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TO STUDY THE EFFECTS OF SOLVENT AND RELATIVE HUMIDITY ON RHEOLOGICAL AND THERMAL PROPERTIES OF MICROCRYSTALLINE CELLULOSE GRANULES USING HYDROXYPROPYL METHYLCELLULOSE AS BINDER

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Keywords:

Powder rheometer, Wet granulation, End point determination, Thermal effusivity, Modulated differential scanning calorimetry, Relative humidity

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ABSTRACT: Solvent used for preparing binder solution in a wet granulation process is one of the major factors which dictate the granule properties. Aim of our current research was to understand the effect of solvents on flow properties of Microcrystalline Cellulose granules prepared using Hydroxypropyl Methylcellulose as a binder by using rheological tools and subsequently studying the effect of relative humidity on the rheology of dried granules. Granules were prepared by using 2.5% w/w binder solution in water and water: ethanol mixture (20:80 v/v). Prepared granules were dried, sieved, and further analyzed. Effect of relative humidity on the flowability of dried granules was studied at 22%, 52%, 75% RH at room temperature for 48 hours. Modulated Differential Scanning Calorimetry and Powder rheometer were used to study the thermal and flow properties of wet, dried, and humidity exposed granules. Results show that the hydro-alcoholic batches show greater resistance to flow in wet granule stage. But, its dried granules display good flow characteristics as evident from Basic flowability energy values. Bulk density of granules depends on the solvent used and in turn, affects the rheological properties of granules. Intragranular moisture levels are affected by solvent used on exposure to different humidity conditions. This work shows that solvent plays a major role on the rheology of microcrystalline cellulose granules which could help formulation scientist for the choice of better solvent for binder preparation and the optimum relative humidity conditions for storage of granules.

INTRODUCTION: Granulation is a size enlargement process in which powders are agglomerated to obtain spherical particles which have an appropriate size, shape, and morphology to improve flow properties, dissolution rates, granule strength, apparent bulk density, *etc*.

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It is the process of adding a liquid binder to an agitated bed of powders under a specified set of conditions to obtain granules of desired characteristics [1, 2].

Wet granulation is one of the most commonly used granulation processes in the pharmaceutical industry for the manufacturing of tablets and capsules which have been the most convenient dosage forms since decades. The performance of any dosage form depends on its final quality which in turn depends on the formulation, processing parameters, and conditions, *etc*. [3] Lot of methods have been developed till now for determining the

endpoint of granulation like Near Infrared Spectroscopy [4], acoustic emission monitoring [5], power consumption [6], *etc*. Previously, powder rheological measurements along with thermal effusivity have been established as a tool to determine the optimum region for wet granulation endpoint, using water and Microcrystalline Cellulose PH 101 (MCC) [7].

Tablet manufacturing by wet granulation is a complex process involving many steps. The entire process has a lot of stages in which granules have to be transferred, fluidized, stored, and compressed. During these processes, understanding of rheological properties of granules, including the bulk, dynamic, and shear properties is essential to obtain a consistent and reproducible final product with desired characteristics [8, 9]. Flow properties of granules depend on its shape, structure, particle size distribution, morphology, intra-granular porosity, *etc*. [10]

Rheology of granules have been characterized by many conventional techniques like the angle of repose, bulk density, tapped density [11], Carr's compressibility index [12], Hausner ratio [13] but the above techniques suffer from several limitations and cannot detect the difference in properties of powders with the similar flow. With technological advancement, new methods for estimating powder flow properties have been developed like cohesivity determination, avalanching determination, gravitational displacement rheometer [14], mixer torque rheometer [15], powder rheometer [16], capacitance tomography [17], atomic force microscopy [18] and penetrometry [19]. Powder rheometer measures the bulk, dynamic, and shear properties of powders. It has been previously used to characterize flow properties of powders and granules with acceptable sensitivity and reproducibility.

MCC is a widely used tableting excipient in the pharmaceutical industry. Different grades of this polymer are available which differ in their particle size and show varying properties for the granules prepared from them [1]. Hydroxypropyl Methylcellulose E5 Premium LV (HPMC) is a low viscosity grade polymer and is widely used as a binder for wet granulation process [20]. Binders used in wet granulation have an influence on the properties of granules and the subsequent tablets manufactured [21]. A variety of solvents are available for binder preparation when a liquid binder is used for wet granulation. The solvent used for the preparation of binder solution affect the granule rheological properties and also the tablet properties [22]. It has been previously reported that binder solution viscosity and surface tension affects the granule flow properties. Greater the viscosity of binder solution less is the amount required for granulation but up to a certain limit. Lower the surface tension of binder solution, easier it is for the binder to spread onto the particles.

Humidity conditions during storage of granules have great impact on flow properties of dried granules. Jenike and Walker showed that flowability of powders first decreased with moisture content until a critical water content, above which it is increased, but the critical moisture content is dependent on the properties of powder [23]. Thus, the effects of different levels of humidity on the rheology of dried granules were also studied.

The present study focusses on comparing the powder rheological and thermal properties and determining the optimum granulation endpoint using HPMC as a liquid binder in water and hydro-alcoholic solvent systems.

MATERIALS AND METHODS: Microcrystalline Cellulose PH 101 (Avicel® PH 101, Lot # P112824635) was a generous sample provided by FMC Biopolymer Corp., Philadelphia, PA, USA. Hydroxypropyl Methylcellulose (MethocelTME5 Premium LV, Lot # YE220124L1) was gifted by Dow Chemicals, Midland, Michigan, USA. De-ionized water (Barnstead Nanopure, Thermo scientific, Model # 7119) was collected fresh and utilized when needed. Ethyl Alcohol 190 Proof USP grade (Lot # C1202101) was purchased from Pharmco- Aaper, Brookfield, CT, USA.

Granulation: For preparing the binder solution in water alone, 2.5 grams of the dry binder was dispersed in 30-40 grams of water at 70-80 ºC, and then cold water was added to make a 2.5% w/w binder solution, and it was stirred until a clear solution was obtained. The hydro-alcoholic solvent system consisted of 20 parts by weight of water and

80 parts by weight of ethanol. 2.5 grams of the dry binder was dissolved in the above solvent to make a 2.5% w/w binder solution. For ease of writing, the granules prepared by using water alone as a solvent would be referred to as "W" batches and the ones prepared using hydro-alcoholic (20:80 v/v) solvent mixture as "HE" batches. The optimum end point of wet granulation was determined using thermal effusivity measurements and Modulated Differential Scanning Calorimeter thermograms (MDSC).

For endpoint determination, small scale batches (10 grams) of MCC were granulated using HPMC binder solution in mortar and pestle. Three levels of binder solution were used to evaluate the rheological and thermal properties of wet, dried and relative humidity exposed granules on a lab scale (700 grams MCC) which are 466.2 grams (40% w/w), 572.6 grams (45% w/w) and 700 grams (50% w/w) of binder solution for W batches. Similarly, HE batches were prepared by adding 576.2 grams (45% w/w), 700 grams (50% w/w) and 855.4 grams (55% w/w) of binder solution. Lab scale wet granulation was done in a Cuisinart Mixer (East Windsor, NJ). Granulating fluid was added at a constant rate during the first 30 sec, and granulation was carried out for 3 min at 100 rpm. The granules were subjected to MDSC and rheological measurements. Wet granules were dried in a gravity convection oven at 70 ºC until the constant value for loss on drying (LOD) was obtained. The wet granules for HE batches were air dried initially and then dried in an oven until constant LOD. The dried granules were passed through sieve no. 12 and were stored in tightly packed containers at room temperature for further characterization.

Thermal Effusivity Measurements: Effusivity measurements were performed using the thermal conductivity (TC) probe (Mathis Instruments, Canada). Thermal effusivity is a dynamic property of the material which is inter-dependent on the thermal conductivity of material, its density and heat capacity given by the equation below [24]. The probe measures the differential heat between its surface and bulk of the material and correlates it with the voltage drop of the sensor element to accurately calculate the thermal effusivity of the material as illustrated in **Fig. 1**.

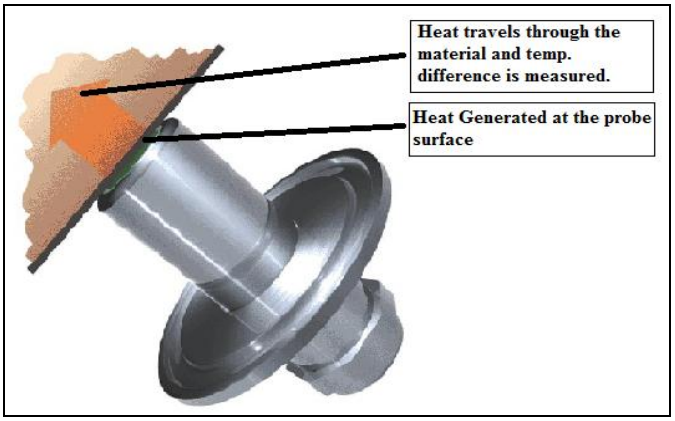

FIG. 1: PRINCIPLE OF THERMAL EFFUSIVITY

$$\text{Effusivity} = \sqrt{(k \times \rho \times C_p)}$$

Where,

k = Thermal Conductivity (W/(m.K))
ρ = Density of the material (Kg/m^3)
C_p = Heat capacity (J/(Kg.K))

Measurements were performed until slurry formation for both the batches.

The instrument was previously calibrated using polydimethylsiloxane as a standard. Samples were taken with a standard spoon to ensure constant volume and were spread evenly to have uniform contact with the thermal effusivity probe. The static test was used with a period of 0.8s. Average of five reading was considered.

Modulated Differential Scanning Calorimetry (MDSC): MDSC analysis was performed using a Q100 (TA Instruments, New Castle, DE) instrument with nitrogen (50 ml/min) as a purge gas. The instrument was calibrated for temperature and cell constant using indium (melting point 156.61 ºC; enthalpy of fusion, 28.71 J/g). Baseline calibration was performed by heating the empty cell, and heat capacity calibration was done using a standard sapphire sample. Hermetically sealed aluminum pans were used, and a sample size of 10 ± 3 mg was maintained. MDSC was used for thermal analysis with a heating rate of 5 ºC/min from 20 ºC to 250 ºC with modulation of ±1.06 ºC every 40s. The enthalpy (ΔH) and temperature (T_e) corresponding to the loss of water were recorded for each sample of wet granules as well as the dried and humidity exposed granules for lab scale batches.

Relative Humidity Exposure Experiments: Dried granules at 50% w/w for W batches and 55% w/w for HE batches were subjected to 22.0% (± 0.88), 52.0% (± 0.74) and 75.0% (± 1.16) relative humidity conditions (RH) for 48 hours. The RH conditions were generated using saturated salt solutions at room temperature (25 ºC ± 2 ºC) in tightly sealed glass chambers. Potassium acetate saturated salt solution was used to generate 22.0% RH, Magnesium nitrate for 52.0% RH, and Sodium chloride for 75.0% RH [25]. The RH in the chambers was confirmed using a digital hygrometer (VWR, Bridgeport, NJ).

Powder Rheology Evaluation: Wet, dried, and RH exposed granules were characterized using FT4 powder rheometer for dynamic, bulk, and shear properties. The instrument was previously calibrated for torque, force, height and spindle measurements. The air control unit was calibrated for air velocity and pressure. A conditioning cycle preceded all the rheology tests to ensure that there was no variable stress generated during the manual filling of granules into the instrument vessel. This cycle comprises of an upward and downward motion of the rheometer blade to remove any residual stress. A split vessel assembly was used to ensure the constant volume of sample for all tests and also for bulk density measurement of the sample. Basic Flowability energy (BFE), Specific energy (SE) and Pressure Drop (PD), Aerated Energy (AE) and shear tests (Wall Friction and Shear cell) were performed for the granules. The helix angle of the blade was maintained at negative 5^0 for all the tests.

BFE and SE Measurements: BFE and SE measurements were performed using a 48.00 mm blade and a 50 mm × 160 ml split vessel. BFE is the integration of force-torque profile vs. distance through the granule bed. For BFE measurement, the energy was measured during the flow pattern generated by the downward anti-clockwise motion of the blade through the granule bed. Blade tip speed was kept at 100 mm/s. SE is the energy measured during the flow pattern generated by the upward clockwise motion of the blade through the granule bed. It is the energy measured for the flow of granules in an unconfined environment. Wet, dried, and RH exposed granules were subjected to these tests.

Permeability Measurements: Permeability of granules was measured during the PD test sequence. It was measured using 48.00 mm blade, and 50 mm × 85 ml split vessel. PD was measured at different applied normal stress, which is 1, 2, 4, 6, 8, 10, 12, 15 kPa by a vented piston. Vented piston applies normal stress to the granule bed and at the same time, measures PD across the granule bed. The aeration base provides a constant air flow rate of 2.00 mm/s throughout the test. Permeability analysis was carried out for the wet, dried, and RH exposed granules. It was calculated using Darcy's law given below at 15 kPa [26],

$$k = q\mu L/\Delta P$$

Where,

k = Permeability (cm^2)
ΔP = PD across powder bed (mbar)
μ = Air Viscosity (Pa.s)
L = Length of powder bed (cm)
q = Flux, or air flow rate (cm/s)

Conditioned Bulk Density (CBD) (Omit the numeral): Dried granules were subjected to bulk density evaluation. CBD is the bulk density of the granule bed measured following the conditioning cycle. It was measured during the stability and variable flow rate test program. A constant volume of granule bed was maintained by the split vessel assembly. Mass of the granule bed was measured by the inbuilt stage balance of powder rheometer, and bulk density was calculated by the following equation,

Conditioned Bulk Density = (Split Mass) / (Split Volume)

Compressibility Test (Omit the Numeral): Compressibility test measures % change in volume of granule bed under increasing normal stress applied by the vented piston. 48.00 mm blade was used for conditioning the granule bed. 50 mm × 85 ml split vessel was used for the test. The applied normal stress were 0.5, 1, 2, 4, 6, 8, 10, 12, 15 kPa, and % compressibility was noted at each applied normal stress.

The compressibility at the highest applied normal stress (15kPa) was considered for evaluation. Compressibility protocol was carried out for the dried and RH exposed granules.

Shear Properties:

Wall Friction Test (Omit the letter 'a'): Wall friction test was conducted using a 50 mm × 85 ml split vessel assembly to examine the effect of solvent on shear properties of dried, and RH exposed granules. 48.00 mm blade was used for conditioning of granule bed before the test. Vented Piston was used to consolidate the granule bed at normal stress greater than 15.00 kPa. Pre-shearing was done to get constant shear stress on an over-consolidated granule bed to avoid localization of the shear plane. The serrated base was used for this test to avoid slippage of the entire granule bed during the test. Stainless Steel (316) wall friction disc with a roughness factor value (Ra) of 0.28 µm was used. Shear stress was measured at 15, 9, 8, 7, 6, 5 kPa applied normal stress. Wall Friction angle (WFA) was calculated from the graph of shear stress vs. applied normal stress using the following equation,

$$\emptyset = \tan^{-1} \tau_w/\sigma_w$$

Where,

τ_w = Shear Stress (torque) at maximum normal stress
σ_w = Maximum normal stress applied (Force)

Shear Cell Test: Shear cell test was performed in a 50 mm × 85 ml split vessel, and conditioning of the sample was done by the 48.00 mm rheometer blade. Vented Piston was used to pre-consolidate the granule bed at normal stress above 15 kPa. Shear cell head was used for pre-shearing until a constant value of shear stress was obtained and within the acceptable range at a normal stress of 15 kPa. The pre-shear protocol was carried out as described by Prof. Dietmar Schulze and Dr. Ivan Peschl in which the shear stress remains constant under a constant normal stress [27].

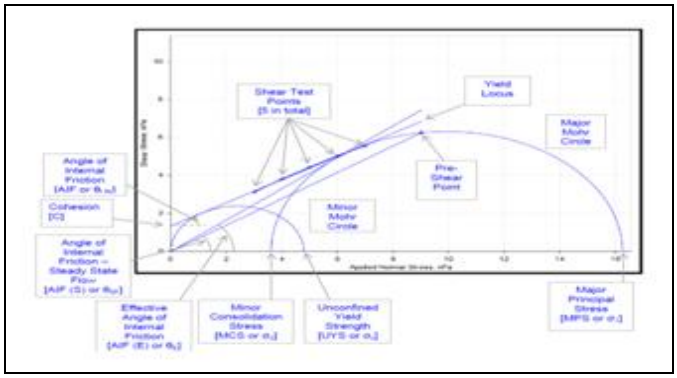

FIG. 2: GRAPHICAL ANALYSIS OF SHEAR CELL TEST

Shear stress was measured by the rotating shear cell head at the following applied normal stress, *i.e.* 9, 8, 7, 6, 5 kPa. Dried and RH exposed granules were studied for the change in their shear properties with the change in solvent for binder preparation. The plot of shear stress vs. applied normal stress gave the Flow Function value (FF) for the granule bed as shown in **Fig. 2** [28].

$$FF = \sigma_1/\sigma_c = MPS/UYS = ff_c$$

Where,

MPS = Major Principal stress acting on the powder
UYS = Unconfined Yield Strength
Higher FF values indicate better flowability of granules concerning each other when at rest.

Tablet Compression and Hardness Testing: A single station Carver tablet press (Indiana, USA) was used for tablet compression. 19/32" flat-faced, beveled with break line on one side D type tooling was used for compression. Dried granules of both batches (50% w/w for W and 55% w/w for HE) were compressed at a force of 3000 pounds. The tablet weight was kept 500 ± 10 mg for both the batches. Twenty tablets were compressed for each batch for hardness testing. Compressed tablets were stored in tightly sealed containers until tested. Tablet hardness was measured in kilopond (kP) using a tablet hardness tester (Schleuniger tablet tester 6D).

RESULTS AND DISCUSSION:

Effusivity Measurements: Effusivity readings for all batches are shown in **Fig. 3**. Small and lab scale readings show acceptable agreement which denotes the reliability of thermal effusivity measurements in the scale-up process also. An increase in effusivity with the increase in % w/w of binder solution is observed for both batches because the effusivity increases as the amount of solvent increase on account of the thermal conductivity of solvent used. A sharp rise at 55% w/w for both batches is observed, which indicates attainment of the granulation endpoint and reaching a stage of physical equilibrium between the diluent and binder solution for granule formation. Also, further addition of binder solution results in surface accumulation of the solvent leading to the slurry formation. It has been previously reported that the region before the sharp rise is the optimum region

for the endpoint of wet granulation [7]. Above that point, particles get over-granulated and finally slurry formation occurs giving a value of effusivity close to that of the plain binder solution.

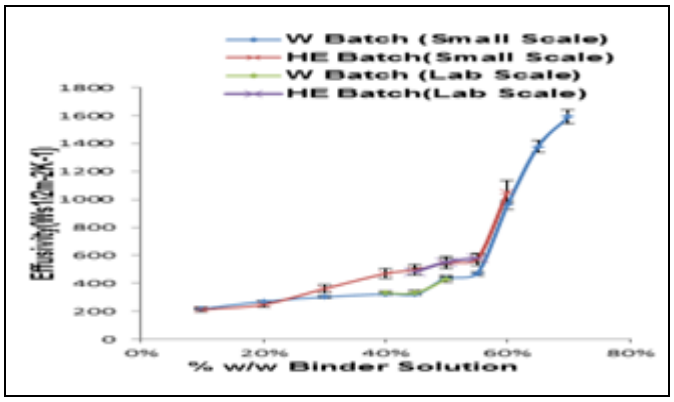

FIG. 3: THERMAL EFFUSIVITY AS A FUNCTION OF % w/w BINDER SOLUTION

55% w/w was considered as the end point for HE batches, but for W batches, 50% w/w was taken as the endpoint because, during the lab scale batch (700 grams), 55% w/w of binder solution produced large lumps which were difficult to process.

MDSC Measurements: MDSC thermograms for lab scale W and HE batches (wet granules) are shown in **Fig. 4**. ΔH values are shown in **Table 1**. Microcrystalline Cellulose PH 101 binds with water in a triphasic process. The portions of water associated with the three phases are referred to as structured water, loosely bound and free or bulk water [29]. As seen in the thermograms, the depth of the endotherm and ΔH values goes on increasing as the amount of binder solution (W Batch) increases, which indicates that at the end point; maximum agglomeration of particles has occurred and the water content is greater on the surface of the granules as bulk water. The T_e also shifts closer to 100 ºC.

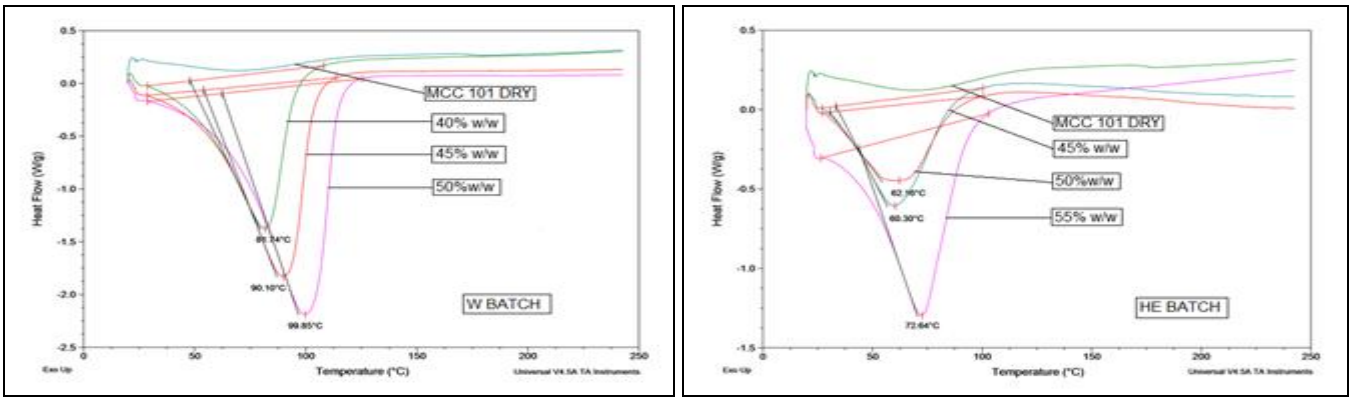

FIG. 4: COMPARISON OF DSC THERMOGRAMS OF WET GRANULES (W & HE BATCH)

TABLE 1: ENTHALPY (ΔH) VALUES OF WET GRANULES

%w/w Binder Sol^n (W)	ΔH (J/g)	%w/w Binder Sol^n (HE)	ΔH (J/g)
40%	548.2	45%	258.4
45%	722.0	50%	207.9
50%	928.6	55%	425.0

A similar trend is seen for the wet granules of HE batches. ΔH values and T_e is similar for 45% and 50% w/w batches. But, at 55% w/w, there is a sharp rise in ΔH value and significant shift in T_e which shows that a greater amount of solvent is present on the surface of granules which again confirms the formation of granules and attainment wet granulation end point.

MDSC analysis reconfirms the phenomenon observed in thermal effusivity readings above.

Fig. 5 shows thermograms of the dried and RH exposed granules of W and HE batches respectively. **Table 2** shows the ΔH values of dried and RH exposed granules. For W batches, the RH exposed granules have similar ΔH values for all %RH points but significantly smaller than for the dried granules. However, in case of HE batches, the RH exposed granules had higher ΔH values than for the respective dried granules. This indicates that the HE batches had greater affinity for free moisture as compared to the W batches which were already saturated with water owing to the use of only water as the solvent for its granulation. Also, the water associated with any solid material depends on the nature of the material, the number of available sites of interaction, and the surface area [30].

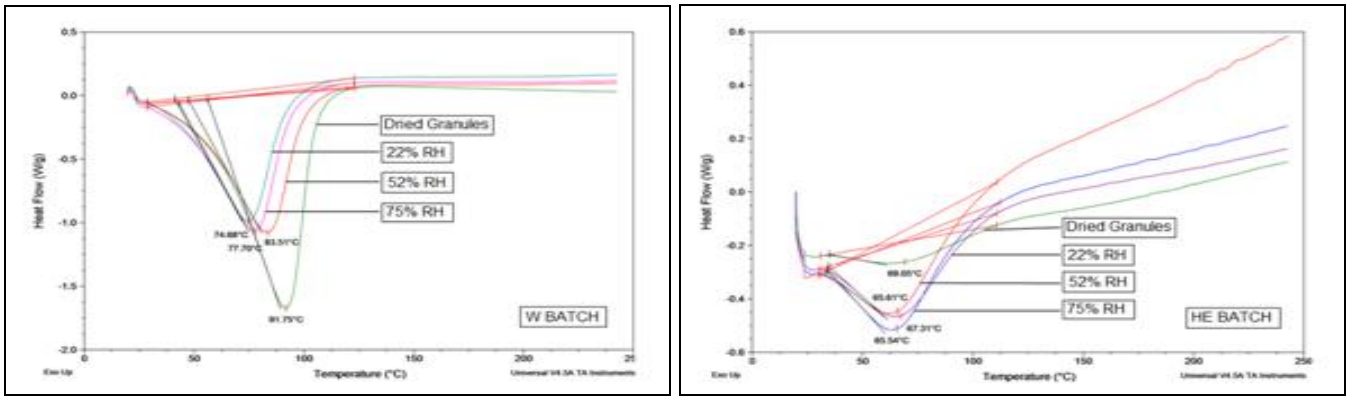

FIG. 5: COMPARISON OF DSC THERMOGRAMS OF THE DRIED GRANULES AND RH EXPOSED GRANULES (W & HE BATCH)

TABLE 2: ENTHALPY (ΔH) VALUES OF DRIED GRANULES AND RH EXPOSED GRANULES

% RH (W)	ΔH (J/g)	% RH (HE)	ΔH (J/g)
50% w/w Dried Granules	658.1	55% w/w Dried Granules	42.2
22%	395.9	22%	132.2
52%	447.3	52%	138.6
75%	415.4	75%	151.8

Powder Rheology Characterization:

BFE and SE Measurements: BFE and SE values for W and HE batches wet granules are shown in **Fig. 6**. Flow energy increases with an increasing amount of binder solution, indicating greater resistance to movement of the blade. This is due to the fact, as we approach the end point of granulation, particles have greater cohesive forces and hence, higher BFE values. However, the BFE values are smaller for W batches as compared to HE batches which is attributable to the fact that Microcrystalline Cellulose PH 101 has a high affinity for water and hence, higher absorption of water by the MCC particles.

In case of HE batches, the solvent on the surface creates greater cohesion between the particles as seen by the sharp rise in ΔH values at the endpoint and hence, higher BFE. SE values almost remained constant on approaching the end point showing that there is little effect of cohesion in an unconfined state of flow with the amount of binder solution. Though, the values are higher for HE batches as seen above.

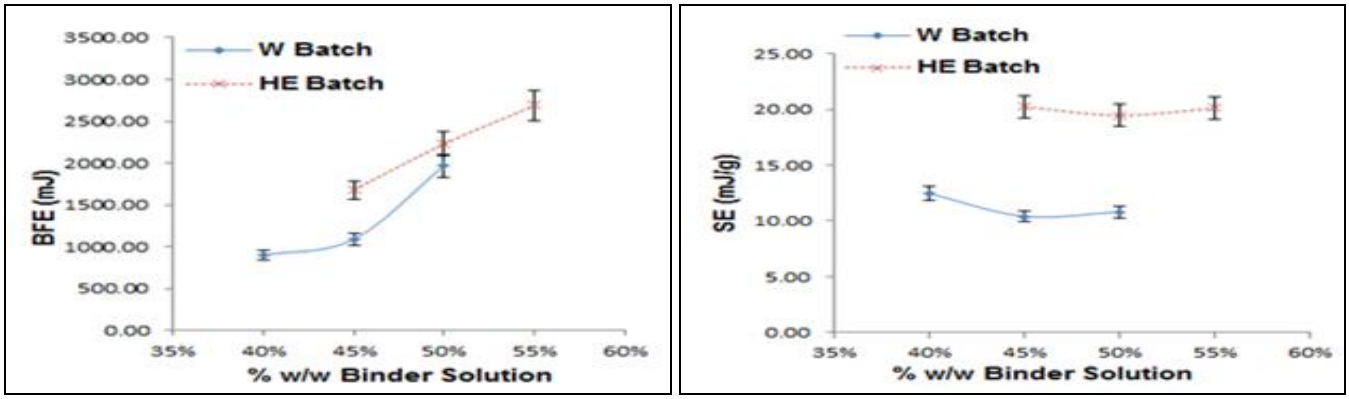

FIG. 6: BASIC FLOWABILITY ENERGY (BFE) AND SPECIFIC ENERGY (SE) AS A FUNCTION OF % W/W BINDER SOLUTION (WET)

In the case of dried granules, BFE values for both batches showed a steady rise with an increasing amount of binder solutions as shown in **Fig. 7**. However, the dried granules at endpoint for W batches show higher BFE values than that of HE batches which is opposite to that observed in case of wet granules **Fig. 6** which can be attributed to the faster and complete evaporation of ethanol as compared to water and also, the hygroscopicity of MCC plays an important role, making the granules cohesive. SE values follow a similar pattern for both W and HE batches. This indicates that flow properties of granules do not very much with different solvents in an unconfined state of flow.

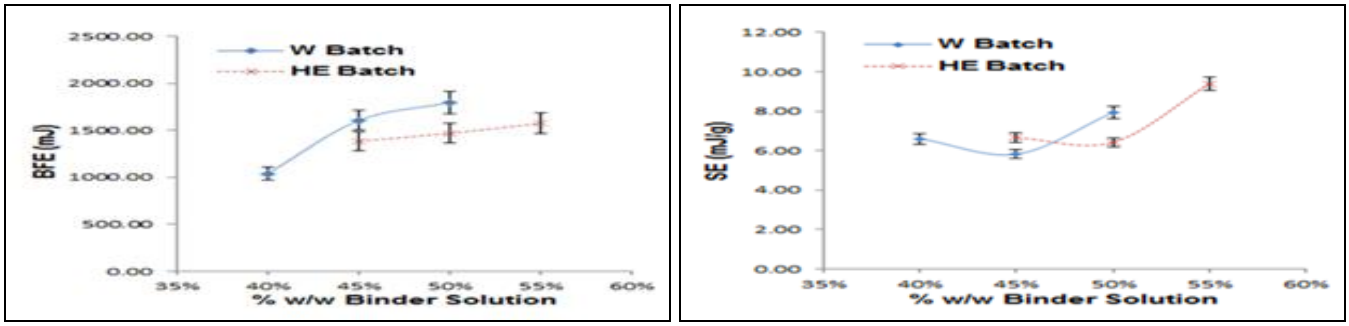

FIG. 7: BASIC FLOWABILITY ENERGY (BFE) AND SPECIFIC ENERGY (SE) AS A FUNCTION OF % w/w BINDER SOLUTION (DRIED)

BFE values for humidity exposed granules for the W, and HE batches are shown in **Fig. 8**. BFE does not show a significant change with humidity for W batches, but it decreases with increase in %RH for HE batches. MDSC thermogram for dried granules of W batches shows a greater ΔH value than the humidity exposed granules which shows that RH conditions did not have a significant effect on the W batches and hence, showed nearly constant BFE values. On the other hand, the thermogram for dried granules of HE batches has lower ΔH value as compared to humidity exposed granules. Hence, the adsorbed moisture in case of HE batches acts as a lubricant and thereby, the decrease in BFE values is observed [31]. Thus, this suggests that MDSC data can also be used as a tool to evaluate the flow behavior of granules. There was no significant change in the SE values for both batches on humidity exposure.

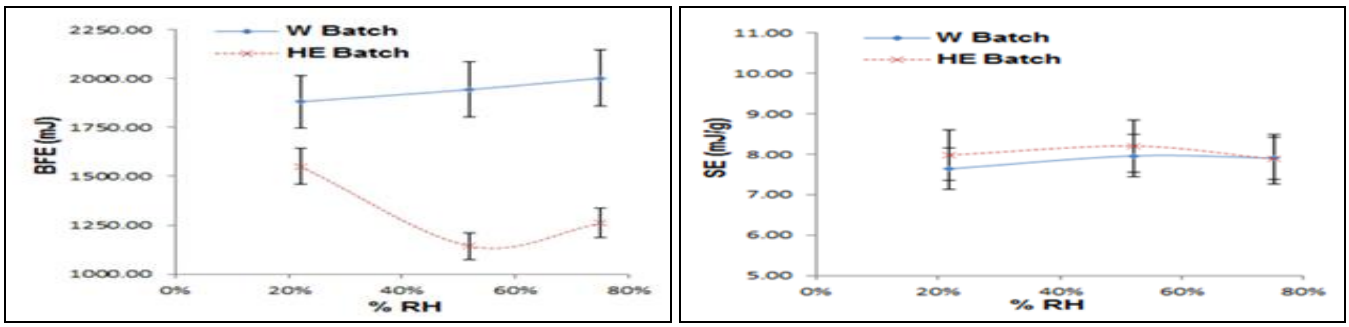

FIG. 8: BASIC FLOWABILITY ENERGY (BFE) AND SPECIFIC ENERGY (SE) AS A FUNCTION OF % RH

Permeability Measurements: A decrease in the values of Pressure Drop (PD) is observed as the amount of binder solution increases for both batches. This suggests that there is an increase in permeability, which is due to the formation of granules as the endpoint is reached. The spherical shape of granules allows greater amount of air to pass and hence, higher permeability. The drop in PD reflects the formation of granules near the endpoint. Granules at the end point for W batches show greater permeability and hence seem to have more uniform and spherical granules as compared to HE batches. This finding also supports the lower BFE values in case of W batches. The PD values for the wet, dried, and RH exposed granules are shown in **Fig. 9**.

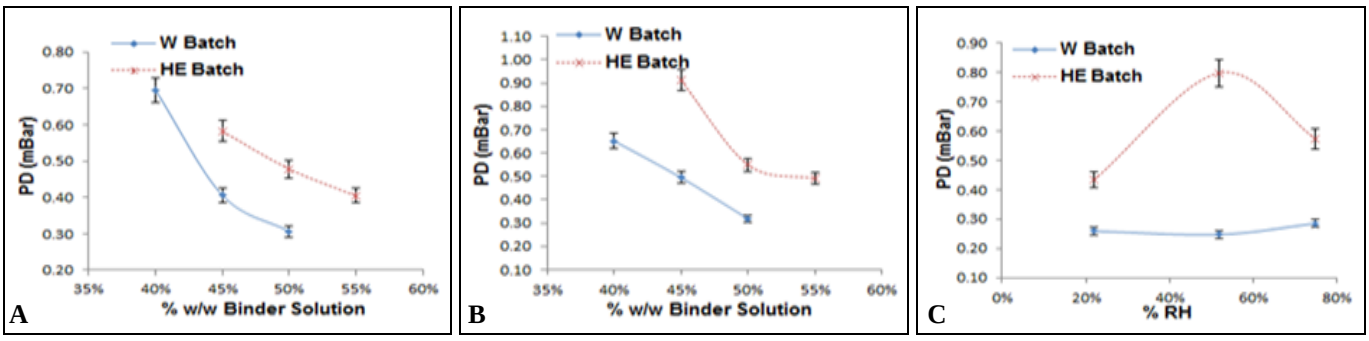

FIG. 9: COMPARISON OF PRESSURE DROP (PD) OF WET (A), DRIED (B) AND RH EXPOSED (C) GRANULES

PD data for dried granules follow a similar pattern as observed for wet granules. Permeability steadily rises as the endpoint is reached for both the batches. It is greater for W batches, which also supports the data of PD measurements of the wet granules shown above. It also indicates that there is no significant transition in the shape and morphology of the granules during drying. In case of RH exposed granules, permeability was constant with %RH for W batches; but for HE batches, it showed a curvilinear trend as shown in the figure above. The above-observed phenomenon can also be attributed to the one observed in the MDSC thermograms.

Conditioned Bulk Density (CBD): The value of the two batches of granules is shown in **Table 3**. For HE batches, it remains constant with the amount of binder solution added. But, for W batches, it shows a curvilinear trend. CBD goes down when 45% w/w of binder solution is added and then rises when 50% w/w is added.

This could be due to changes in porosity during the granule development stage or due to insufficient bonding between the particles. This change in the CBD explains the pattern of bulk properties, which is observed for W batches.

TABLE 3: CONDITIONED BULK DENSITY (CBD) VALUES OF DRIED GRANULES

% w/w Binder Sol^n (W)	Average CBD (g/mL)	% RSD	% w/w Binder Sol^n (HE)	Average CBD (g/mL)	% RSD
40%	0.35	4.65	45%	0.38	4.90
45%	0.27	2.88	50%	0.39	5.87
50%	0.48	3.87	55%	0.40	4.45

Compressibility: As shown in **Fig. 10**, the compressibility of the dried granules shows a similar trend to that of the CBD of granules for W batches. A good correlation is seen between the CBD and compressibility behavior of granules. HE batches show a steady rise in % CPS with the amount of binder solution added. The value of % CPS for W batches at endpoint was greater than HE batches suggesting greater cohesion. The % RH did not have a significant effect on the compressibility of the granules for both the batches as evident.

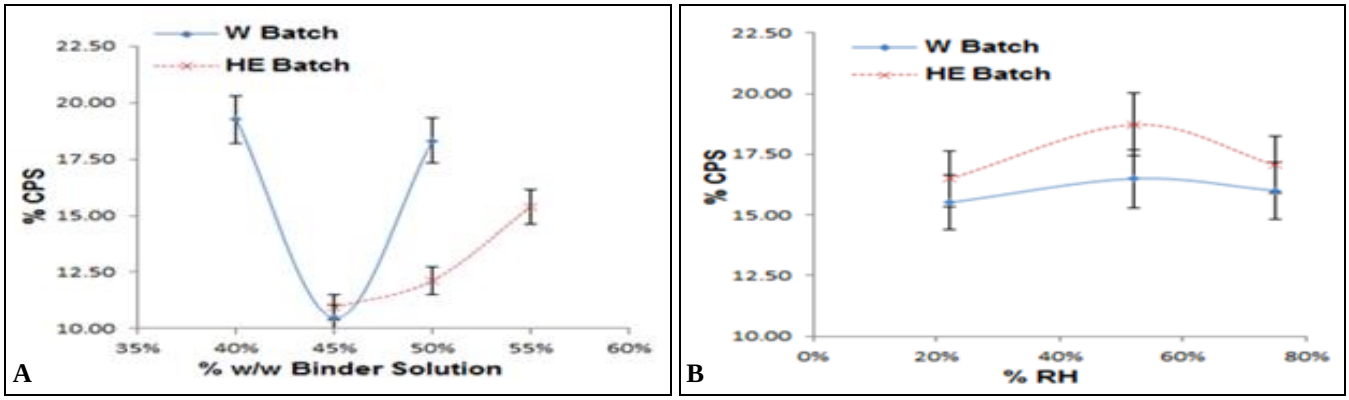

FIG. 10: COMPARISON OF %COMPRESSIBILITY (CPS) OF WET (A) AND RH EXPOSED (B) GRANULES

Shear Properties: Wall friction angle does not change much for both the batches. Shear cell data shows that the %RH does not affect the W batch granules but, in case of HE batches, the Flow Function (FF) value initially is higher and then lowers and remains constant for 52% and 75% RH reflecting better flowability which could be due to the lubricant action of the adsorbed moisture at low moisture levels.

For both binder solutions, shear properties of dried granules remain almost constant at the endpoint. Data from Shear cell and Wall Friction tests are shown in **Fig. 11 and 12,** respectively. With an increasing amount of binder solution, HE batches follow a linear pattern while the W batches follow a curvilinear pattern in case of the flow function values. But, the opposite trend is observed while studying the flow pattern when in contact with the wall friction disc. From the above findings, a probable conclusion is that the pattern observed in shear properties of granules for both batches can be correlated to the changes in bulk density observed

above during the granule formation. It indicates an efficient packing of powder particles, and hence, greater shear stress was required for the incipient failure. Whereas, in the case of Wall Friction, the frictional forces between the wall material and powder bed seem to have dominated this effect.

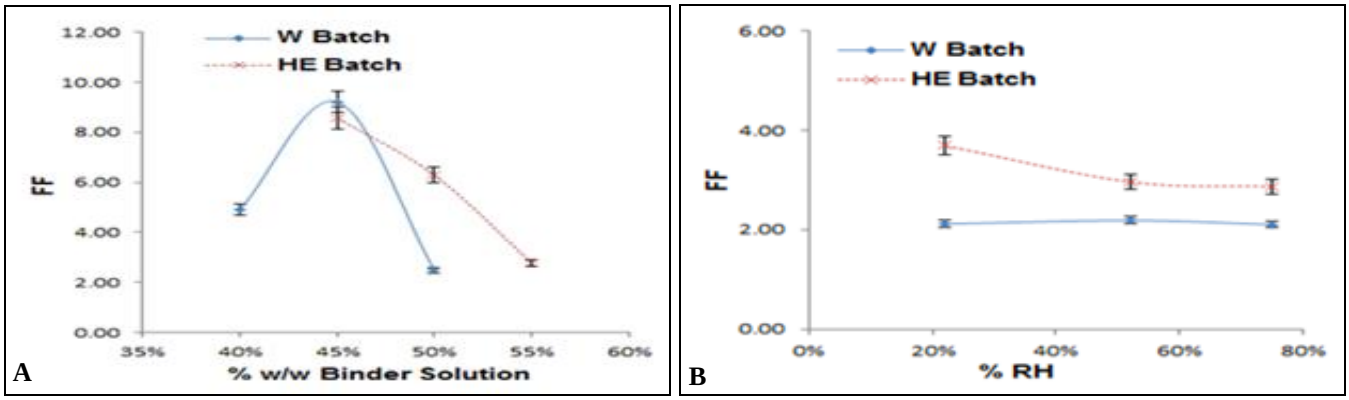

FIG. 11: COMPARISON OF FLOW FUNCTION (FF) OF WET (A) AND RH EXPOSED (B) GRANULES

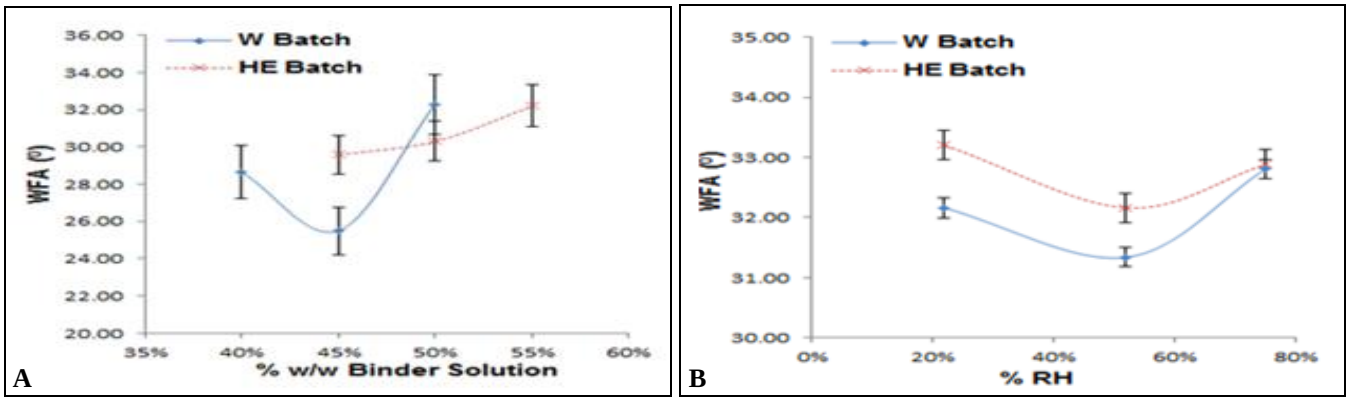

FIG. 12: COMPARISON OF WALL FRICTION ANGLE (WFA) OF WET (A) AND RH EXPOSED (B) GRANULES

Tablet Hardness: The hardness of the tablets compressed is shown in **Table 4**. It is evident that the tablets from HE batches have significantly higher hardness than that of W batches. It has been previously reported that the hydro-alcoholic solvent system for binders in wet granulation produces harder tablets.

TABLE 4: COMPARISON OF HARDNESS VALUES OF TABLETS

% w/w Binder Sol^n (W)	Average Tablet Hardness (kP)	% RSD	%w/w Binder Sol^n (HE)	Average Tablet Hardness (kP)	% RSD
40%	9.3	5.32	45%	33.46	4.96
45%	11.86	1.90	50%	34.74	5.87
50%	13.12	2.08	55%	39.46	3.72

CONCLUSION: Wet granulation is a complex process, and flow properties of granules are an integral part of this process. The above work explains the effect of different solvent systems used for wet granulation binder preparation on the quality attributes of MCC granules. The solvent also plays an important role in the equilibration process with moisture on exposure to different relative humidity conditions. This method can also be utilized to determine the optimum region for wet granulation and will be beneficial for formulation scientists during early development or scale-up.

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