch, microcrystalline cellulose (MCC) is another filler that is commonly used in pharmaceutical applications, mainly as a binder or diluent in oral tablets and capsules, where it is used in both wet-granulation and direct-compression processes. MCC is extremely compact, and its integration can add strength and robustness to tablets.[8]

GranuLac 200 and SorboLac (400 types) fillers consist of fine, sharp-edged lactose monohydrate 17-µm particles with cohesive powder properties that can be beneficial during granulation processes. The advantages of using GranuLac 200 are the same as those of SorboLac.[4] Milled alpha-lactose monohydrate grades have been historically used as diluents in dry- and wet-granulation processes by numerous global and regional pharmaceutical manufacturers.[4] CombiLac is an integrated, lactose-based, co-processed excipient. The composition of Combilac is 70% of α-lactose silicon dioxide, monohydrate; 20% MCC; and 10% white, native corn povidone. CombiLac shows improved compaction property and friability compared to an equivalent admixture of individual ingredients.[9]

Materials and Methods

Materials

Starch (Lot No. 9005-25-8) and lactose monohydrate (Lot No. 20180507) were purchased from Techub Allied Services, Bukit Bintang, Kuala Lumpur, Malaysia. Microcrystalline cellulose (Lot No. 18050801), Magnesium stearate (Lot No. 20190704), and Colloidal silicon dioxide (Lot No. 20120715) were obtained from Pro Prima, Petaling Jaya, Selangor, Malaysia. SorboLac 400 (Lot No. L103842816A545), GranuLac 200 (Lot No. L1004 A4020), and CombiLac (Lot No. 5610230545) were purchased from MEGGLE Pharma, Wasserburg am Inn, Germany. Povidone (Lot No. 9003-39-8) was supplied from Bio3 Scientific, Puchong, Selangor, Malaysia.

Methods

The conventional compressed, uncoated tablet was prepared using the wet-granulation method. The weight of excipients was kept constants for all formulations, except for the fillers. Five different fillers were used in this study, namely: Starch, SorboLac 400, CombiLac, Microcrystalline cellulose and GranuLac 200.

In this study, each filler had 3 different batches with concentrations of 150 mg, 200 mg, and 250 mg. Lactose monohydrate, which acts as an additional filler, was added to make up a total weight of 300 mg for one tablet. The list of all formulations was presented in Table 1.

Table 1. Formulations of Blank Tablet Using Different Types of Fillers

Formulation	**Filler (mg)**	**Concentration of each filler (mg)**	**Binder (mg)**	**Disintegrant (mg)**	**Glidant (mg)**	**Lubricant (mg)**
F1	Starch	150	7	24	1.2	4
F2		200	7	24	1.2	4
F3		250	7	24	1.2	4
F4	SorboLac 400	150	7	24	1.2	4
F5		200	7	24	1.2	4
F6		250	7	24	1.2	4
F7	Combi Lac	150	7	24	1.2	4
F8		200	7	24	1.2	4
F9		250	7	24	1.2	4
F10	Microcrystalline cellulose	150	7	24	1.2	4
F11		200	7	24	1.2	4
F12		250	7	24	1.2	4
F13	GranuLac 200	150	7	24	1.2	4
F14		200	7	24	1.2	4
F15		250	7	24	1.2	4

For each type of filler, a total of 50 tablets were manufactured. All excipients were weighed, crushed, and sieve-screened throughout the wet-granulation process. Except for magnesium stearate, all the excipients were combined. They were sieved again after being pounded in a pestle mortar. The povidone solution was then gradually added and stirred again to ensure that the mixture was thoroughly mixed and formed a damp mass. The damp mass was sieved through a number 18 sieve to form granules and was dried in an oven at 40ºC for 2 hours. The dried granules were screened through number 18 sieve again and were mixed with magnesium stearate. Then, the tablet powder flowability was analyzed using angle of repose, Hausner ratio (HR), and Carr's index (CI).

Angle of Repose

The angle of repose was measured by fixed funnel method, determined by Equation 1.

$$\tan \theta = \frac{\text{Height}}{\text{Radius}}$$

θ = Angle of Repose

Equation 1 (Angle of repose)

Hausner Ratio and Carr's Index

Of each excipient, 30 g was placed in a measuring cylinder to determine the bulk density (BD). The volume of the excipients was then measured, and the BD was calculated using Equation 2. Meanwhile, a mechanical tapped density tester was utilized to determine the tapped density (TD). The *United States Pharmacopeia (USP)* Method I was utilized, which involved subjecting the mix to 500 tappings and 750 tappings at 300 drops/minute. Following the tappings, the volume of the excipient was measured, and the TD was calculated using Equation 3.[10] HR and CI were calculated using bulk and tapped densities. They represented the interparticle friction state and were calculated using Equations 4 and 5, respectively.

$$\text{Bulk Density} = \frac{\text{Mass (g)}}{\text{Bulk Volume (ml)}}$$ Equation 2 (Bulk Density)

$$\text{Tap Density} = \frac{\text{Mass (g)}}{\text{Tap Volume (ml)}}$$ Equation 3 (Tapped Density)

$$\text{Hausner Ratio} = \frac{\text{Tap Density}}{\text{Bulk Density}}$$ Equation 4 (HR)

$$\text{Carr's Index} = \frac{\text{(Tapped density-Bulk density)}}{\text{Tapped density}} \text{ X } 100\%$$ Equation 5 (CI)

The dried granules were compressed into 300-mg tablets using a Single Stroke Tablet Press Machine (Type SSTP-12; Shakti) with appropriate compression pressure. Formulated tablets should be tested to determine the quality of the formulations. Tablet testing procedures included weight uniformity, thickness, hardness, friability, and disintegration testing.

Hardness

For hardness testing, ten tablets were randomly picked from the batch. Each tablet was placed between two anvils of the hardness test machine. Force was then applied to the anvils and the crushing strength that caused the tablet to break was recorded. Based on the *USP*, tablet hardness should be between 5 kg/cm^2 and 10 kg/cm^2 and with a result limit of ±5%.[11]

Weight Variation

The tablet weight variation was calculated using Equation 2.6, where 20 tablets were weighed individually. As per the *USP*, the test is considered as pass if no more than two of the individual masses deviate from the average mass by more than 7.5% for tablets weighing 130 to 324 mg and 5% for tablets weighing more than 324 mg. Furthermore, no deviations must be greater than twice that percentage.[11]

$$Weight\ Variation\ = \frac{(Iw-Aw)}{Aw} X\ 100\% \quad \text{Equation 2.6}$$

(Weight Variation)

Iw = Individual weight of tablet

Aw = Average weight of tablet.

Thickness

A tablet's thickness should be controlled within 5% or less of the average thickness. A random sample of 10 tablets was taken.[12] The tablet thickness was then measured using a tablet tester (Model EBT-2PL; Electrolab).

Friability

20 tablets were weighed and placed in the Roche friabilator for a friability test at 25 rpm for 4 minutes, which was then operated for 100 revolutions.[11] The tablets were then dedusted and weighed again. The differences in the two weights were used to calculate the percentage of weight loss using Equation 7. As stated by the *USP*, typical compressed tablets with a weight loss of less than 0.5% to 1% (after 100 revolutions) are normally deemed appropriate.[11]

$$\text{Friability} = \frac{(Iw-Fw)}{Iw} X\ 100\%$$

Equation 7 (Percentage of Weight Loss)

Iw = Total Initial weight of tablets

Fw = Total final weight of tablets

Disintegration

If all the tablets disintegrate completely and all particles pass through the 10-mesh screen in the time specified, the tablets is considered as comply to *USP* standards. If any residue remains, it must have a soft mass without a palpably firm core.[11] Based on the *British Pharmacopeia (BP)*, the maximum disintegration time for uncoated tablets is 15 minutes.[13]

Results and Discussion

Analysis of Blank Tablet Powder Flowability

Flow properties of the tablets was determined by measuring the powder characteristics such as angle of repose, bulk density, tapped density, HR, and CI. Table 2 shows the evaluation of precompression parameters of granules for blank tablet formulations.

Table 2. Evaluation of Precompression Parameters of Granules for Blank Tablet Formulation

Formulation	Angle of repose (°)	Hausner Ratio	Carr's Index (%)
F1	1.20	1.20	16.7
F2	1.28	1.28	21.1
F3	1.40	1.40	28.6
F4	1.44	1.44	30.5
F5	1.35	1.35	26.1
F6	1.33	1.33	25.0
F7	1.13	1.13	11.8
F8	1.07	1.07	6.2
F9	1.07	1.07	6.2
F10	1.20	1.20	16.7
F11	1.07	1.07	6.2
F12	1.00	1.00	0.0
F13	1.25	1.25	20.0
F14	1.29	1.29	22.7
F15	1.35	1.35	26.1

Based on the *USP*, the powder flowability improves when the angle of repose approaches 0º. The angle of repose of Formulations 1, 2, 7, 8, 9, 10, 11, and 12 indicated an excellent powder-flow property. The angle of repose of Formulations 3 and 13 suggested a good powder-flow property. Meanwhile, the angle of repose of Formulations 4, 14 and, 15 suggested a fair powder-flow property. Lastly, the angle of repose of Formulations 5 and 6 indicated a passable powder-flow property.

In terms of the HR, closer values to 1.00 indicate a better powder-flow ability. According to the results tabulated in Table 3, only Formulations 8, 9, 11, and 12 demonstrated an excellent flow property. Formulation 7 was considered to have a good powder-flow property, whereas Formulations 1, 10, and 13 were rated to have a fair powder-flow property. Formulations 2, 6, and 14 were considered to have a passable powder-flow property. Lastly, four formulations, demonstrated by Formulations 3, 4, 5, and 15 produced a poor flow property.

The closer the reading of CI to 10 or below than 10, the better the powder flowability. The CI of Formulations 8, 9, 11, and 12 were considered to have an excellent powder-flow property. The CI of Formulation 7 indicated a good powder-flow property, whereas Formulations 1, 10, and 13 showed a fair powder-flow property. Formulations 2, 6, and 14 suggested a passable powder-flow property and lastly, Formulations 3, 4, 5, and 15 indicated a poor powder-flow property.

Based on the HR and CI results, Formulations 8, 9, 11, and 12 gave an excellent powder-flow property. The integration of MCC in those four formulations, as indicated by Odeniyi,[14] was one of the elements that may contribute to the outstanding powder-flow characteristic. When compared to lactose monohydrate, the combination using MCC as a diluent was shown to be more porous and less compressible. It had high flowability and low cohesion as a result of its less compressible nature. The inclusion of MCC should theoretically enhance the flowability of powder mixes. When using MCC in Formulations 7 and 10, however, it was discovered that the concentration used was insufficient to provide a satisfactory flow property. It has also been claimed that raising the diluent content in the powder combination has a substantial impact on the flow characteristics of binary mixes. As a result, when switching from one diluent to another, an evaluation of the new diluent concentration was required to determine its impact on the mixtures' flow characteristics.

Quality-control Tests of Blank Tablets

The formulated blank tablets containing different types of fillers with three different concentrations can be evaluated by various methods such as the hardness, weight variation, thickness, friability, and disintegration tests. Table 3 shows the results of the produced tablet valuation.

Table 3. Tablet Evaluation

Formulation	**Hardness (kg)**	**Average Weight (mg)**	**Thickness (mm)**	**Friability (%)**	**Disintegration (sec)**
F1	06.314 ± 0.045	299.0 ± 7.379	4.177 ± 0.080	0.64	547.33 ± 1.63
F2	05.183 ± 0.098	300.0 ± 8.165	4.218 ± 0.027	0.67	434.33 ± 1.03
F3	03.077 ± 0.120	298.0 ± 7.888	4.230 ± 0.031	0.98	229.33 ± 1.03
F4	18.325 ± 0.209	302.0 ± 7.888	4.161 ± 0.038	0.00	389.50 ± 0.84
F5	14.578 ± 0.268	301.0 ± 5.677	4.194 ± 0.015	0.31	462.00 ± 2.45
F6	12.384 ± 0.230	301.0 ± 8.756	4.164 ± 0.019	0.33	530.33 ± 2.16

F7	06.011 ± 0.177	300.0 ± 6.667	4.188 ± 0.017	0.66	150.00 ± 1.79
F8	09.002 ± 0.138	299.0 ± 8.756	4.194 ± 0.018	0.66	110.50 ± 1.22
F9	13.764 ± 0.298	299.0 ± 8.756	4.206 ± 0.011	0.66	81.00 ± 2.45
F10	11.060 ± 0.133	301.0 ± 5.677	4.168 ± 0.023	0.33	75.00 ± 1.67
F11	13.277 ± 0.266	303.0 ± 8.233	4.159 ± 0.024	0.33	54.00 ± 1.79
F12	15.699 ± 0.183	298.0 ± 7.888	4.183 ± 0.028	0.33	36.50 ± 1.05
F13	11.033 ± 0.125	300.0 ± 6.667	4.238 ± 0.034	0.31	629.50 ± 0.55
F14	10.864 ± 0.289	302.0 ± 7.888	3.965 ± 0.038	0.60	449.00 ± 0.89
F15	10.474 ± 0.220	299.0 ± 5.677	4.071 ± 0.034	0.64	244.83 ± 0.75

Hardness

Based on Table 3, only Formulations 1, 2, and 7 passed the tablet hardness test since they showed hardness within 5 kg/cm^2 to 10 kg/cm^2. The hardness of blank tablets containing different types of fillers with three different concentrations is tabulated in Table 3. The result shows that a higher concentration of starch as the filler reduced the tablet hardness. Based on the study done by Lawal,[15] cornstarch compacts exhibited a low crushing strength, indicating that the compacts were weak in the structure. Meanwhile, the higher the concentration of SorboLac 400 and GranuLac 200, the lower was the tablet hardness. Based on the study done by Duangjit, Itharat, & Kraisit,[16] an increase in the lactose content resulted in a slight decrease in hardness and thickness. The only difference between SorboLac 400 and GranuLac 200 was their particle size, which was smaller in SorboLac 400 than in GranuLac 200.

This might explain why SorboLac 400's tablet hardness was higher than that of GranuLac 200. Based on the study done by Rajani, Kumar, & Jaya,[17] granule size plays an important role in the hardness of tablets. Generally, the tablet hardness decreases as the granule size rises. Tablets with higher concentrations of CombiLac and MCC (as the filler) will have a higher hardness. Based on the study done by Saigal et al, MCC produced tablets with high hardness levels and excellent compression.

When comparing the hardness of tablets made using CombiLac and MCC, MCC had a greater hardness than CombiLac. The tablet hardness was lower than MCC alone because CombiLac is comprised of a combination of starch, lactose monohydrate, and MCC. This is due to the fact that starch and lactose monohydrate can make tablets softer. According to Hasegawa,[18] the impact of MCC on tablet hardness diminishes as the amount of lactose increases.

Weight Variation

In this study, the formulated weight for the blank tablets containing different types of fillers with three different concentrations was 300 mg. The tablet passed the *USP*'s weight-variation test for uncoated tablets with an average weight of 130 mg to 324 mg if no more than two individual masses deviated from the average mass by more than 7.5% and none by more than twice that proportion.

Based on the results in Table 3, none of the tablets weighed over or lower than 7.5% from the mean. This indicates that the numerous types of fillers employed in varied concentrations had an insignificant effect on the weight. Furthermore, this ensured consistency during the die-filling process, resulting in a similar weight for all blank tablets.

Thickness

Any change in tablet thickness should not be visible to the unaided eye in order to preserve customer acceptability and simplify packing. Tablet thickness fluctuates with variations in die fill and tablet weight under continuous compressive stress. There is no difference in the variation between the die fill and the "variable" die fill.

To achieve a consistent tablet thickness, the compressive force, the die fill, and the tablet weight were all kept constant in this investigation. According to the results provided in Table 3, all blank tablet formulations passed the thickness test, with none of the tablet thicknesses being more than 5% thicker or thinner than the thickness mean.

Friability

For friability testing, a range of 0% to 1% was considered acceptable. According to the table 3, the percentage of weight reduction for all formulations is within the permitted range of 0% to 1%. According to Hartesi et al,[7] unmodified starch does not compress well and, when utilized in large quantities, tends to enhance tablet friability and cause capping. Furthermore, according to Lawal,[15] maize starch compacts have a high friability, indicating that their structure is fragile. This explains why, as the amount of carbohydrate in the diet increases, the proportion of weight loss increases.

According to a 2015 study by Duangjit et al,[16] the friability of banana extract tablets rose as the lactose concentration increased. The higher the concentration of lactose monohydrate in SorboLac 400 and GranuLac 200, the more friable the tablet. Furthermore, GranuLac 200 has a larger particle size than SorboLac 400. This might explain why GranuLac 200 is more friable than SorboLac 400. According to Rajani et al,[17] as the granule size grows, the friability of the tablets increases. MCC creates tablets with low friability levels and good compression, according to research by Saigal et al.[19] This might explain why, as the concentration of MCC increased, the tablet friability remained low. Meanwhile, CombiLac provided a consistent percentage of weight reduction, although not as low as MCC since CombiLac also contains lactose monohydrate and starch, which may have contributed to an increased tablet friability.

Disintegration

According to the *BP*, uncoated tablet disintegration durations must be under 15 minutes (900 seconds). According to the findings, all tablet formulations passed the test since they dissolved entirely within 15 minutes. When the disintegration times of various formulations are compared, it is discovered that the higher the starch concentration, the faster the disintegration time. According to a study conducted by Hartesi et al,[7] tablets manufactured using official maize starch disintegrant had the quickest disintegration times. However, all tablets containing experimental starches passed the official disintegration time test.

In a study conducted by Duangjit et al,[16] the disintegration time of banana extract tablets rose as the lactose concentration increased. In this current study, the disintegration time decreased as the concentration of GranuLac 200 increased. Meanwhile, the longer the disintegration period, the higher the SorboLac 400 concentration. Despite the fact that both SorboLac 400 and GranuLac 200 are made of lactose monohydrate, the particle sizes of the two products differ, resulting in differing disintegration times. Keleb et al[20] found that granulating lactose monohydrate with a high particle size resulted in weak granules.

MCC is commonly used as a disintegrant in both dry and wet granulation processes. MCC improves medication solubility by accelerating tablet disintegration, offers the maximum degree of disintegration force at low usage levels, and uses dual disintegration processes of wicking and swelling for more rapid disintegration, according to research by Saigal et al.[19] This might explain why the shorter disintegration period resulted in higher concentrations of MCC and CombiLac. Because CombiLac contains not only MCC but also starch and lactose monohydrate, the disintegration time was greater than when MCC was used alone.

CONCLUSION

This study was done to compare various types of fillers on the physical properties of a blank tablet that would be chosen and incorporated into a tablet containing *A. muricata* extract. Formulations 1, 2, and 7 are the only formulations that passed all of the tests. This was because the physical tests done for these formulations met all the criteria specified. It was found that the type of filler and different concentration of filler would affect the physical characterization of tablets.

Selecting the right filler and filler concentration for tablet dosage-form formulations were critical to achieving the necessary physicochemical characteristics. As a result, Formulations 1, 2, and 7 may be appropriate formulations for future tablet formulations incorporating A. muricata extract as a tablet supplement.

REFERENCES

Sarraguça MC, Cruz AV, Soares SO et al. Determination of flow properties of pharmaceutical powders by near infrared spectroscopy. J Pharm Biomed Anal. 2010; 52(4): 484–492.

Alves P, Rodrigues S, Guedes IF. A review on biological activitie4s and medicinal properties of clerodendrum. Innovare academic sciences. Int J Pharm Pharm Sci. 2014; 6(10): 19–22.

United State Pharmacopoeia 40-National Formulary 35. (2017). Thirty Five edition. United State Pharmacopoeia Convention, Stationery Officer, USA.

MEGGLE Pharma. Technical brochure. Milled and Sieved. MEGGLE crystalline alpha-lactose monohydrate grades: Milled and sieved. [MEGGLE Website.] 2014. Available at: pharmaceutical-networking.com. Accessed March 3, 2022.

Nagpal N, Kaur P, Kumar R et al. Pharmaceutical diluents and their unwanted effects: A review. Bull Pharm Res. 2016; 6(2): 45–49.

Rashid I, Al Omari M, Badwan A. From native to multifunctional starch-based excipients designed for direct compression formulation. Starch/Staerke. 2013; 65(7–8): 552–571.

Hartesi B, Sriwidodo, Abdassah M et al. Starch as pharmaceutical excipient. Int J Pharm Sci Rev Res. 2016; 41(2): 59–64.

Al-Snafi AE. The pharmacology of Apium graveolens – A review. IJPRS. 2014; 3(1): 671–677.

MEGGLE Pharma. Technical brochure. MEGGLE co-processsed lactose grades for direct compression: CombiLac®. [MEGGLE Website.] 2015. Available at: pharmaceutical-networking.com. Accessed March 3, 2022.

Kumadoh D, Kwakye K. Dosage forms of herbal medicinal products and their stability considerations – An overview. JCR. 2017; 4(4): 1–8.

United States Pharmacopeial Convention, Inc. United States Pharmacopeia 38–National Formulary 33. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2010.

Chee TL, Majid FA, Iqbal MC. Development of DiabecineTM tablet and confirmation of its physical properties and pharmaceutical safety analysis. Sains Malaysiana. 2017; 46(4): 597–604.

British Pharmacopoeia Commission. British Pharmacopoeia. 13th Edition. Great Britain; 2013.

Odeniyi M, Abobarin T, Itiola O. Compressibility and flow characteristics of binary mixtures of metronidazole with lactose and microcrystalline cellulose. Farmacia. 2008; 56(6): 625–638.

Lawal MV. Modified starches as direct compression excipients – effect of physical and chemical modifications on tablet properties: A review. Starch/Staerke. 2019; 71(1–2): 1–10.

Duangjit S, Itharat A, Kraisit P; HTM-2015. Relationship between lactose and microcrystalline cellulose as diluents on physical characteristics of banana extract tablet using computer program. The International Conference on Herbal and Traditional Medicine. 2015: 251–258.

Nagpal N, Kaur P, Kumar R et al. Pharmaceutical diluents and their unwanted effects: A review. Bull Pharm Res. 2016; 6(2): 45–49.

Hasegawa M. Direct Compression: Microcrystalline cellulose grade 12 versus classic grade 102. Pharm Tech. 2002; 26(5): 50–60.

Saigal N, Baboota S, Ahuja A et al. Microcrystalline cellulose as a versatile excipient in drug research. 2009; 1(1): 6–12.

Keleb EI, Vermeire A, Vervaet C et al. Extrusion granulation and high shear granulation of different grades of lactose and highly dosed drugs: A comparative study. Drug Dev Ind Pharm. 2004; 30(6): 679–691.