



Original article

Investigate the effect of solvents on wet granulation of microcrystalline cellulose using hydroxypropyl methylcellulose as a binder and evaluation of rheological and thermal characteristics of granules



Dharti Tank, Kapish Karan, Bhavin Y. Gajera, Rutesh H. Dave*

Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Division of Pharmaceutical Sciences, Long Island University, Brooklyn, NY 11201, USA

ARTICLE INFO

Article history:

Received 3 December 2017

Accepted 5 February 2018

Available online 6 February 2018

Keywords:

Granulation

Microcrystalline cellulose

Effusivity

Rheometer

End-point

Flow properties

ABSTRACT

Wet granulation is the most commonly used technique in the pharmaceutical industry for delivering oral solid dosage forms. In wet granulation, the binder solvent is one of the critical factors affecting granule properties. In the current study, an attempt was made to investigate the effect of solvents (aqueous and hydro-alcoholic) on thermal and flow properties of Microcrystalline Cellulose (MCC) granules prepared using two different grades of Hydroxypropyl Methylcellulose (HPMC), which served as an effective binder. The granulation endpoint was evaluated using thermal effusivity sensor. Rheometer and Modulated Differential Scanning Calorimetry (mDSC) was used to study the flow and thermal properties of wet and dried granules. Furthermore, physical characterization was carried out by granule strength, particle size distribution and tablet hardness for all granules under the study. Thermal effusivity sensor results indicate 55% w/w concentration of binder solution as the endpoint by measuring thermal effusivity for both binders. Additionally, powder rheometer results show that the wet granules of hydro-alcoholic batches show greater resistance to flow whereas the dried granules display excellent flow characteristics as evident from Basic flowability energy values and specific energy values. Permeability results suggest that the granules formed with hydro-alcoholic binder solvent exhibit better porosity and permeability. Tablet hardness data showed that tablets formulated using hydro-alcoholic solvent granules have greater hardness than tablets formulated using water based solvent granules. The granule strength for water based granules is relatively higher than that of hydro-alcoholic based granules. mDSC thermograms show a sharp rise in enthalpy value at 55% w/w binder solution which is indicative of a more significant amount of solvent being present on the surface of granules and formation of optimal granules. To summarize, we have determined a technique to measure endpoint determination and simultaneously investigate the role of solvent systems on the rheology of MCC granules, which could assist in selecting an appropriate solvent system for granulation.

© 2018 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Since decades, granulation is operational as a critical size enlargement process for powder agglomeration in tablet manufacturing. Dry granulation (Kleinebudde, 2004), melt granulation (Gajera et al., 2006; Dugar et al., 2016) and wet granulation

(Chaturvedi et al., 2018) are some of the most common techniques utilized for granulation in the pharmaceutical industry. However, in pharmaceutical tablet production, wet granulation is the most frequently used process consisting of agglomerating powder particles with a liquid binder, in a fluidized bed, high shear mixer or low shear mixer (Iveson et al., 2001). All required features for compression, namely a good flow, appropriate compactibility and uniform drug distribution can be achieved using wet granulation and hence it is extensively employed granulation technique (Sinko, 1997).

In wet granulation, it is imperative to determine the optimum quantity of binder solution as granule properties affect dosage form performance (Achanta et al., 1997; Leuenberger et al., 2009). The end-point in wet granulation process is a point at which a formulator achieves a target particle size, after addition of an

* Corresponding author.

E-mail address: rutesh.dave@liu.edu (R.H. Dave).

Peer review under responsibility of King Saud University.



optimum amount of granulating fluid (Dave et al., 2012). The rapidity with which granulation proceeds, makes endpoint determination difficult and further necessitates monitoring of the process (Levin, 2006). The potential for various methods to determine the end point of wet granulation has been reviewed extensively (Jørgensen, 2004). In the present article, an end-point determination is carried out by one such technique, namely Thermal Effusivity, which is an emerging Process Analytical Technology (PAT) tool for optimizing wet granulation (Fariss et al., 2006).

Tablet production is an intricate process consisting of several steps, each of which subjects the powder to a specific set of environmental conditions. It is therefore essential to have an understanding of rheological characteristics of granules, which include bulk, dynamic and shear properties (Kristensen and Schaefer, 1987; Parikh, 2016). Thus, to study the rheological properties of granules, FT4 powder rheometer was used (Freeman, 2004).

Diluents or bulking agents serve as the vital component of a dosage form. Microcrystalline cellulose is one such widely used diluent in pharmaceuticals due to its diverse characteristics based on different particle size. The model diluent selected for this study was MCC 105 due to its small particle size, high cohesiveness, and superior compactibility, making it an attractive candidate for size enlargement process using wet granulation (Sun, 2008; Patel and Podczek, 1996). Furthermore, granulating solvent significantly affects the granule properties. Changing the solvent system leads to a change in wettability and solubility of formulation constituents, and thus influences binder distribution, which in turn affects the granule strength and porosity (Wikberg and Alderborn, 1993; Shah et al., 1996). In the pharmaceutical industry aqueous, hydro-alcoholic, and alcoholic solvent systems are widely used. Therefore, in the present study, aqueous and hydro-alcoholic solvent systems are employed for wet granulation. Hydroxypropyl methylcellulose (HPMC) cellulose ethers are water-soluble polymers derived from cellulose, used as vital binding ingredients in the pharmaceutical processes. HPMC polymers are considered as versatile binding agents as they work well with soluble and insoluble drugs and at high and low dosage levels. Methocel™ K4M CR and K100M CR are selected based on their utilization in wet granulation to formulate hydrophilic matrix systems, one of the widely used means for controlled drug delivery in solid oral dosage (Biswas et al., 2014; Jain, 2008). The viscosity of the binder is another important parameter which has to be taken into account during granulation since the binder viscosity impacts the strength of the resulting granules (Chitu et al., 2011; Keningley et al., 1997; Knight, 2004; Johansen and Schæfer, 2001; Lieberman and Pharmaceutical, 1980). L. Stubberud et al. described that an increase in viscosity has a beneficial effect on the granulation, up to a specific critical value (Stubberud et al., 1996).

The present study focuses on comparing rheological properties, thermal properties and granule strength of MCC granules by using two grades of HPMC as a liquid binder, prepared with water and hydro-alcoholic solvent systems, whereby studying the effect of both, solvent and binder viscosity on granules produced by low shear granulator.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel® PH 105, lot # 51207C) was received as a generous sample from FMC Biopolymer Corp (Philadelphia, PA). HPMC K100M CR (Methocel™ K100M CR, Lot # ZG12012N01) and HPMC K4M CR (Methocel™ K4M CR, Lot # ZG07012N02) used as binders, were kindly supplied by Dow Chemicals (Midland, Michigan, USA.). Deionized water (Barnstead Nanopure model # 7119, Thermoscientific system,

Waltham, MA) was collected above 13 mΩ·cm and Ethyl Alcohol 190 Proof USP (Lot # C1202101) purchased from Pharmaco - Aaper (Brookfield, CT, USA), were used as solvents for the current study.

2.2. Binder solution preparation

Four types of binder solutions were prepared using two types of HPMC binders, HPMC K100M CR (Methocel™ K100M CR and HPMC K4M CR (Methocel™ K4M CR) with deionized water and hydro-alcoholic mixtures as solvents (Table 1). The binder solutions with de-ionized water were prepared using the hot-cold method. About 35 g of water was heated to 80–90 °C and 0.5 g of the binder was added to the heated water and mixed. Later, volume was adjusted using cold water to form a 0.5% w/w binder solution. The hydro-alcoholic binder solution was prepared by using 50 parts of water and 50 parts of ethyl alcohol (50:50), mixed with 0.5 g of the binder forming a 0.5% w/w binder solution. The viscosity of binder solutions was a determined using RV spindle with Brookfield Viscometer (DV-II+ Pro, Middleboro, Massachusetts, USA).

2.3. Preparation of wet and dried granules

Preliminary screening experiments were performed to determine the optimum amount of binder solution for MCC PH 105 batches. They were carried out by using 10 g of MCC granulated in a mortar and pestle with different binder solutions added in a geometric progression starting at 5% w/w until a drastic increase in effusivity reading was observed. For large scale studies, 700 g batches were prepared following optimum endpoint range obtained from thermal effusivity measurements of small-scale batches (10 g). The granules were prepared using a lab scale Cuisinart mixer (East Windsor, NJ) with a batch size of 700 g of MCC PH 105 with 45, 50, 55%w/w of all four binder solutions. The granulator was set at 100 rpm for 3 min, and the binder solution was added at a constant rate. The end-point of mixing was also determined using the thermal effusivity sensor (C-therm ESP, New Brunswick, Canada). The wet granules formed at the end of the granulation were subjected to thermal evaluation using Modulated Differential Scanning Calorimetry (mDSC) and powder rheometer for additional testing. The remaining granules were passed through sieve # 14 and dried in a tray dryer at 60 °C until ≤5% w/w moisture was observed. Percentage of moisture retained was determined using Loss On Drying (LOD) (Ohaus, MB 200, Pinebrook, NJ). After drying, all the batches were subjected to thermal and rheological characterization.

2.4. Thermal effusivity measurements

Thermal Effusivity is a non-destructive method to determine the end point of wet granulation using intrinsic properties such as heat capacity, thermal conductivity, and density of the material/material mixture. Effusivity measurements were conducted using the thermal conductivity (TCi-D12) Probe (Mathis Instruments, Fredericton, NB, Canada) (Fig. 1) which was calibrated before testing, using polymethyl siloxane. Samples were placed in direct contact with the probe and were as flat as possible to ensure maximum connection with the probe, which supplies heat to the sample (<2 K) for about 0.8–1 s. The sensor detects interfacial heat flow change from the materials based on their intrinsic properties, which induces a voltage drop, and this is representative of its thermophysical property (Kleinebudde, 2004). Preliminary trials were carried out with small-scale batches of 10 g each. Based on initial experiments, lab scale batches of 700 g were prepared by adding 45% w/w (572.3 g), 50% w/w (700 g) and 55% w/w (855.4 g) of each binder solution, and were exposed to the TCi – D12 probe, to determine their effusivity reading.

Table 1
Binder solution.

Binders (0.5%) w/w	Solvent ratio (% w/w)		Viscosity @ 25 °C (cP)	Labeled
	Deionized water	Ethyl alcohol		
HPMC K4M CR	100	0	34.00	B1
HPMC K100M CR	100	0	146.60	B2
HPMC K4M CR	50	50	44.00	B3
HPMC K100M CR	50	50	276.30	B4



Fig. 1. Effusivity measurement probe.

$$\text{Effusivity} = \sqrt{\kappa \rho C_p} \quad (1)$$

where

κ = thermal conductivity (W/m·K)

C_p = heat capacity (J/kg·K)

ρ = density of the material (kg/m³)

2.5. Modulated Differential Scanning Calorimetry (mDSC)

Enthalpy change (ΔH) was analyzed using mDSC (Q100, TA Instruments, New Castle, DE), with nitrogen (50 mL/min) as purge gas. The experiments were performed in hermetically sealed aluminum pans with pin-hole, and the weight of each sample was 8 ± 3 mg. Thermograms were obtained at a heating rate of 5 °C/min from 20 to 250 °C, modulated ± 1.59 °C every 60 s.

2.6. Granules characterization

An FT4 Powder Rheometer (Freeman Technology, Gloucestershire, U.K.) was used to measure the flow properties of granules regarding the energy required to make them flow. The methodology employed granule samples that were tested in a 50 mm bore borosilicate glass cylinder. The granules were made to flow by moving a 48.00 mm diameter twisted blade rotationally and axially so that it moved along a helical path through the test sample. Basic Flow Energy (BFE), Specific Energy (SE), Conditioned Bulk Density (CBD) and permeability measurements samples were subjected preliminary to a conditioning process in which the blade causes gentle displacement of the powder to establish a consistent and reproducible packing density.

2.7. Basic flowability energy (BFE) and specific energy (SE) measurements

BFE and SE were measured in a single test using 50 mm × 160 ml vessel (Fig. 2) and calculated using Eq. (2). The test cycle moved the blade along a downward helical path (-5°) at a blade tip speed of 100 mm/s, thereby forcing the powder to flow around the blade. The axial and rotational forces acting on the blade during the cycle were measured continuously and used to derive the work done, or energy consumed in displacing the powder, this energy is known as BFE. Specific Energy was measured during the upward clockwise motion of the blade, generating a low-stress flow on the powder. The specific energy was calculated from the energy required per gram of powder mix to displace through transverse upward movement of the blade from bottom to the top of the vessel. The conditioning cycle preceded this test measurement.

$$\text{Total Energy Consumed} : dE = (T/(r \tan \alpha) + F) \cdot dH \quad (2)$$

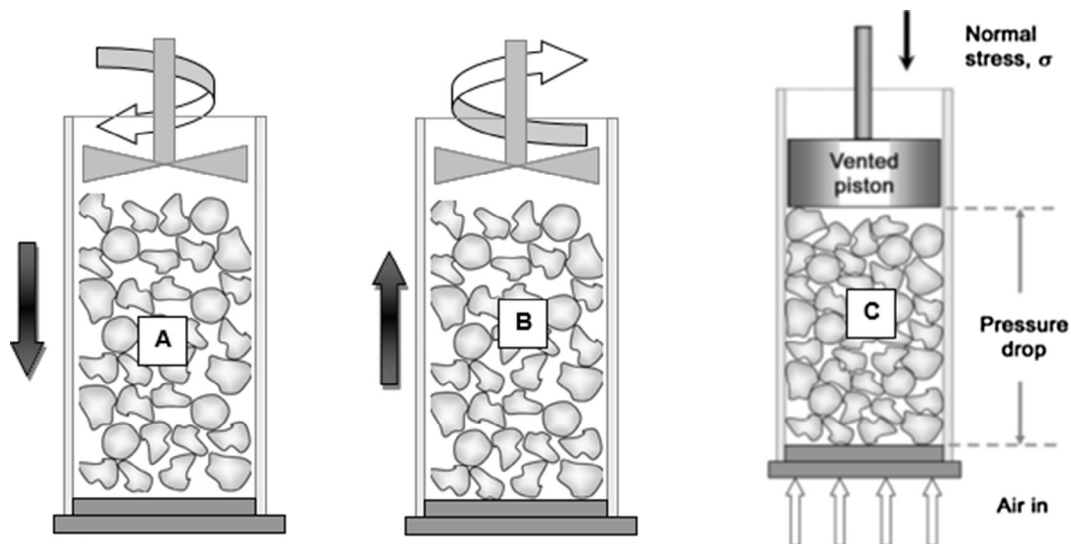


Fig. 2. (A) BFE, (B) SE, (C) permeability.

where

- r = Blade radius
- dH = Increment or decrement of vertical displacement
- α = Helical path angle
- F = Axial force on the blade (N)
- T = Torque acting on blade (N·m)

2.8. Conditioned Bulk Density (CBD)

Conditioned Bulk Density (CBD) is bulk density calculated after the conditioning cycle, which was measured along with BFE and SE (Fig. 2). Conditioning the powder bed helps to establish a consistent packing, maintaining the volume (160 ml). An inbuilt weighing scale measured the mass of the sample.

2.9. Permeability measurement

The pressure drop across the powder bed was determined during the permeability test which predicts materials ability to transmit air through its bulk under applied pressure, using a cylindrical vessel (50 mm × 85 ml) covered with an aeration base at its bottom (Fig. 2). During the test, a constant air velocity of 2.0 mm/s was maintained and varying normal stress (0.5, 1, 2, 4, 6, 8, 10, 12 and 15 kPa) applied using a vented piston. The permeability of the powder bed was measured using modified Darcy's Law (Eq. (3)).

$$k = q\mu L / \Delta P \quad (3)$$

where

- k = Permeability (cm²)
- μ = Air viscosity (Pa·s) (1.74×10^{-5} Pa·s)
- q = Air flow rate (cm/s)
- L = Length of powder bed (cm)
- ΔP = Pressure drop across the powder bed (mbar)

2.10. Sieve analysis test

The particle size distribution (PSD) of dried granules was performed by sieve analysis (Octagon 200, Endecotts, UK). 50 g of each batch was passed through a set of U.S. Standards sieves # 14 (1.40 mm), 16 (1.20 mm), 18 (1.00 mm), 20 (0.853 mm), 40 (0.422 mm), 60 (0.251 mm), 170 (0.089 mm), and 200 (0.075 mm), which were run, for 10 min at 5 amplitude. Sets of sieves are fitted with a collecting pan at the bottom to collect the fines. Sieves were weighed before and after the experiments to determine PSD and mean particle size.

2.11. Granule strength

Granule strength was determined using Texture Analyzer (TA XT Plus, Stable Micro Systems Ltd., Godalming, UK) with a 5.0 kg load cell. Twenty granules of each batch were screened through sieve #14 and were used to determine the granule strength using a flat tipped cylindrical stainless steel probe with dimensions of 30.00 mm length and 5.00 mm diameter (TA-54). During the test, each granule was positioned on a flat platform, and the probe was set to travel at a speed of 0.2 mm/s and penetrate a distance of 1.00 mm of granule with a data collection set to 250 points per seconds. Force versus Displacement curve was plotted, and the average reading for maximum crushing force (Fmax) was reported as granule strength.

2.12. Scanning Electron Microscopy (SEM)

The samples were mounted on a sample stub, coated with a thin layer of Au/Pd to make the sample surface conductive, followed by

examination in SEI (Secondary Electron Imaging) mode. SEI records the topographical features of the sample surface (Lu et al., 2016). The representative photomicrographs were digitally captured using Hitachi S-4000 FE-SEM at 100X magnification.

2.13. Tablet breaking force

Granules were lubricated using magnesium stearate and compressed into tablets using a single station Carver Press (Indiana, USA) at a compression force of 15 kN using 'B' tooling, round flat-head punches (0.44") with a target tablet weight of 500 ± 10 mg for all the batches. Tablet weight and thickness were measured before evaluating the tablet breaking force. Tablets were stored in a tightly sealed container and checked for tablet breaking force after 24 h using Schleuniger tablet tester 6D (Pharmatron, Uttigenstrasse, Switzerland).

3. Results and discussion

3.1. Thermal effusivity

The viscosity of binder solutions was determined using Brookfield viscometer before the granulation study (Table 1). A marginal difference in viscosity was observed on changing the binder solvent between K4M CR binder solutions, B1 and B3 as well as K100M CR binder solutions, B2 and B4. From the Table 2 and Fig. 3, it was observed that effusivity of microcrystalline cellulose 105 enhanced with an increase in the amount of binder solution in the powder bed. This increase in thermal effusivity was detected for all the binder solutions since thermal conductivity linearly increases with an increase in solvent content. The effusivity readings almost steadily increased to 40% w/w depicting initial granule formation. After that, a continuous rise from 45% w/w to 55% w/w was observed. The thermal effusivity readings dramatically increased till 65% w/w with values approaching 1100–1400 ($W s^{\frac{1}{2}} m^{-2} k^{-1}$) suggesting that MCC particles are completely surrounded by binder solution, symbolizing over granulation. The increase in effusivity reading with the addition of binder quantity is presumably due to enhanced thermal conductivity of the solvent. A sharp rise is reported after addition of 55% w/w of binder solution, which indicates that it's the optimum region of end point for wet granulation and attainment of physical equilibrium between the diluent and binder solution for granule formation.

A similar trend was observed with binder solution prepared using the hydro-ethanolic solvent system, B3, and B4. During over granulation, the effusivity readings are lower ($\sim 1100 W s^{\frac{1}{2}} m^{-2} k^{-1}$) than observed with water as solvent ($\sim 1300 W s^{\frac{1}{2}} m^{-2} k^{-1}$) due to the presence of ethanol and its thermal conductivity.

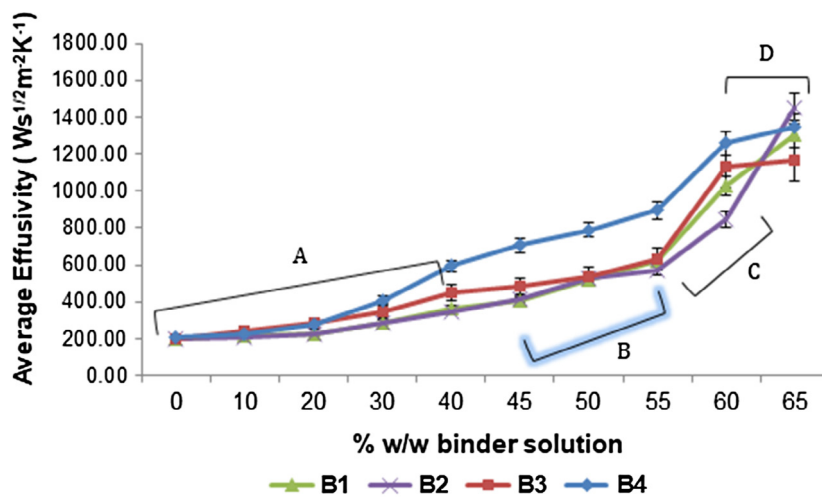
With such less significant difference in viscosity (Table 1) between both types of solvent for K4M CR and K100M CR, it can be hypothesized that both types of binder solutions might exhibit similar wetting properties and hence correspond to the same optimum end-point range. The similarity between the small scale and lab scale thermal effusivity readings (Tables 2 and 3) depicts the reproducibility of thermal effusivity measurements during scale-up.

3.2. Modulated Differential Scanning Calorimetry

The enthalpy change (ΔH) values are enlisted in Table 4. As observed in Table 4, ΔH values continue to increase as the amount of binder solution increases due to increase in heat capacity upon binder addition. At 55% w/w, a sharp rise in enthalpy value was observed indicating the presence of higher amount of solvent on

Table 2
Thermal effusivity as a function of % w/w binder solution (small scale batch).

%w/w Binder solution	Average thermal effusivity ($W s^{1/2} m^{-2} K^{-1}$) (n = 3)							
	B1 Batch	% RSD	B2 Batch	% RSD	B3 Batch	%RSD	B4 Batch	%RSD
0	201.4	2.3	202.2	2.1	199.0	2.1	205.3	2.3
10	218.8	3.0	207.7	1.8	241.0	2.9	222.1	1.9
20	221.7	2.2	226.1	1.6	280.9	2.3	279.4	3.2
30	284.3	1.9	285.7	4.2	344.5	2.7	409.6	2.1
40	362.1	2.5	343.8	3.5	448.1	2.9	591.9	2.6
45	403.1	3.3	415.7	2.6	481.3	2.2	704.2	1.9
50	519.9	3.4	527.2	2.6	533.0	4.2	790.2	3.2
55	623.4	3.4	573.0	2.5	631.2	3.3	895.1	2.6
60	1028.4	4.7	846.8	3.2	1134.9	3.7	1257.0	5.1
65	1302.4	4.3	1453.1	4.3	1170.0	3.5	1350.6	4.2



A) Initial granule seed formation B) Optimum granule formation range C) Over granulation
D) Slurry Formation

Fig. 3. Thermal effusivity of wet granules (small scale batches).

Table 3
Thermal effusivity as a function of % w/w binder solution (lab scale batch).

%w/w Binder	Average thermal effusivity ($W s^{1/2} m^{-2} K^{-1}$) (lab scale batch, n = 3)							
	B1 Batch	% RSD	B2	% RSD	B3	% RSD	B4	% RSD
45	439.06	5.1	410.68	4.8	460.10	4.9	700.78	3.8
50	541.34	4.6	557.23	3.6	536.96	3.5	785.22	4.3
55	647.52	4.1	583.01	2.9	640.54	3.3	896.2	4.0

Table 4
 ΔH values of wet granules.

%w/w binder solution	ΔH values of wet granules (J/g)			
	B1	B2	B3	B4
45%	665.8	961.5	473.3	429.7
50%	1083.0	1046.0	664.3	583.4
55%	1165.0	1134.0	712.0	756.5

the surface of the granule, which confirms the formation of granules and attainment of wet granulation endpoint. For granules prepared with the hydro-alcoholic solvent system, the change in enthalpy values is relatively less with the increase in binder solution percentage. mDSC thermograms for all four batches are shown in Fig. 4, which reconfirms the phenomenon observed in thermal

effusivity readings, reported in the previous section. mDSC thermograms for all four batches are shown in Fig. 4. The sharp endothermic peak near 100 °C reflects the presence of water confirming endpoint at 55% for B1, B2, B3 and B4 (Fig. 4). When comparing the solvent systems, water-based granules, B1 and B2, has relatively higher enthalpy values as compared to hydro-alcoholic

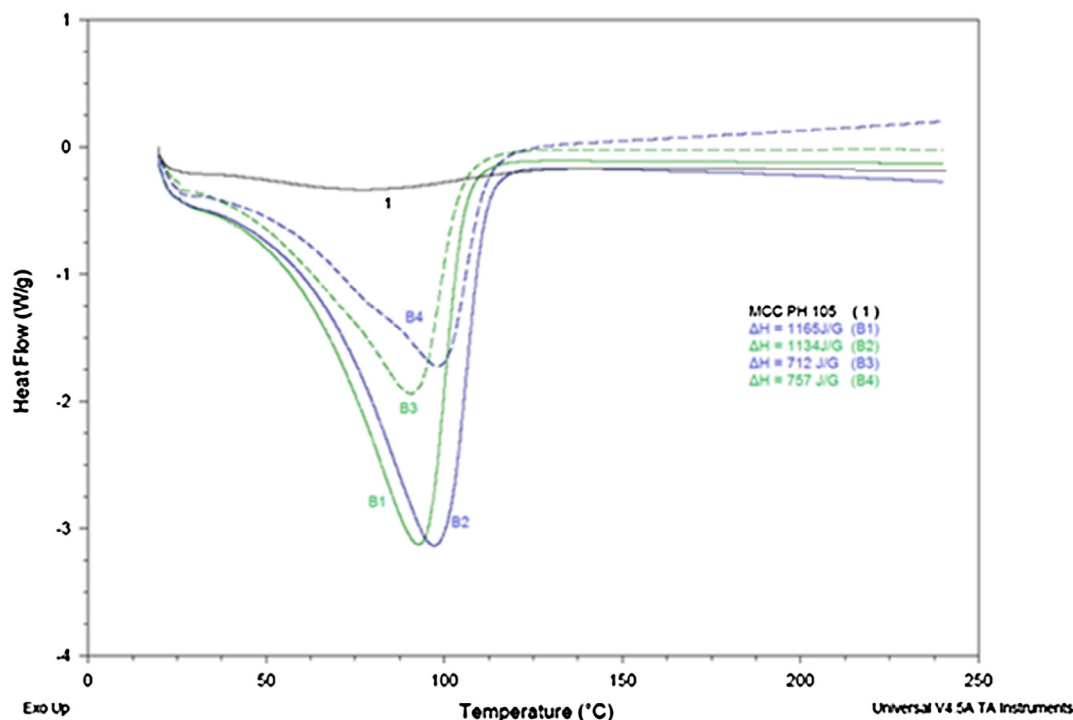


Fig. 4. Comparison of mDSC thermograms at 55% w/w binder solutions.

based granules, B3 and B4. A higher presence of structured water in the water-based granules than those with hydro-alcoholic granules can be a contributing factor for the difference in enthalpy values.

3.3. Basic Flowability Energy (BFE) & Specific Energy (SE) Measurement

It was observed that BFE increases gradually with an increase in the amount of granulating fluid followed by a sudden rise in BFE (Fig. 5). This phenomenon can be explained by efficient rearrangement of granules leading to the absence of air pockets which increases the energy required by the blade to push through the granular mass (Kristensen and Schaefer, 1987). From Figs. 5 and 6, it was apparent that wet granules exhibit higher BFE values than dried granules for all binder solutions because granulating fluid displaces the air voids between the particles. When comparing BFE values of granules formed by water and the hydro-alcoholic solution it was observed that BFE value for hydro-alcoholic solution granules was lower as compared to that of water as a solvent

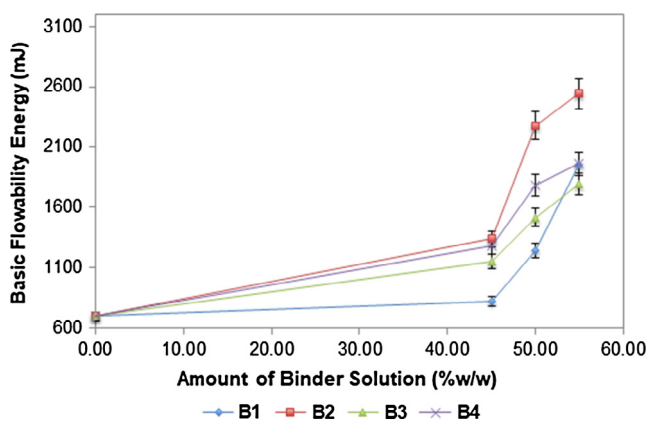


Fig. 5. BFE as a function of amount of binder solution (Wet Granules).

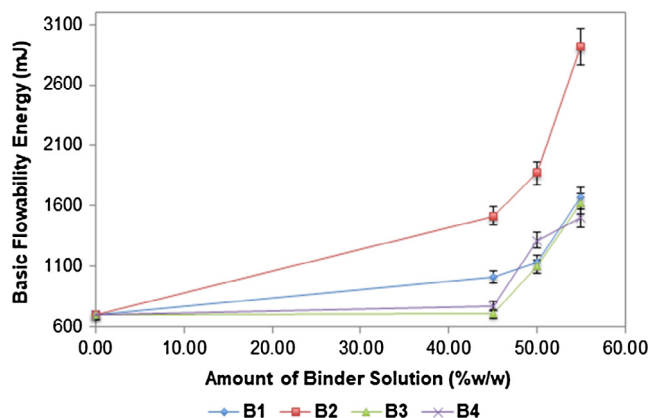


Fig. 6. BFE as a function of amount of binder solution (Dried Granules).

with both grades of HPMC (Figs. 5 and 6). Water tends to form a stable hydrogen bond with MCC. The hydrogen bond formation tendency of hydro-alcoholic solvent is relatively less; managing to hold the particles less firmly in the latter. While comparing both binders, it was observed that granules formed with B2 & B4 show relatively higher BFE values. It may be due to the fact that granules formed with high viscosity binder exhibit a more closely packed arrangement (Figs. 5 and 6). As a result of this, higher energy is required by the blade to travel through the granular mass, which corresponds, to a high BFE value.

SE measures the powder flow in unconfined low-stress environments. It correlates with powder flow when being fed gravimetrically. This process is analogous to die filling process. It has been found by several researchers that, higher the SE values, higher is the cohesion (Chaudhari and Dave, 2015). Due to a small particle size of MCC 105 (20 μm), the SE of pure powder is very high as compared to that of granules formed by either of the binders (Table 5). In the case of wet granules, the solvent on the surface

Table 5
Specific energy (SE) values for wet and dried granules of B1, B2, B3 and B4.

% w/w binder solution	Average specific energy (SE) (mJ/g) (n = 3)															
	B1				B2				B3				B4			
	Wet	% RSD	Dried	% RSD	Wet	% RSD	Dried	% RSD	Wet	% RSD	Dried	% RSD	Wet	% RSD	Dried	% RSD
0%	–	–	15.48	2.89	–	N/A	15.48	2.9	–	–	15.48	2.9	–	–	15.48	2.9
45%	8.38	3.6%	13.14	2.4	8.02	3.1	9.77	2.4	11.22	4.1	5.41	2.2	29.84	3.8	6.88	2.3
50%	15.06	3.3%	9.03	2.8	12.03	2.3	8.6	3.2	11.34	3.5	4.50	1.6	15.67	2.6	7.43	2.1
55%	17.23	2.1%	8.64	2.6	11.72	3.0	8.91	2.0	17.47	3.7	6.57	2.9	16.9	3.0	7.04	1.7

promotes cohesion of particles leading to higher SE values. For Dried granules, the lower SE values indicate a reduction in the cohesiveness of MCC 105 upon formation of granules. These SE values were similar for both types of solvent systems.

3.4. Conditioned Bulk Density (CBD)

Conditioned Bulk Density of dried granules prepared by all four binder solutions is reported in Table 6. For water-based granules (B1 and B2) CBD values decrease gradually whereas, for hydro-alcoholic granules (B3 and B4) CBD value increases. The changes in CBD values may be due to changes in porosity during the granule development stage or due to insufficient bonding between the particles. CBD values also correlate with the compressibility of the mass (Kristensen and Schaefer, 1987).

3.5. Permeability measurement

The pressure drop values predict material's ability to transmit air through its bulk under applied pressure. The pressure drop values of wet granules for all four batches B1, B2, B3 and B4 (Fig. 7) show a dramatic decrease at 45% w/w binder addition, compared to the respective original dry powder (MCC 105). The reduction in pressure drop is presumably due to the addition of binder which leads to wetting of the powder and the aggregation of the fine particles. For dried granules (Fig. 8), the resistance to airflow decreases with the formation of granules, which leads to a drastic decrease in pressure drop at 45% w/w binder solution. The particle sizes enlarge with high efficacy and transform into irregularly shaped granules by forming the gel-layer. Additionally, without the fine particles to block the air pathways, the space between the particles will be more significant, which can easily trap more air. For the 45% w/w to 50% w/w binder addition, the pressure drop remains at the same level with slight differences. This result further validates the hypothesis that this range contains the consolidation and coalescence stages, during which the addition of binder reinforces the bonding systems among the particles and the granules are not forming any connection or agglomerates. The values of the pressure drop significantly decrease at 55% w/w binder addition because the particles continue to grow. The granules near endpoint are believed to be more spherical, symmetrical and uniform sized whereby they offer more air permeability and least pressure drop. Granules formed with the hydro-alcoholic solvent system (B3 and B4) show relatively less pressure drop and thus exhibit better permeability as compared to granules formed with the water-based

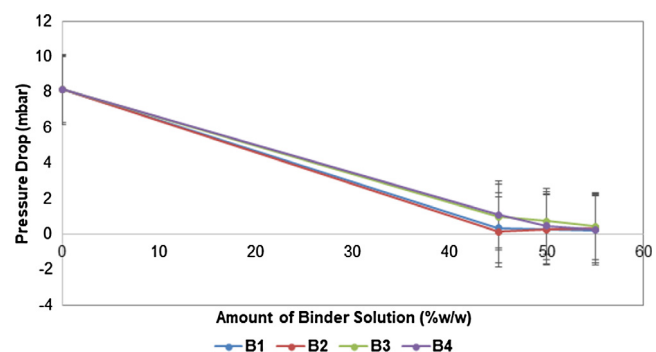


Fig. 7. Pressure Drop (PD) as a function of amount of binder solution (Wet Granules).

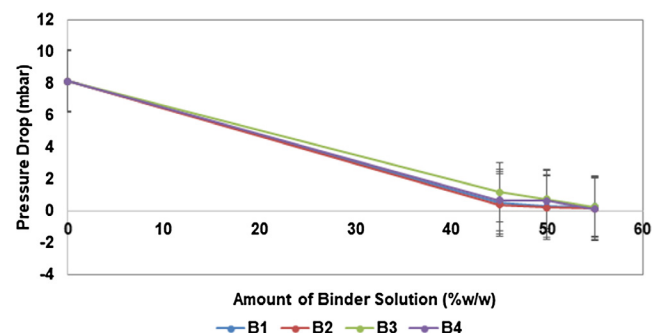


Fig. 8. Pressure Drop (PD) as a function of amount of binder solution (Dried Granules).

binder solution (B1 and B2). Also amongst two binders, granules formed using K100M CR (B2 & B4) show better permeability than those established by K4M CR (B1 & B3).

3.6. Sieve analysis test

For the B1, B2, B3 and B4 (Table 7) (Figs. 9 and 10), 45% w/w dried granule has a high amount of fine particles, suggesting improper granule formation. At 50% w/w binder level, particle size distribution is relatively broader. Granules formed with 55% w/w binder solutions exhibit a broad and even particle size distribution, suggesting that the granules being formed are appropriate and

Table 6
Conditioned bulk density (CBD) values for dried granules of B1, B2, B3 and B4.

% w/w binder solution	Average conditioned bulk density (g/mL) (n = 3)							
	B1	%RSD	B2	%RSD	B3	%RSD	B4	%RSD
45%	0.49	2.2	0.52	3.8	0.31	2.9	0.32	4.0
50%	0.45	3.1	0.52	4.6	0.36	3.9	0.35	3.7
55%	0.42	3.4	0.48	3.4	0.37	3.0	0.38	3.3

Table 7
Amount of particles retained on each sieve for of dried granules of B1, B2, B3 and B4.

Sieve No.	Amount of particles retained on each sieve (g)											
	B1			B2			B3			B4		
	45% w/w	50% w/w	55% w/w	45% w/w	50% w/w	55% w/w	45% w/w	50% w/w	55% w/w	45% w/w	50% w/w	55% w/w
14	0.4	0.9	2.4	0.1	0.1	0.4	0.2	0.2	1.4	0.37	0.8	0.48
16	2.5	1.7	3.6	0.8	1.2	4.0	1.0	1.3	4.3	3.41	4.65	6.63
18	2.1	2.5	5.2	2.0	2.4	3.7	1.4	2.5	4.7	6.28	5.95	8.01
20	2.3	3.0	5.1	2.6	2.7	4.4	2.0	2.8	4.3	5.64	5.96	7.76
40	13.4	14.1	19.2	8.6	11.5	18.3	4.0	9.9	14.9	15.66	17.25	18.31
60	8.7	10.2	7.1	5.4	10.1	12.4	5.0	7.1	8.6	6.23	7.31	4.88
170	12.4	13.2	5.2	12.0	13.3	8.0	17.2	17.2	9.3	4.84	6	2.53
200	1.5	1.3	1.0	3.9	0.9	0.2	2.0	2.1	0.1	0.62	0.13	0.15
Pan	6.2	3.0	0.7	14.6	7.9	0.7	15.5	6.8	2.3	6.23	2.03	1.04

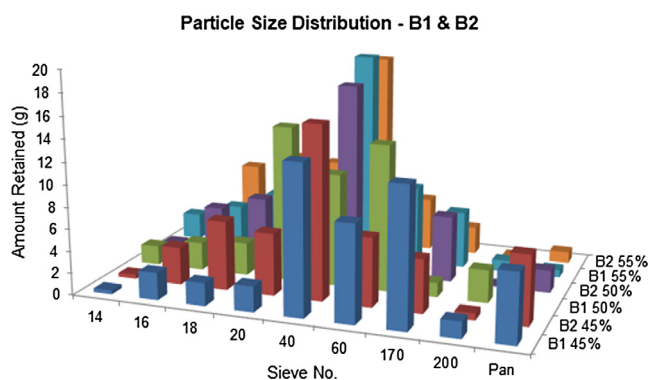


Fig. 9. Particle size distribution of B1 & B2.

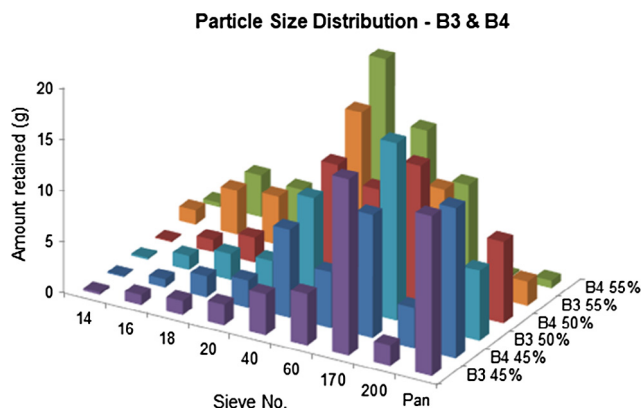


Fig. 10. Particle size distribution of B3 & B4.

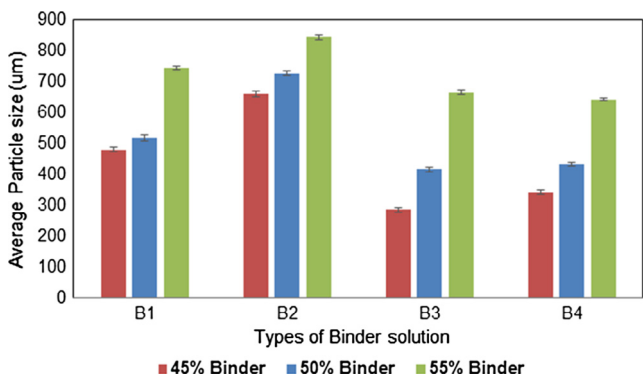


Fig. 11. Average particle size as a function of percent w/w binder solution.

uniform, which would contribute to better flowability and superior compressibility. Fig. 11 illustrates the calculated average particle size, displaying the above findings. Therefore, the hypothesis that the end-point for K4M CR and K100M CR lies within 50% w/w–55% w/w is further confirmed.

3.7. Physical characterization

The granule strength for K100M CR granules is relatively higher than K4M CR granules (Table 8), which further supports the theory that viscosity is the dominant factor for granule strength and granule properties. The higher viscosity of HPMC can be correlated with the formation of a thicker gel layer around MCC particles, leading to a more efficient self-binding system, and limiting the breakage of granules (van den Dries et al., 2003). The granule strength also reflects the weak plasticity and elasticity characteristics of the K100M CR granules. The granule strength of 45% w/w water-based dried granules (B1 and B2) have a similar advantage to that of the 50% w/w samples. However, the 45% w/w water based granules exhibit a high%RSD, indicating an unstable and non-uniform granule formation. The 50% w/w water-based granules have more uniform granules with moderately strong bonds formed within the granules. The 55% w/w water based granules have a very high granule strength that may attribute to a lowered elasticity and poor compressibility. The granule friability of hydro-alcoholic batches (B3 & B4) is observed to be higher than the water-based batches (B1 & B2), due to the formation of porous granules.

The SEM images illustrate granule enlargement and a simultaneous reduction in a number of fines for all the batches with an increase in percent w/w binder solution (Figs. 12 and 13). Tablet hardness for all the batches considerably varies as shown in Table 8 and Fig. 14. The tablet breaking force for B1 batch linearly increased with the addition of binder solution (45% w/w to 55% w/w). On the contrary, tablet breaking force for B2 batch decreased with the addition of binder solution which can be due to the relatively higher granule size of B2 with stronger inter-particle bonds and poor compressibility characteristics as previously reported in the study. The higher granule strength further confirms this hypothesis seen in the B2 batch (Table 8). For hydro-alcoholic batches (B3 and B4), there was no significant difference in the tablet breaking force values (Table 9). Overall tablet breaking force values of the hydro-alcoholic system (B3 & B4) was higher when compared to the aqueous system (B1 & B2). The tablet weight and thickness data further support the tablet breaking force values.

This work shows the fundamental difference between HPMC K4M CR and HPMC K100M CR as binding agents, its effect on the rheological properties of MCC PH 105 and also the effect of solvent and solvent combination on wet granulation using rheological and thermal properties of the powder. Rheological properties characterized using FT4 rheometer such as Basic flowability energy,

Table 8
Granule strength (crushing force) of dried granules of B1, B2, B3 and B4.

% w/w binder solution	Average granule strength [crushing force (lb)] (n = 15)							
	B1	%RSD	B2	%RSD	B3	%RSD	B4	%RSD
45	0.08	3.3	0.36	4.0	0.04	3.7	0.05	4.4
50	0.13	3.1	1.01	3.2	0.07	4.0	0.08	3.8
55	1.17	2.5	1.61	3.0	0.15	2.8	0.37	2.2

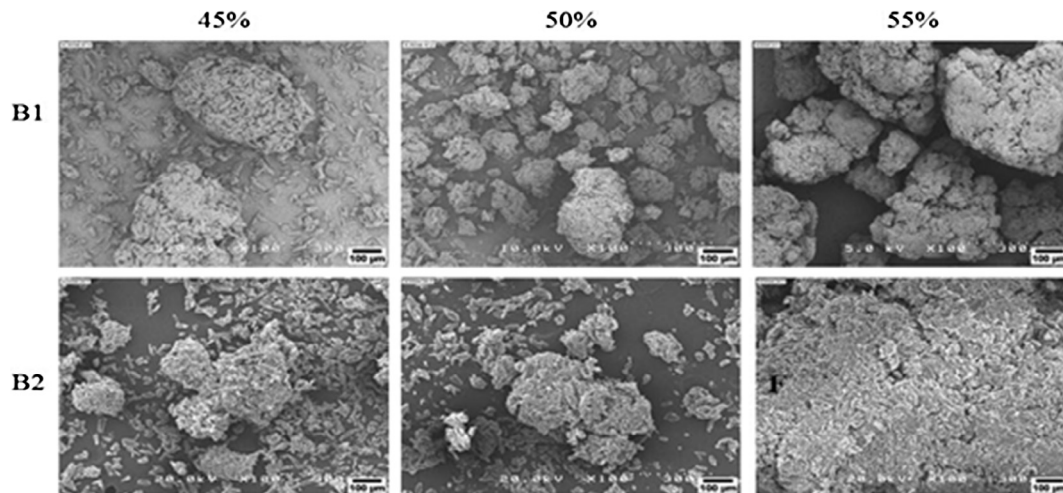


Fig. 12. Scanning Electron Microscopy – B1 & B2 at 100X magnification.

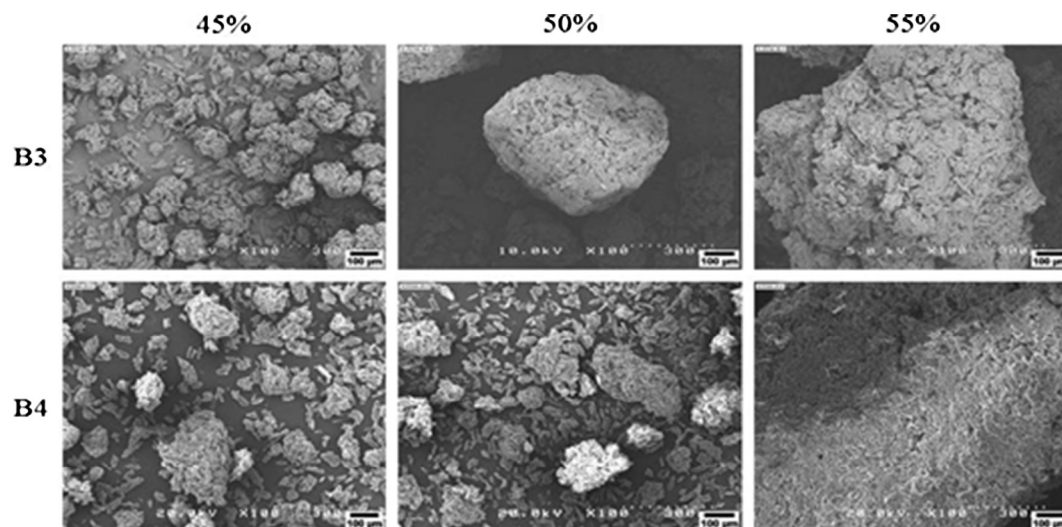


Fig. 13. Scanning Electron Microscopy – B3 & B4 at 100X magnification.

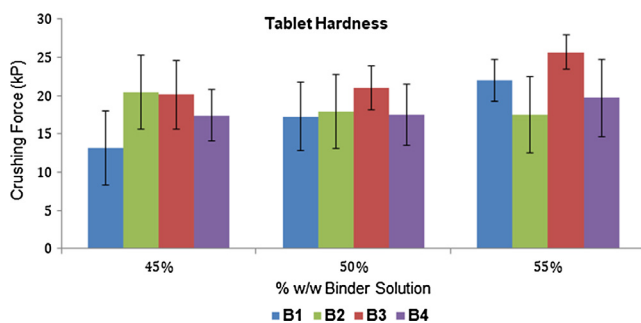


Fig. 14. Tablet hardness as a function of percent w/w binder solution.

Specific Energy, and Permeability show the cohesive nature and poor flow behavior of MCC 105 due to its finer particle size. Using HPMC polymers, we have managed to improve its flow properties and granule strength. In a wet granulation process, an End-point determination has been one of the most crucial and complex phenomena to be defined. In the present study, we tried to determine the end point of MCC PH 105 wet granulation process, carried out using Methocel™ K4M CR and K100M CR binders by measuring thermal properties and flow properties of the granules. Effusivity sensor probe identifies the thermal property of wet granules and suggests 55% w/w concentration of binder solution as our end-point by measuring its heat capacity, thermal conductivity and density for all four batches (B1 - B4). The end-point range determi-

Table 9
Tablet Breaking Force, Tablet weight and Thickness as a function of% w/w binder solution.

% w/w binder solution	Average tablet breaking force (kP), weight (g) and thickness (mm) data (n = 10)											
	B1			B2			B3			B4		
	F (kP)	W (g)	T (mm)	F (kP)	W (g)	T (mm)	F (kP)	W (g)	T (mm)	F (kP)	W (g)	T (mm)
45%	13.10 ± 0.29	0.507 ± 1.6	5.4 ± 0.08	20.41 ± 0.31	0.504 ± 1.9	4.9 ± 0.09	20.09 ± 0.41	0.508 ± 0.7	5.2 ± 0.05	17.41 ± 0.36	0.500 ± 1.6	5.4 ± 0.09
50%	17.21 ± 0.36	0.500 ± 1.1	5.3 ± 0.05	17.88 ± 0.28	0.499 ± 1.1	5.4 ± 0.07	20.95 ± 0.28	0.505 ± 1.0	5.1 ± 0.1	17.48 ± 0.33	0.505 ± 1.1	5.1 ± 0.05
55%	21.80 ± 0.21	0.505 ± 0.5	5.0 ± 0.04	17.49 ± 0.23	0.500 ± 0.6	5.2 ± 0.05	25.67 ± 0.21	0.500 ± 0.5	4.9 ± 0.06	19.69 ± 0.23	0.504 ± 0.5	5.0 ± 0.04

F = Tablet Breaking Force, W = Tablet Weight, T = Tablet Thickness.

nation was supported by mDSC data and rheological properties such as BFE, SE and permeability measurements where a sharp increase was observed at the end-point of granulation.

4. Conclusion

Wet granulation is a frequently employed process during the manufacture of oral solid dosage forms. The objective is to convert the often fine and cohesive active ingredient and excipients, into more uniform, free-flowing granules that are optimized for downstream processing. Granules that possess ideal properties result in efficient process function, including high throughput and tablets of the desired critical quality attributes. The above work explains the effect of different solvent systems used for wet granulation binder preparation on the quality attributes of MCC granules. Thermal effusivity measurements and rheological parameters can be a sensitive marker of the transition point from wet mass to granules and a precise tool for detecting an end-point range, where the granules have attained their optimal properties.

Conflict of interest

The author declares no conflict of interest.

References

Achanta, A., Adusumilli, P., James, K., 1997. Endpoint determination and its relevance to physicochemical characteristics of solid dosage forms. *Drug Develop. Ind. Pharm.* 23 (6), 539–546.

Biswas, S., Nahar, K., Hossain, M.K., Bhuiyan, J.R., Abdullah-Al-Mamun, M., Rana, M. S., 2014. Formulation design and in-vitro release profile evaluation of theophylline hydrochloride sustained release tablet using different polymer at different concentration. *J. Chem. Pharm. Res.* 6 (8), 12–23.

Chaturvedi, K., Gajera, B.Y., Xu, T., Shah, H., Dave, R.H., 2018. Influence of processing methods on physico-mechanical properties of Ibuprofen/HPC-SSL formulation. *Pharm. Dev. Technol.*, 1–9.

Chaudhari, S.P., Dave, R.H., 2015. To prepare and characterize microcrystalline cellulose granules using water and isopropyl alcohol as granulating agents and determine its end-point by thermal and rheological tools. *Drug Develop. Ind. Pharm.* 41 (5), 744–752.

Chitu, T.M., Oulahna, D., Hemati, M., 2011. Wet granulation in laboratory scale high shear mixers: effect of binder properties. *Powder Technol.* 206 (1), 25–33.

Dave, R.H., Wu, S.H., Contractor, L.D., 2012. To determine the end point of wet granulation by measuring powder energies and thermal properties. *Drug Develop. Ind. Pharm.* 38 (4), 439–446.

Dugar, R.P., Gajera, B.Y., Dave, R.H., 2016. Fusion method for solubility and dissolution rate enhancement of ibuprofen using block copolymer poloxamer 407. *AAPS PharmSciTech.* 17 (6), 1428–1440.

Fariss, G., Keintz, R., Okoye, P., 2006. Thermal effusivity and power consumption as: PAT tools for monitoring granulation end point. *Pharm. Technol.* 30 (6),

Freeman, R., 2004. SOLID DOSAGE predicting flowability and characterizing powders. *Pharm. Technol. Europe* 16 (1), 41–45.

Gajera, B.Y., Dugar, R.P., Dave, R.H., 2016. Formulation development and optimization of ibuprofen poloxamer melt granules using hydrophilic excipients. *Br. J. Pharma. Res.* 13 (6).

Iveson, S.M., Litster, J.D., Hapgood, K., Ennis, B.J., 2001. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. *Powder Technol.* 117 (1), 3–39.

Jain, K.K., 2008. *Drug Delivery Systems*. Springer Science & Business Media.

Johansen, A., Schaefer, T., 2001. Effects of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. *Eur. J. Pharm. Sci.* 12 (3), 297–309.

Jørgensen, A.C., 2004. Increasing process understanding of wet granulation by spectroscopic methods and dimension reduction tools.

Keningley, S., Knight, P., Marson, A., 1997. An investigation into the effects of binder viscosity on agglomeration behaviour. *Powder Technol.* 91 (2), 95–103.

Kleinebudde, P., 2004. Roll compaction/dry granulation: pharmaceutical applications. *Eur. J. Pharm. Biopharm.* 58 (2), 317–326.

Knight, P., 2004. Challenges in granulation technology. *Powder Technol.* 140 (3), 156–162.

Kristensen, H.G., Schaefer, T., 1987. Granulation: a review on pharmaceutical wet-granulation. *Drug Develop. Ind. Pharm.* 13 (4–5), 803–872.

Leuenberger, H., Puchkov, M., Krausbauer, E., Betz, G., 2009. Manufacturing pharmaceutical granules: is the granulation end-point a myth? *Powder Technol.* 189 (2), 141–148.

Levin, M., 2006. Wet granulation: End-point Determination and Scale-up. *Encyclopedia of Pharmaceutical Technology*. Marcel Dekker, New York, pp. 4078–4098.

Lieberman, H.A., Lachman, L., 1980. *Pharmaceutical Dosage Forms: Tablets*: 1980. Marcel Dekker.

Lu, Z., Yang, Y., Covington, R.-A., Bi, Y.V., Dürig, T., Ilies, M.A., et al., 2016. Supersaturated controlled release matrix using amorphous dispersions of glipizide. *Int. J. Pharm.* 511 (2), 957–968.

Pariikh, D.M., 2016. *Handbook of Pharmaceutical Granulation Technology*. CRC Press.

Patel, R., Podczek, F., 1996. Investigation of the effect of type and source of microcrystalline cellulose on capsule filling. *Int. J. Pharm.* 128 (1–2), 123–127.

Shah, N.H., Railkar, A.S., Phuapradit, W., Zeng, F.-W., Chen, A., Infeld, M.H., et al., 1996. Effect of processing techniques in controlling the release rate and mechanical strength of hydroxypropyl methylcellulose based hydrogel matrices. *Eur. J. Pharm. Biopharm.* 42 (3), 183–187.

Sinko, C., 1997. Granulation characterization: methods and significance. *Drugs Pharm. Sci.* 81, 419–470.

Stubberud, L., Arwidsson, H.G., Larsson, A., Graffner, C., 1996. Water solid interactions II. Effect of moisture sorption and glass transition temperature on compactibility of microcrystalline cellulose alone or in binary mixtures with polyvinyl pyrrolidone. *Int. J. Pharm.* 134 (1–2), 79–88.

Sun, C.C., 2008. Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose. *Int. J. Pharm.* 346 (1), 93–101.

van den Dries, K., de Vegt, O.M., Girard, V., Vromans, H., 2003. Granule breakage phenomena in a high shear mixer; influence of process and formulation variables and consequences on granule homogeneity. *Powder Technol.* 133 (1), 228–236.

Wikberg, M., Alderborn, G., 1993. Compression characteristics of granulated materials. VII. The effect of intragranular binder distribution on the compactibility of some lactose granulations. *Pharm. Res.* 10 (1), 88–94.