The importance of binder moisture content in Metformin HCL high-dose formulations prepared by moist aqueous granulation (MAG)

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The aim of this study was to evaluate binders to improve the flowability of granulates and compactability of Metformin HCL (Met) using the moist aqueous granulation (MAG) process. The effect of the binder moisture content on granulate and tablet quality was also evaluated. Vinylpyrrolidone–vinyl acetate copolymer (Kollidon VA64 fine: VA64), polyvidone (Povidone K12: PVP), hydroxypropyl cellulose (HPC SSL SF: HPC) and hydroxypropyl methylcellulose (Methocel E5 LV: HPMC) were evaluated as binders. These granulates, except for HPMC, had a lower yield pressure than Met active pharmaceutical ingredient (API). HPMC Met was not sufficiently granulated with low water volume. No problems were observed with the VA64 Met granulates during the tableting process. However, HPC Met granulates had a bowl-forming tendency, and PVP Met granulates had the tendency to stick during the tableting process. These bowl-forming and sticking tendencies may have been due to the low moisture absorbency of HPC and the high volume of bound water of PVP, respectively. VA64 Met granulates had the highest ambient moisture content (bulk water, bound water) and moisture absorbency. It was concluded that the type of binder used for the Met MAG process has an impact on granulate flow and compactibility, as well as moisture absorbency and maintenance of moisture balance.

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1. Introduction

The selection of excipients is very important for the formulation development of solid oral dosage forms. The fundamental function of excipients is to act as a diluent, or filler. Further functions include the controlled release of the active pharmaceutical ingredient (API), permeability enhancement to aid absorption of the API, stabilization of the API, and improved manufacturability of the formulation [13]. Many types of excipients are available to improve powder flow, compactibility, and disintegration [28].

The selection of excipient is especially critical for high-dose formulations, due to the need to minimize the volume of excipient utilized to keep the tablet size acceptable for swallowing despite the increased drug load. There have been previous reports evaluating the properties and considerations necessary for high-dose formulations.

Cantor et al. evaluated the physicochemical properties of high drug load formulations manufactured using conventional wet or foam granulation process. Acetaminophen (APAP), Metformin HCL (Met), and Aspirin were used as model APIs (80% w/w). According to their results, foam granulation improved the plasticity of granulates containing a brittle drug such as APAP. On the other hand, foam granulation did not enhance the plasticity for viscoelastic material such as Met [5].

Barot et al. described the feasibility of directly compressing Met by the spray-drying process in the presence of polymer. Their results showed that the use of polyvidone (PVP) during the spray-drying process resulted in better properties of the Met formulation [1].

Uroš et al. evaluated the hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) polymer threshold amount for robust drug release from matrix tablets containing high dose levetiracetam (BCS class I compounds). The evaluation of the amount of HPC and HPMC achieved a good correlation of in vitro results and in vivo results [11].

Tan et al. evaluated the combination of hydrophilic binder and hydrophobic binder on the dissolution profile of the verapamil high dose tablet produced by direct-molding melt granulation process with the twin-screw extruder design of experiment (DOE) approach. The hydrophilic binder had a significant impact on the release profile of verapamil [27].

Lakshman et al. evaluated the use of the melt granulation (MG) process to enhance the tableting properties of poorly compactable (Met), and Aspirin were used as model APIs (80% w/w). According to their results, foam granulation improved the plasticity of granulates containing a brittle drug such as APAP. On the other hand, foam granulation did not enhance the plasticity for viscoelastic material such as Met [5].

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Lakshman et al. evaluated the use of the melt granulation (MG) process to enhance the tableting properties of poorly compactable
high-dose drugs. Using Met as the model drug (88.2% w/w) and HPC as the polymeric excipient, the formulation was granulated by twin screw extruder and resulted in high compactibility and low friability [12].

Moisture-activated dry granulation (MADG) may be an interesting alternative which combines the benefits of high shear granulation while avoiding the issues of drying as found in the processes described above. This process was initially described by Ullah et al. in 1987 [29] and may be performed within a conventional high shear granulator, with pre-blending of all components intended for granulation and then a final blending prior to compression with further functional excipients, such as disintegrants or lubricants.

The MADG process can be divided into two different stages: the agglomeration stage and the moisture absorption stage [31,32]. The API, water-soluble fillers, and binders are initially pre-mixed in the granulator followed by activation of the binder by a small volume of water to form granulates. MADG typically requires a significantly smaller volume of granulation liquid compared to the conventional HSG process (1–4% (m/m)) [31]. During the agglomeration stage, moisture within the granulates is reduced and distributed throughout the whole blend by subsequent addition of a water insoluble filler as an absorbent component.

MADG has been previously evaluated by some researchers [7,20,21]. Ullah et al. described the manufacturability of a high-dose drug formulation (62.5%) using MADG [30]. Tablets produced with the MADG process showed higher tensile strength and faster disintegration compared to tablets produced with high shear granulation [26].

Met is an oral antihyperglycemic drug used for treatment of non-insulin-dependent diabetes mellitus [3]. Commercial Met products consist of 500 mg, 850 mg, and 1000 mg doses. The drug load of Met IR tablets must be greater than 90% w/w to ease swallowing. If MADG is used for Met 90% w/w formulation, the moisture absorbents must be omitted or reduced to retain the proper tablet size.

Lakshman et al. utilized the moist aqueous granulation (MAG) process for Met formulation development [12]. This manufacturing process is similar to MADG; however, MAG employs only the agglomeration stage without the moisture absorbent stage. In their study, the components of their formulation consisted of API, binder, and magnesium stearate. Met and binder were activated with a small volume of water, and the agglomerates were then blended with magnesium stearate. Their results showed that the Met granulates prepared by MAG showed poor flow during the tableting process due to extreme moisture sensitivity.

MAG is a simple process compared to other granulation processes. In general wet granulation, moisture control is necessary in the drying process. Air flow, temperature and other manufacturing conditions should be evaluated to determine the critical process parameter (CPP) of the drying process. And because MAG omits the drying process, it is beneficial for drugs which are less heat-resistant. Met is shown to be highly susceptible to moisture and will change its flow and form a large agglomerate depending on the moisture content. Therefore, the moisture content of Met granules should be controlled during the wet granulation and drying process. On the other hand, because MAG requires a significantly small volume of granulation liquid, the drying process is omitted. Moisture content can be easily controlled by adjusting the amount of liquid added, which could reduce CPP. This manufacturing method may be beneficial to the Met granulation process.

The binder is the most important excipient for wet granulation [2,10,23]. However, little is known about the choice of binder most appropriate for high-dose Met formulation using MAG. The aim of this study was to evaluate the binder types for improved granulate flow and compactibility of Met using MAG without moisture absorbents, as well as the effect of moisture content on granulate and tablet quality.

2. Materials and methods

2.1. MAG batches

Met (Weifá) was passed through a 1.0 mm screen and then mixed with one of the following binders: vinylpyrrolidone–vinyl acetate copolymer (Kollidon VA64 fine: VA64, BASF), polyvidone (Povidone K12: PVP, BASF), hydroxypropyl cellulose (HPC SSL SF: HPC, Nippon Soda), and hydroxypropyl methylcellulose (Methocel E5 LV: HPMC, Dow Chemical). Batch scales of 250 g were processed in a high shear granulator (Dionsa P1/6, Dionsa) equipped with a 1 L granulation bowl. Processing parameters were kept constant throughout the agglomeration (1 min) and massing (3 min) stage: impeller 500 rpm, chopper 1200 rpm. The mixtures were granulated by spraying 1.0%, 1.5%, or 2.0% (m/m) water for about 10–15 s (nozzle diameter 0.3 mm, atomizing air pressure 2.5 bar) into the granulation bowl. The pre-sieved lubricant magnesium stearate (vegetable magnesium stearate, Faci) was blended directly into the granulator for 0.5 min at a reduced impeller speed of 250 rpm. The final blends were sieved by a conical sieving machine (1.0 mm rasp sieve, Quadro Comil US, Powrex).

The final blends were compressed to flat-faced tablets with a diameter of 8 mm and mass of 200 mg on an eccentric press (FlexiTab, Manesty) at different compression stages of 2.5 kN, 5 kN, 7.5 kN, 10.0 kN, and 15.0 kN.

2.2. Particle size distribution

Particle size distribution of the final blends was measured by sieve analysis (Robot Shifter RPS-95, Seishin) employing the following screens: 355 μm, 250 μm, 180 μm, 125 μm, 90 μm, 75 μm, and 63 μm for a sifting time of 5 min on vibration level 4 and pulse interval of 1 s.

2.3. Bulk and tapped densities

Bulk and tapped densities of the final blends were determined in a 100 mL sample cup on a powder property measurement system (Powder Tester PT-R, Hosokawa micron) by applying 180 taps. The Hausner ratio as a surrogate for flowability was calculated as the ratio of tapped and bulk densities: (ρ tapped/ρ bulk). The flowability was classified according to USP from excellent (1.00–1.11), good (1.12–1.18), fair (1.19–1.25) to passable (1.26–1.34).

2.4. Tablet porosity

Tablet porosity (ε) was calculated by employing the equation 

\[ ε = 1 - \left( \frac{m}{V_{true}} \right)^{\frac{1}{V}} \]

where m and V are the mass and volume of the tablets, respectively. True density (ρ true) was measured by using a mercury penetration porosimeter (Accupyc II 1340, Micromeritics).

2.5. Compaction analysis

The Heckel equation is widely used for obtaining information from the compression properties of pharmaceutical powders [6]. The final blends were compressed to flat-faced tablets with a diameter of 11 mm and a mass of about 300 mg on an eccentric press (FlexiTab, Manesty) at a compression force of 25 MPa. The reduction of volume and density by the applied compression force can be calculated using the Heckel equation [24]. The compactibility of the final Met blends was calculated using the Heckel
expressed as $P_y = K_0 P_a + A$, where $D$ is the relative density, $P_a$ is the applied pressure, $K_0$ is the Heckel coefficient, and $A$ is the Heckel intercept. $K$ and $A$ are the regression coefficients of the linear portion of the Heckel profile. Yield pressure ($P_y$) was expressed as $P_y = 1/K_0$. Materials with high compactability showed higher slope than that of brittle fracture, implying the former has a lower yield pressure [34]. The elastic recovery was calculated based on the compaction profile during the decomposition phase of compaction [24] using the FlexiTab software.

2.6. Tablet hardness and thickness

Crushing strength of the tablets and tablet height were measured using a tablet hardness tester (TBH425, ERWEKA). Tensile strength was calculated as $2F/(\pi D^2 T)$: where $F$ is the hardness, and $D$ and $T$ are the diameter and thickness of the tablets.

2.7. Near infrared spectroscopy (NIRS)

NIR spectra of Met granulates were measured between 1100 and 2500 nm at 2 min increments using a Foss NIR system Model 6500 equipped with a Rapid-Content™ analyzer. NIR data analysis was calculated using Vision® software (Vision 2.51, Foss NIR system).

2.8. Water vapor sorption isotherms

The Dynamic Vapor Sorption Intrinsic (DVS INTRINSIC) system was used for the determination of water vapor adsorption and desorption isotherms at 25.0°C. Water vapor was introduced to the sample at increments of 0% RH to 95% RH.

2.9. Thermogravimetry (TG)

The absorbed water from the Met granulates was measured using the Rigaku Dynamic TG–DTA system (Thermo plus TGS8120). Thermal analyzers have a controlled rate thermal analysis mode that can be used to automatically raise the temperature for quasi-isothermal thermogravimetry. This mode makes it possible to isolate the various reactions that occur at similar temperature. The constant reaction-rate control mode was used for evaluating detailed evaporation behavior [19]. The weight of the samples was approximately 15 mg. The samples were loaded into aluminum pans and heated from 20°C to 130°C in a nitrogen atmosphere. The initial heating rate was 2°C/min, and the water evaporation rate of 0.001%/s was maintained at a constant level.

2.10. Scraping force

Scraping force is the force required to scrape the tablet off the punch face. The force is measured by using the shear stress of the scraper. Scraping force is related to the sticking tendency during the tableting process.

The final blends were compressed to flat-faced tablets with a diameter of 8 mm and a mass of 200 mg on an eccentric press (Korsch EK0, Korsch) at 5 kN. The scraping force of this evaluation was defined as the shear stress after producing 30 tablets.

3. Results and discussion

3.1. MAG process and granulate characteristics

Table 1 shows the formulations in this study. The granulates produced with VA64 and HPC and 2.0% water failed due to bowl-forming during the MAG process. The other MAG formulations performed better, with no wall adhesions or formation of big lumps observed.

Granulate characteristics are shown in Table 2. The mean particle size of Met granulates produced with VA64 (added water 1.0%, 75 μm; 1.5%, 164 μm) and HPC (added water 1.0%, 111 μm; 1.5%, 152 μm) increased with increasing volume of added water. The PVP Met granulates had similar sizes (136 μm) when made with either 1.5% or 2.0% added water, which might not have an impact on the granule enlargements. The volume of water for granulation may have been too low for the HPMC Met granulates, which may be why the particles were smaller than other formulations.

The physical state of binders during the granulation process has a significant impact on the wet granulation process and granule, tablet properties. Li et al. evaluated the physical state of a binder on wet granulation and granule properties using the binary model system. PVP K12 needed a small amount of water to change from glassy to the rubbery/solution state for granule enlargement. On the other hand, HPMC required longer granulation time and more water to reach the solution state [14]. PVP might reach the rubbery/solution state faster compared to the other binders, which caused the granule enlargement with a small amount of water (added water 1.0%, 111 μm). HPMC might not change from glassy to the rubbery/solution state with a small amount of added water (1.0%, 1.5%, 2.0%).

The Hausner ratio of all Met granulates was acceptable (1.13–1.33).

3.2. Compaction analysis

Fig. 1 shows the Heckel plots of Met API and the Met granulates produced with the various binders, and Table 3 shows the summary of the Heckel analysis. The yield pressure and elastic recovery was calculated by the Heckel plots profile (see Section 2.5). For this analysis, the volume of added water was 1.5%. Intact Met API was also evaluated for the comparison. Oleic acid was coated thinly over the punches for prevention of sticking.

Material with a high-yield pressure results in brittle-fracturing or fragmentation. On the other hand, material with a low-yield pressure results in plastic deformation [18]. Met is a well-known viscoelastic drug [5], and the yield pressure of Met API was 227 MPa. The addition of binders resulted in a lower yield pressure than Met API. The granulation process might have improved the compactability of Met. The yield pressures of Met granulates produced with VA64 (114 MPa), PVP (167 MPa), and HPC (157 MPa) were significantly lower (VA64 49.7%, PVP 26.4%, HPC 30.8%) than Met API. However, the yield pressure of HPMC Met granulates (220 MPa; 96.8%) was very similar to that of Met API.
Granulate characteristics are shown in Table 2. HPMC Met granulates had a small particle size and high Hausner ratio compared to other granulates, indicating that HPMC Met granulates are unable to be properly granulated when the volume of added water is low. For the MADG process, binders should be easily wettable and become tacky with a small volume of water for the agglomeration stage [31]. HPMC was unable to be activated with a small volume of water. Therefore, the yield pressure of the HPMC Met granulate was the same as that of Met API. On the other hand, Met granulates produced with other binders were able to be activated with a small volume of water, indicating that the yield pressure when using these binders was lower than those of Met API and HPMC Met granulates.

The elastic recovery of all granulates was very similar to Met API. HPMC Met granules showed higher elastic recovery (0.87%) than other Met granules. Nokhodchi et al. evaluated the effect of moisture content on HPMC K4M compaction properties [18]. The elastic recovery of HPMC K4M was changed from 17% to 6%, as the relative humidity increased from 23% to 75%. But the elastic recovery difference of this study was below 1.0%. This difference might not have a big impact on the tablet properties. The binder type did not have any impact on elastic recovery.

3.3. Tensile strength (Met granulates produced with VA64, PVP and HPC)

The effect that binder type may have on the tensile strength of the tablets was investigated using VA64, PVP, and HPC. Fig. 2 shows the tensile strength of the tablets as a function of compression force. No problems were observed when tableting VA64 Met granulates, but the tablets showed poor tensile strength when the volume of added water was 1.0% (0.41 MPa at 10 kN). However, when the volume of added water was increased from 1.0% to 1.5%, VA64 Met granulates achieved adequate tensile strength (1.59 MPa at 10 kN). As VA 64 did not reach the rubbery/solution state with a small amount of added water (1.0%), the VA 64 Met granule may have inadequate granulation and show a low gain in hardness.

The tableting of PVP Met granulates showed high sticking tendency when the volume of added water was 1.5% or 2.0%. In particular, continuous tableting was difficult due to sticking when the volume of added water was 2.0%, resulting in the discontinuation of the tableting process. The tensile strength did not
3.4. Evaluation of water vapor sorption isotherms (Met granulates produced with VA64, PVP, and HPC)

After tableting, Met granulates produced with various binders exhibited different behaviors. No problems were observed for the VA64 Met granulates during the tableting process. However, HPC Met granulates had a bowl-forming tendency, and PVP Met granulates had the tendency to stick. Because the binder type was the only difference between the formulations, these may have had an impact on the moisture content of the Met granulates.

Fig. 3 shows the water vapor sorption isotherms of Met API and Met granulates produced with VA64, PVP, and HPC. Met API is able to absorb only a very small amount of moisture (0.011%: at 50% RH, 0.097%: at 90% RH). Solubility of Met API is over 100 mg/ml in water [4]. When the added water amount was 1.5% during the MAG process, the Met API may be crystalline (over 99%) during the MAG process based on the calculation of the added water amount in MAG and Met API solubility. On the other hand, Met granulates produced with the various binders showed much higher moisture absorbency than Met API. Therefore, binders may have a significant impact on the moisture uptake of Met granulates.

HPC Met granulates absorbed 0.29% moisture at 50% RH. On the other hand, VA64 and PVP Met granulates absorbed 0.49% and 0.80% moisture, respectively, at 50% RH. VA64 and PVP Met granulates absorbed 1.7–2.8 times more moisture than HPC Met granulates. HPC Met granulates had the lowest moisture absorbency; therefore, HPC may have a limited capacity of water uptake compared to VA64 and PVP. The binder may have an impact on the moisture absorbency of Met granulates. Addition of 1.0% or 1.5% of water was too high for HPC Met granulates, and a tendency to block was observed during the tableting process.

3.5. Evaluation of the molecular state of water by NIRS (Met granulates produced with VA64 and PVP)

The NIR band around 1900–1950 nm shows the molecular state of water, with the water band split into peaks of 1900 nm and 1930 nm, reflecting the bulk water and bound water volumes, respectively. The peak position reflects the moisture mobility of absorbed water [19].

A difference in the tableting properties was observed between VA64 and PVP Met granulates. Therefore, the moisture distribution (bound water and bulk water) of VA64 and PVP Met granulates was evaluated by NIRS. Fig. 4 shows second derivative NIRS spectra, with the peak of the VA64 Met granulates wider compared to the peak of the PVP Met granulates. In particular, the peak position of the VA64 Met granulates around 1930 nm reflecting bound water was wider than the peak position of the PVP Met granulates. Additionally, the peak intensity of the PVP Met granulates around 1930 nm was strong. Therefore, the distributions of bound and bulk water were completely different between the VA64 and PVP Met granulates.

3.6. Evaluation of the molecular states of water by TG (Met granulates produced with VA64 and PVP)

Many researchers have investigated the effect of moisture content on tablet compactibility. It was found that for paracetamol powder, the mean yield pressure decreased with increasing moisture content [9]. However, tensile strength reached a maximum, and then declined, when moisture content approximately doubled [15]. Conflicting results on tensile strength may be due to the moisture state of the powders [18]. Based on these results, by increasing or decreasing the amount of moisture, tensile strength may be increased or decreased.

The NIRS results showed that the moisture contents of the VA64 and PVP Met granulates were different; however, these results were unable to clarify the detailed distribution of moisture in the Met granulates. Ohtake et al. reported that NIR spectral analysis and TG measurement for pharmaceutical additives enabled us the evaluation of molecular states of water existing in the samples. McCrystal and Ford et al. evaluated water distribution within the range of polymer by using DSC. Water molecules of the polymer could be classified into 2 groups: bound water and bulk water [16]. The molecules of bound water showed a lower wave-number region due to interaction with the polar group of the polymer by FTIR spectroscopy. The strongly hydrogen-bonded water molecules moved to free water with increasing water content due to the saturation of the strong binding site of polymer.

![Fig. 3. Water vapor isotherms of Met granules containing various binders at 25 °C (volume of added water, 1.5%).](image1)

![Fig. 4. Second derivative of the NIR spectra in the region 1850–1950 nm for Met granules (volume of added water 1.5%, mean n=3).](image2)
The binding energy of free water seems to be lower than the energy of bound water.

TG was used to evaluate the distribution of moisture content in this study, which was divided into two states: bulk water and bound water. The bulk water was calculated by measuring the water loss around room temperature. The bound water was calculated by measuring the water loss above room temperature. Fig. 5 shows the water states for the VA64 and PVP Met granulates. The bulk water content in the VA64 Met granulates was 0.35% (volume of added water, 1.0%) and 0.34% (volume of added water, 1.5%), approximately the same despite an increase in added water from 1.0% to 1.5%. On the other hand, bound water content in the VA64 Met granulates increased from 0.11% to 0.21% with an increasing volume of added water. Tablet tensile strength also increased with increasing volume of added water, suggesting that the volume of bound water may have an impact on tensile strength.

PVP Met granulates had 3.5 times (volume of added water, 1.0%) and 1.9 times (volume of added water, 1.5%) higher bound water content compared to the VA64 Met granulates. PVP Met granulates had 1.7 times (volume of added water, 1.0%) and 2.3 times (volume of added water, 1.5%) higher bulk water content compared to VA64 Met granulates.

These results show that Met granulates produced with VA64 and PVP have very different volumes of bound and bulk water.

3.7. Impact of the state of water on tablet sticking (Met granulates produced with VA64 and PVP)

Sticking refers to granulate adhesion to the punch and die surfaces, with powder moisture having a significant impact on sticking. Tablet sticking is estimated by measuring the scraping force [8,33], which is the force required to scrape the tablet off the punch face; scraping force increases with increasing sticking [17]. TG–DTA showed that the VA64 and PVP Met granulates had different moisture contents. However, the relationship between moisture content and sticking was not clear, and the association between the volume of bound water, bulk water, and scraping force was evaluated.

Fig. 6 shows the association between the volume of bound water, bulk water, and scraping force. A powder in dry form exhibits cohesiveness due to electrostatic charge, and may become more free-flowing as humidity is increased. If humidity is further increased, liquid bridge formation may result in a return to cohesive behavior [22]. Therefore, if the moisture content is increased beyond the threshold, the scraping force significantly increases. Measurement of total moisture content may not be a good approach for understanding the effects of water. Therefore, the impact of bulk and bound water on the scraping force was evaluated. The threshold of the bound water content was about 0.4%. On the other hand, the threshold of the bulk water content was higher, at 0.6–0.7%. These results show that a higher content of bound water may be the cause of sticking tendencies.

PVP Met granulates had a higher content of bound water compared to the VA64 Met granulates. Therefore, the sticking tendency of PVP Met granulates may be due to the higher content of bound water.

It has been shown that moisture content has a significant impact on tablet properties [18]. The VA64 Met granulates’ bound water content of below 0.4% and moisture absorbency (3.0% at 90% RH, 11% at 95% RH) might have a positive impact on the tablet properties.
4. Conclusion

Using MAG, we have prepared Met granulates using VA64, PVP, HPC, and HPMC as binders. The compactibility of the Met final blends was evaluated using the Heckel equation. Met API was also evaluated for comparison. These granulates, except for HPMC (yield pressure 220 MPa), have a lower yield pressure compared to Met API (yield pressure 227 MPa). HPMC Met granulates have a higher Hauser ratio (13, volume of added water 2.0%) compared to Met granulates produced with other binders. The granulation process was able to improve granule compactability and flowability. HPMC Met granulates are unable to be sufficiently granulated at low water volumes (volume of added water 2.0%). During the tableting process, VA64 Met granulates exhibited no problems, but HPC Met granulates exhibited a bowl-forming tendency, and PVP Met granulates had a tendency to stick during the tableting process. VA64 and PVP Met granulates absorbed 1.7–2.8 times more moisture than HPC Met granulates at 50% RH. HPC Met granulates had the lowest moisture absorbency (0.29% at 50% RH). HPC may have a limited capacity for water uptake compared to VA64 and PVP. The distribution of moisture content (bulk water, bound water) of PVP and VA64 Met granulates was evaluated by TG. PVP Met granulates had higher bound water and bulk water contents compared to the VA64 Met granulates. Tablet sticking was estimated by measuring the scraping force, and the association between the bound water and bulk water content with the scraping force was evaluated. The threshold of bound water (0.4%) was lower than that of bulk water (0.6–0.7%). The high content of bound water may be the cause of the sticking tendency of the PVP Met granulates. The VA64 Met granulates’ bound water content of below 0.4% for preventing sticking tendencies and moisture absorbency (3.0% at 90% RH, 11% at 95% RH) might have a positive impact on the Met tablet properties.

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