IJPSR (2018), Volume 9, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 May, 2017; received in revised form, 20 July, 2017; accepted, 30 October, 2017; published 01 January, 2018

TO EVALUATE PHYSICOCHEMICAL CHARACTERISTICS OF GRANULATION FOR LACTOSE AND ACETAMINOPHEN BY UTILIZING RHEOLOGICAL AND THERMAL TOOLS

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Keywords:

Granulation, Crystalline form, Rheological, Effusivity, Flow Energy, Texture Analyzer, Granule Strength

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ABSTRACT: The purpose of the study is to evaluate the effect of the granulation properties of Lactose depending upon the use of its crystalline forms and the impact of active (Acetaminophen) concentration using rheological and thermal tools. Lactose was chosen as an excipient available in different hydrate forms (anhydrous and monohydrate) and Acetaminophen (APAP) was selected as a model drug for the subject research. Preliminary research was performed to determine wet-granulation end-point utilizing a real time off-line PAT tool, thermal effusivity. Further research was continued for low-shear wet granulation for the powder blends of drug and excipients. The properties of wet and dried granulation were determined using Powder Rheometer, Thermal effusivity and DSC. The dried granules crushing strength were evaluated using Texture Analyzer. Acetaminophen is a strong cohesive active, which upon wet granulation was found to bind strongly with Lactose particles to form more flowable and compressible granular mass. The granulation prepared using anhydrous form of Lactose with APAP showed higher bulk density and permeability as compared to hydrate form of Lactose. The evaluation of dried granules indicated that % compressibility was lower and peak crushing force was higher for Lactose anhydrous as compared to Lactose monohydrate. A clear distinction in granulation properties using the approach presented in the current research using Lactose and Acetaminophen will provide a time and cost effective approach for formulation scientists for an early on formulation design and selection of excipients using advanced techniques of rheological and thermal tools.

INTRODUCTION: Preformulation activities in pharmaceutical research and development are foundations for understanding a complete profile of particular active pharmaceutical ingredient (API). The preformulation study which includes drug - excipient interaction is essential from a dosage form design point of view.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(1).382-92

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(1).382-92

A study involving interaction between drug and excipients based on the rheological and thermal properties can provide an insight into formulation approaches to be used for the materials in the formulation.

There are various strategies available for improving powder flow to formulate a solid dosage form. Two most prevalent approaches are dry and wet granulation methods which have distinct advantages and disadvantages [1]. There are various drugs and excipients available in different crystalline forms which may lead to a phase transformation during pharmaceutical processing [2 - 4].

It is well established that the pharmaceutical process may lead to a physical form transformation of drug or excipient [5, 6]. However, Investigation must be carried out regarding how the rheological and thermal properties can be changed in relation to such physical transformations. Lactose is a widely used excipient available as various forms such as β-Lactose anhydrous, α - Lactose monohydrate. The anhydrous form of Lactose is commonly chosen for its better compatibility compared to Lactose monohydrate in tablet formulations [3]. Wet granulation is an approach where components of the formulation are blended together and a wet granulating agent is added to form the granules through liquid bond formation between primary particles [7].

Detailed studies have been conducted at various stages of wet granulation explaining nucleation of primary particles with granule growth by coalescence which is greatly dependent on quantity of liquid material added [8]. When dealing with wet granulation, a thorough understanding is required with respect to the end of the process as the process is subjective in nature and can lead to different resulting products. The end point of wet granulation is not a discrete point but can be determined as a wide zone in the torque curve [9].

The authors in previous study have shown the use of rheological and thermal analyses to conduct end point of wet granulation [10]. In the current study, the establishment of a wet-granulation endpoint is primarily confirmed through thermal effusivity measurements. The objectives of the current research is to evaluate the effect of the wet-granulation end point for Lactose depending upon the use of its crystalline forms and the effect of API concentration on the granulation properties through rheological and thermal parameters.

MATERIALS AND METHODS: Lactose anhydrous (Lac-A) and Lactose monohydrate (Lac-M/ FloLac) were generously donated by Mutchler Inc., (Harrington Park, NJ). Acetaminophen (APAP) was supplied by Mallinckrodt Inc., (Hazelwood, MO). Deionized water (Barnstead Nanopure - Thermoscientific system, Waltham, MA) was collected below 15 mΩ -cm. All the materials were used as received.

Preparation of Drug-Excipient Blends: Drug-Excipient blends were prepared using Acetaminophen (APAP) as a model drug and hydrate forms of pharmaceutical excipients *i.e.*, Lactose anhydrous (Lac-A) and Lactose monohydrate (Lac-M). Lactose (1 kg) was mixed with APAP in appropriate quantity to prepare 0, 5, 20, 35 and 50% w/w drug (APAP) loading in a turbula blender for a mixing time of 10 min. The blending time was determined using thermal effusivity measurements based on % RSD determination [11, 12].

Preliminary Studies for Determining End-Point of Wet Granulation: Initial studies on wet granulation end point determination were performed using 10 g of prepared powder blends in a small 100 mL glass beaker to which Deionized (DI) water was added gradually at 5% (0.52 g), 10% (1.25 g), 15% (1.76 g), 20% (2.50 g), 25% (3.33 g) and 30% (4.28 g) concentrations. The material was gently stirred with a glass rod for about 30 - 45 sec. Approximately 5 g of the wet mass was sampled out and was subject to thermal effusivity measurements.

Method of preparation for Wet and Dried granules: From initial studies, a 1 kg of powder blend was subject to wet granulation in a using a low shear granulator, Cuisinart mixer (East Windsor, NJ). DI water was gradually added into the powder blend within 30 sec at a 40 rpm blade speed. The wet granulation in Cuisinart mixer represents the low shear wet granulation process. After addition of appropriate amount of DI water, the blade speed was increased to 100 rpm for 2 min to uniformly disperse water and form granules.

A part of the wet granules was subjected to rheological and thermal analysis. The remaining wet granules were dried in an oven at 50 °C for 24 hrs and % Loss on drying (LOD) was measured using LOD apparatus (Ohaus, MB 200, Pinebrook, NJ) to confirm the complete drying of granules (approximate 5% w/w LOD). The dried granules were passed through US mesh # 12 (1400 µm). The rheological and thermal properties of dried granules were measured along with granule strength measurements using Texture analyzer ((Texture Technologies, Scarsdale, NY).

Various Characterization Methods for Wet and Dry Granules:

Rheological characterization of granules: Rheological characterizations were performed on initial powder blends, wet granules and dried granules using Freeman technology rheometer (FT-4) (Worcestershire, UK). The instrument was calibrated for force, torque and height measurements before performing the actual tests. Initially before performing the tests, the powder rheometer was programmed to condition the powder bed using the rheometer blade by gently lifting powder and depositing it behind the blade providing loosening of powder bed and slightly aerate powder bed.

Conditioning was performed in both upward and downward directions. The tests were performed using 50 mL borosilicate glass vessels with 48 mm blade. During testing two kinds of forces namely, rotational (torque) and axial force act on the rheometer blade. Based on the properties of sample, variations in such forces are measured as flow energies. Various flow energies and bulk properties of powder blends and granules were characterized using following tests [13].

Basic Flow Energy (BFE) Measurement: A cylindrical borosilicate glass vessel with specified dimension (50 mL) was filled with sample material and set on platform of the rheometer. To measure BFE, particular flow pattern was generated by downward anti-clock wise motion of appropriate diameter (23.5 mm or 48.0 mm) twisted blade at 100 mm/s tip speed and -5° helix angle imparting high stress flow mode in the powder bed and energy was calculated by work done during this downward traverse (see **Fig 1**.)

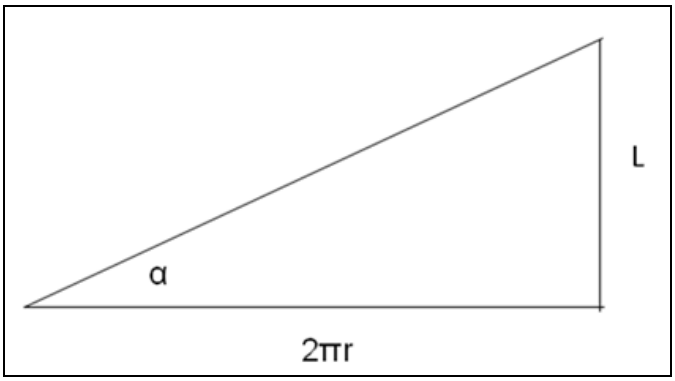


FIG. 1: SCHEMATIC DIAGRAM FOR MOVEMENT OF BLADE FOR ENERGY CALCULATION

The force - displacement profile of the powder through the distance blade travelled was integrated for basic flow energy calculation.

Energy consumed: $dE = (T/(R \tan \alpha) + F)\, dH$.....(1)

R = Blade radius (m)
dH = Vertical displacement (m)
α = Helical path angle (°)
F = Axial force on the blade (N)
T = Torque acting on blade (Nm)

Specific Energy (SE) Measurement: SE was carried out using the flow pattern generated by upward clock wise motion of rheometer blade at 100 mm/s tip speed and 5° helix angle providing low stress flow mode on the powder bed. The measurement was conducted during BFE test where SE was calculated by work done during this upward traverse.

Conditioned Bulk Density (CBD) Measurement: Along with Flow energies measurements (BFE and SE), CBD was also calculated based on the ratio of mass of powder sample by its volume occupied in the vessel. While filling the powder sample in the vessel up to volume of (160 ml), the mass of the powder sample was measured using inbuilt electronic weighing balance and the volume of powder sample was fixed (160 ml).

Pressure Drop (PD) Measurement: For PD measurement, the cylindrical vessel was affixed with an aeration base at the bottom to allow passage of air through the powder bed with an air velocity of 10 mm/s. The test was carried out using a vented piston which provided normal stress on powder bed upto 15kPa. PD across the powder bed was measured using modified equation of Darcy`s Law and is represented by following equation 2.

$$K = q\mu L/\Delta P \text{.....(2)}$$

K = Permeability (mm^2)
μ = Air viscosity (Pa.s) (1.74×10^{-5} Pa.s)
q = air flow rate (mm/s)
L = Length of powder bed (mm)
ΔP = Pressure drop across the powder bed (mbar).

Compressibility Measurement: In contrast to PD measurement, the powder bed was filled in the cylindrical vessel and was affixed with a non-

permeating solid base at the bottom and the test was carried out using a vented piston which provides normal stress on powder bed of 15 kPa. The change in density as function of applied normal stress is measured. % Compressibility of powder material is calculated using equation 3.

$$\% \text{ Compressibility} = \frac{\text{Final volume (Vf)}}{\text{Initial volume (Vo)}} \times 100$$

Thermal Characterization: Dry blends, wet and dried granules were subject to thermal analysis using modulated differential scanning calorimetry (DSC) and thermal effusivity measurements.

Differential Scanning Calorimetry Analysis: DSC analysis was performed using Q100 (TA Instruments, New Castle, DE) instruments with nitrogen (50 mL/min) as purge gas. The experiments were performed in hermetically sealed pin-holed aluminium pans and the weight of each sample was 5 + 3 mg. DSC was calibrated using Indium before performing the tests. Thermograms were obtained with heat cool heat cycle at the scanning rate of 5 °C/min from 25 °C to 265 °C. The thermograms were integrated using Universal Analysis software.

Thermal Effusivity Measurements: Thermal Effusivity measurements were conducted using the TCi Probe (Mathis Instruments, Canada). Approximately 5 g sample was weighed using an electronic balance and placed in direct contact with the probe. Effusivity is a function of thermal conductivity, density and heat capacity of the sample material, which is calculated using equation 4 [14].

$$\text{Effusivity} = \sqrt{K \rho C_p} \quad \text{.....(4)}$$

Where,
K = Thermal Conductivity (W/ m. K)
ρ = Density (kg/m^3)
Cp = Heat Capacity (J/ kg. K)

The probe has a sensor which is a heat reflectance device supplying heat to the sample (< 2 K) for about 0.8^{-1} sec. Depending upon the above mentioned properties of the sample, it takes up the heat and cause rise in temperature at the interface which induces change in voltage connected to the sensor and recorded as a reading of effusivity.

Single Granule Crushing Strength Measurement: The dried granules passed through US sieve #16 (1180 µm) and collected on US mesh #20 (850 µm) were used for crushing strength measurements. The single granule crushing strength measurements were performed using TA.XT plus Texture Analyzer (Texture Technologies, Scarsdale, NY) using a 5.0 kg load cell with + 0.1 g sensitivity. During the testing, each granule was positioned on a flat platform and a flat-tipped cylindrical stainless steel probe (TA-54) with specific dimension (5.0 mm length and 30.0 mm diameter) was used to apply load on the granule. The probe travelled at 0.1 mm/s pretest speed and penetrated a predetermined distance of 1.0 mm in the granule and withdrawn back to original position at post-speed of 0.5 mm/s with data collection of 250 points per second was set [15].

Using TA.XT plus software, Force *vs* Time curve was analyzed and peak force required to crush the granule (travel 1.0 mm distance) was recorded for each measurement. Total of 20 measurements were made for each set of granules and average reading was taken for peak load (maximum crushing force, Fmax) as granule strength. **Fig. 2** shows the photographic image of experimental set up of single granule crushing strength and a representative graph recorded to observe peak crushing load on a granule.

RESULTS AND DISCUSSION:

Thermal Effusivity Measurements: Wet - granulation leads to increase in particles agglomeration and so the particle size affecting the density of the material. Water has highest effusivity (~1600 $Ws^{1/2}$ / m^2K). Using water as a wet granulating agent, there is formation of denser wet mass with formation of agglomerates. Thermal effusivity is an intrinsic property which changes with density, thermal conductivity and heat capacity of the materials.

Due to water addition to the material, the wet mass formation becomes more conductive to heat, so thermal conductivity also increases with granulation. The behavior of Lac-A and Lac-M powders with APAP upon addition of water can be obtained by observing thermal effusivity as a function of amount of water added **Fig. 3** and **4**.

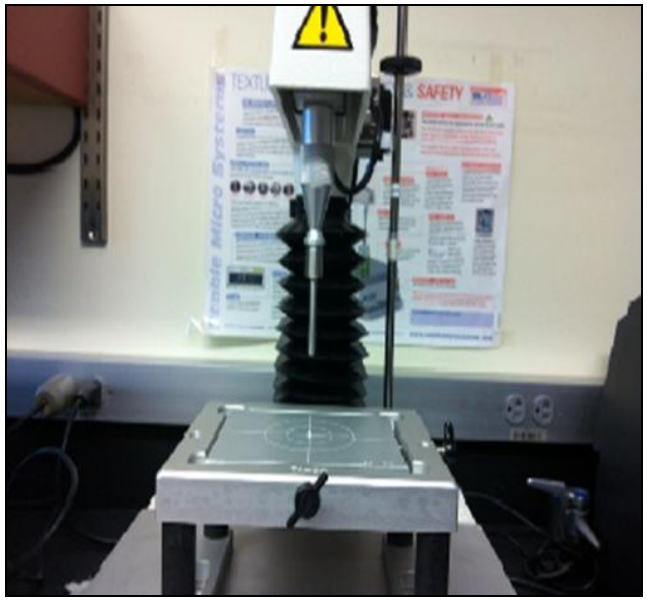


FIG. 2: EXPERIMENTAL SET-UP AND REPRESENTATIVE GRAPH SHOWING PEAK FORCE FOR LACTOSE SINGLE GRANULE PEAK CRUSHING FORCE

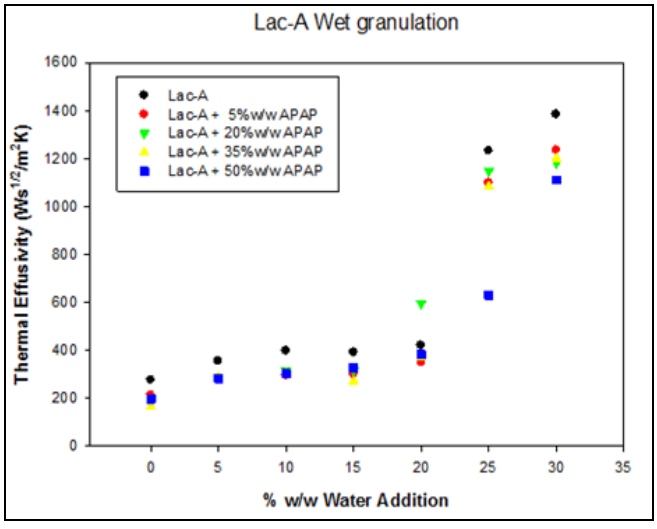


FIG. 3: THERMAL EFFUSIVITY VALUES FOR LACTOSE ANHYDROUS - APAP BLENDS

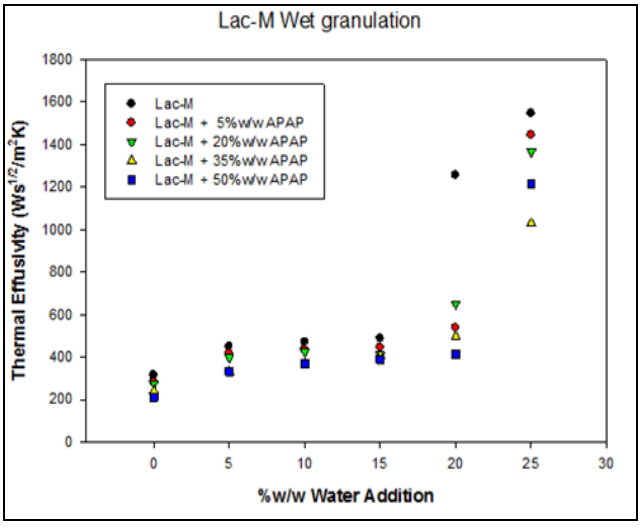


FIG. 4: THERMAL EFFUSIVITY VALUES FOR LACTOSE MONOHYDRATE-APAP BLENDS

Initial studies were conducted to determine the particular range of the wet granulation end point based on the thermal effusivity of various blends with an incremental addition of water as the granulating agent. **Fig. 3** and **4** show graphical observations of Lactose anhydrous and monohydrate with APAP blends. Thermal effusivity values of Lac-A and Lac-M are 273 $Ws^{1/2}$ / m^2K and 330 $Ws^{1/2}$ / m^2K respectively. APAP has very low thermal effusivity value of 113 $Ws^{1/2}$ / m^2K. Use of thermal effusivity as a tool to determine a possible range for the end point of wet granulation has previously been reported [16, 17].

In the beginning of granulation process (upto 5% w/w addition of water), as the material absorbs water and forms wet mass, it gives rise to effusivity. Further incremental addition of water into the wet mass leads to nuclei formation for granule growth. At this stage of granulation, the values for effusivity remain steady over the range of 5 - 15% w/w water content. After which, a sudden rise in effusivity values are observed due to complete granules formation and the excess water added onto the granules reach at the surface, this is indicated by rise in effusivity values. It is obvious that with further water addition, it will turn granules into slurry formation giving rise in effusivity values.

Although Lactose anhydrous and monohydrate blended with APAP when subjected to wet granulation from 0 to 30% w/w water content, they showed similar trends in thermal effusivity measurements showing similar stages of wet granulations from nuclei formation to granule growth. The study suggested that for Lactose (Lac-A and Lac-M) and APAP blends, the end point for wet granulation occurs between 15 - 20% w/w of water. The blends made from Lactose and APAP (50 - 50% w/w) did not show steep rise in effusivity which indicates that rheological properties of blends must be investigated during wet granulation. Based on these observations, the mid-range (17% w/w) for 15 - 20% w/w was considered for further investigation for 0, 20 and 50% APAP addition into Lactose anhydrous and monohydrate.

Rheological Characterization of Wet Granules: In **Fig. 5a** and **5b**, Powder energies (BFE and SE) of wet granules of LAC-A and Lac-M are plotted against% w/w APAP at 17% w/w of water. It is observed that powder energies increase as a function of APAP addition into the blend. BFE is calculated from the work done by blade during downward travel through the powder bed which imparts a high stress mode on the powder bed while SE is the upward travel through the powder bed imparting relatively low stress mode.

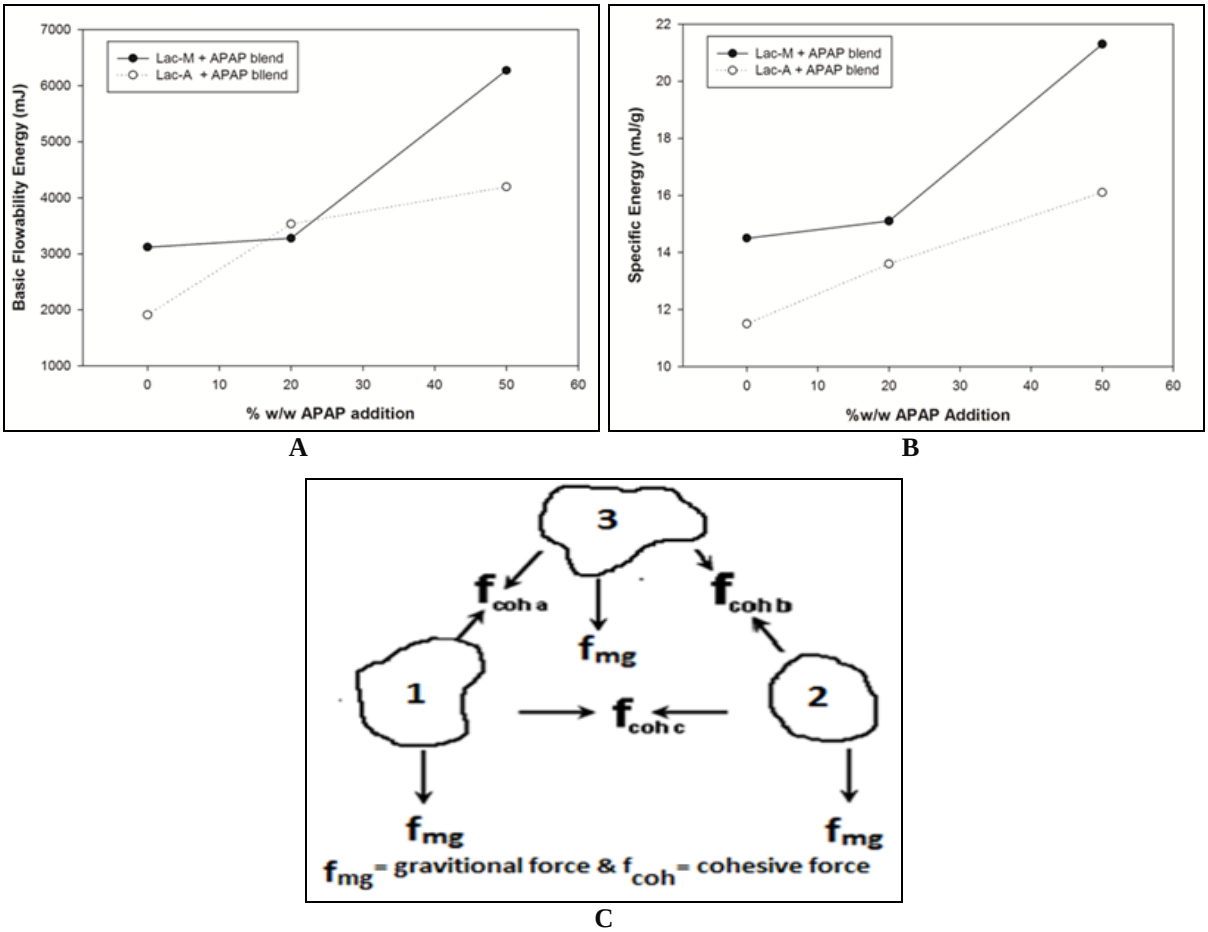
Granulation is a process used to convert fine or coarse primary particles which undergo agglomeration with the help of granulating agent forming bonding between them [18, 19]. This causes interlocking between the agglomerates. The phenomena leads to formation of the powder bed having strong bonding between primary particles and create a closely packed powder bed which imparts greater resistance to the movement of blade which results in high BFE values of the powder energies observed. This phenomenon is more prominent in which granules formed with higher concentration of APAP.

Fig. 5c shows the graphical presentation of kinds of forces acting on powders. It shows that mainly two kinds of forces act on powders, (i) Gravitational force (fmg); which gives powder free - flowing characteristics (ii) Cohesive force (fcoh); which leads powders to have strong inter-particle interactions **Fig. 5b**. During upward movement of the rheometer blade through the powder bed in SE testing, the particles with cohesive tendencies resist the movement of the blade due to inter-particle interactions resulting in higher SE values as compared to particles which are freely flowing under gravity as they would impart less resistance to blade movement. APAP is a cohesive powder with poor flowability characteristics [20]. The effect of its cohesivity can be clearly seen on wet granules with increased SE values.

Upon granulation, the agglomerate formation and size enlargement are commensurate with higher bulk density values. The granules when tested for PD analysis under stress of 15 kpa, the inter-particle interaction increases and it often leads to higher resistance to passage of air through the powder bed creating greater difference in pressure across the powder bed. From **Fig. 6b**, with the addition of APAP into the granulation, large

difference in PD is seen. It is also noticeable that Lactose monohydrate shows greater differences in PD as compared to anhydrous form at all concentrations of APAP.

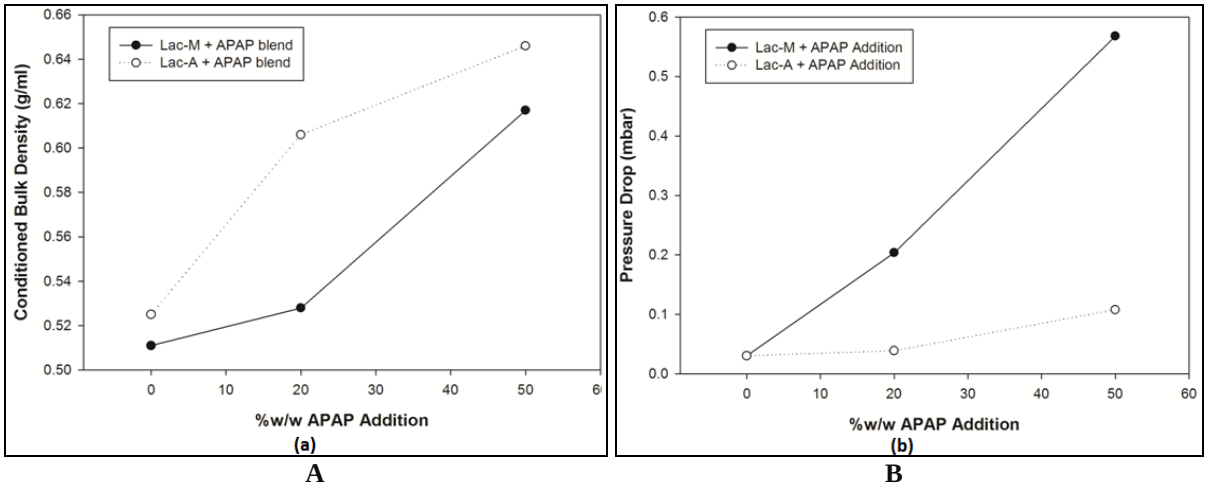
Lactose Wet Granules with 17% w/w Water Addition



A **B** **C**

FIG. 5: (A) BASIC FLOWABILITY ENERGIES OF LACTOSE WITH APAP (WET GRANULES), (B) SPECIFIC ENERGIES OF LACTOSE WITH APAP (WET GRANULES), AND (C) FORCES ACTING ON POWDERS

Lactose Wet Granules with 17% w/w Water Addition



A **B**

FIG. 6: (A) CONDITIONED BULK DENSITY OF LACTOSE AND APAP WET GRANULES (B) PRESSURE DROP OF LACTOSE AND APAP WET GRANULES

Rheological Characterization of Dried Granules: The main purpose for conducting wet granulation is to improve the powders flowability and compressibility. After subject to drying, the granule

properties are measured for rheological characterization focusing on flowability and compressibility. The results from the observations of % Compressibility values and the crushing strength of dried granules are shown in **Fig. 7**.

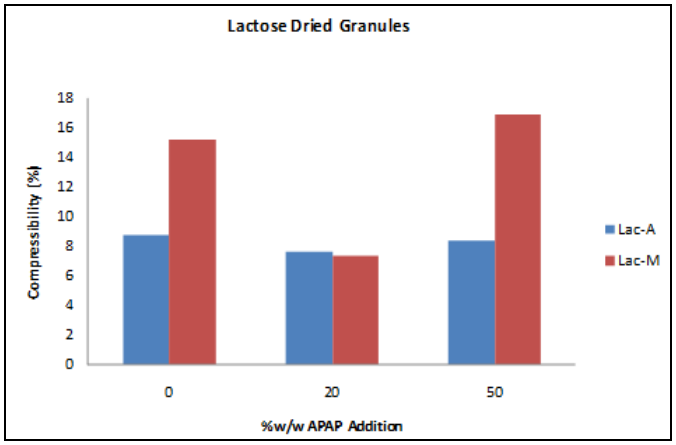


FIG. 7: % COMPRESSIBILITY OF LACTOSE AND APAP DRIED GRANULES

Granulation leads to increased inter-granular porosity with agglomerate formation. The powder bed becomes loosely packed which when under goes stress application. Due to the fact of loosely packed nature of granular mass, there is inter-particle void volume that will lower under given normal stress and produce higher % compressibility values.

The phenomenon becomes more prominent with higher addition of APAP into blends, producing higher % Compressibility **Fig. 7**. PD analysis of wet granules showed that wet granules prepared from Lac-M were more permeable and having more void spaces filled with liquid binder, upon drying the water escapes the granular structure and leaves behind the hollow granular mass. The formation of such mass results into higher compressible volume and higher % Compressibility. **Fig. 8** shows the effect of APAP addition into crushing strength of granules, recorded as maximum force required to crush granules. With APAP addition, the granules formed exhibit lower strength to crushing load.

The crushing strength of granules was calculated as peak force required to crush a single granule where crushing was termed as distance (1.0 mm) travelled by the probe inside the granule. The results from average of twenty dried granules of Lac-A and Lac-M with different concentration of APAP are shown in **Fig. 8**. It is seen that Lac-A granules have higher strength than Lac-M granules. At 20 and 50% w/w APAP concentration the granule strength is similar for both Lac-A and Lac-M granules. The results indicate that peak crushing force for Lac-A granules decrease and Lac-M granules increase with increasing APAP concentration. This effect can be useful in forming better tabletting properties upon compression of granular mass.

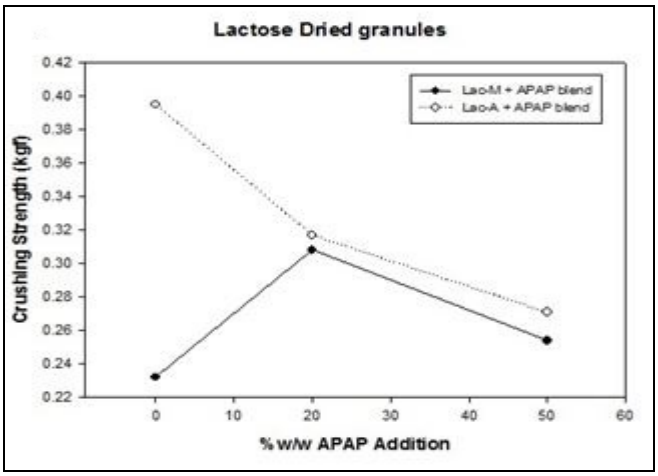


FIG. 8: GRANULE CRUSHING STRENGTH OF LACTOSE AND APAP DRIED GRANULES

Fig. 9a and **b** show the BFE and SE of Lac-A and Lac-M dried granules as a function of % w/w APAP addition into powder blends. BFE for dried granules decrease with higher APAP concentration. This is due to the fact that granular particles with higher APAP addition form more loosely packed powder bed formation which allows the easy travel of the blade through powder bed which corroborates to lower BFE values. APAP is a strong cohesive powder, which upon wet granulation binds with lactose particles to form more flowable and compressible granular mass having lower interparticle cohesivity. These properties of flowability and cohesivity are indicated by the energy values of BFE and SE respectively.

Thermal Characterization of Powders and Wet Granules: The DSC thermograms of Lac-A and Lac-M with different concentrations of APAP granules (dried) prepared with 17% w/w water addition are shown in **Fig. 10a** and **b**. The DSC thermogram of Lac-M shows characteristic strong dehydration endotherm at 140 °C, followed by melting peak near 215 °C with associated energies of 92.0 J/g and 110.1 J/g respectively. The DSC

thermogram of Lac-A shows characteristic melting peak of β-Lactose anhydrous at 230 °C with associated energy of 138.1 J/g and residual endothermic peak at 126 °C due to presence of small quantity of α-Lactose monohydrate. Thermogram for APAP shows melting endotherm at 170 °C with associated energy of 198.0 J/g. The combination of Lac-A with 20% w/w and 50% w/w APAP in dry powder blend form showed neither peak shifts nor any interference peaks in the thermogram. Upon wet granulation, the dried granules showed changes in the thermogram indicating conversion of Lac-A into Lac-M due to presence of prominent endothermic transition dehydration at 138 °C with associated energy of 61.7 J/g and endothermic melting transition at 217°C with 64.2 J/g associated energy.

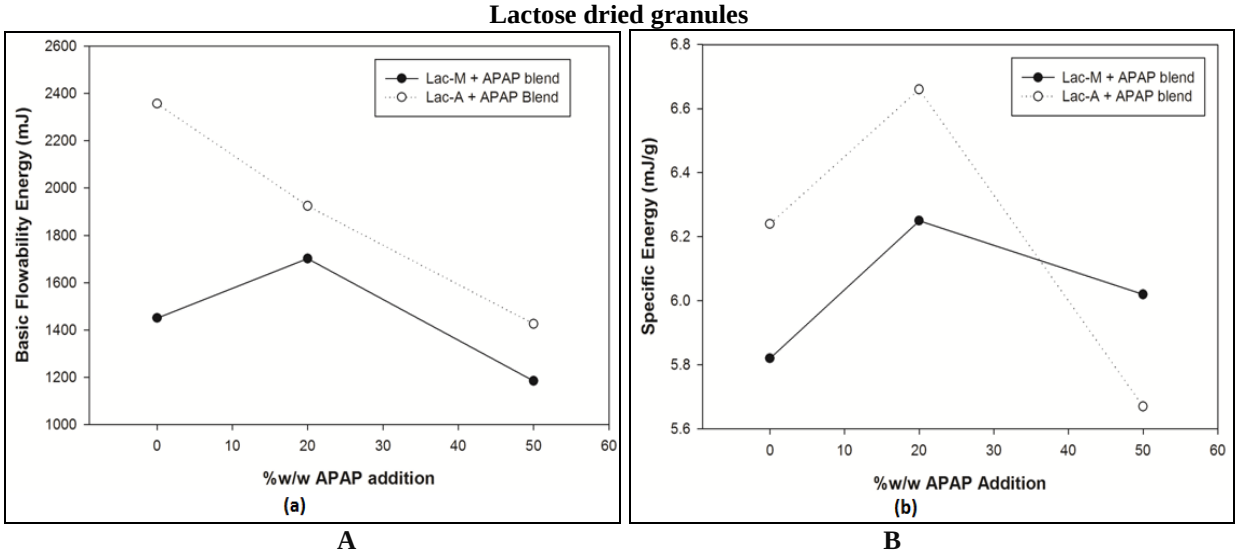


FIG. 9: (A) BASIC FLOWABILITY ENERGY OF LACTOSE AND APAP DRIED GRANULES AND (B) SPECIFIC ENERGY OF LACTOSE AND APAP DRIED GRANULES

The changes in peak shifts and conversion to Lac-M was more prominent in Lac-A + 20% w/w APAP concentration due to higher amount of Lac-A in the granules. In case of Lac-M with different APAP concentrations, there was absence of any peak shift event in thermograms. All the characteristic peaks of Lac-M and APAP were retained in dry powder blend form as well as dried granules of the blend prepared with 17% w/w water as a granulating liquid.

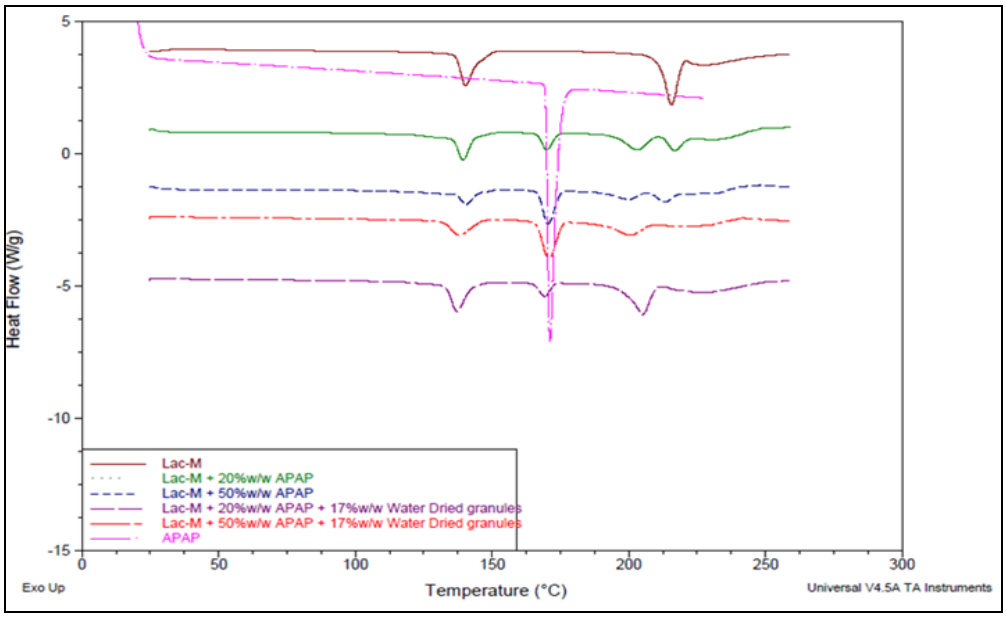


FIG. 10A: DSC THERMOGRAMS OF LACTOSE MONOHYDRATE AND APAP

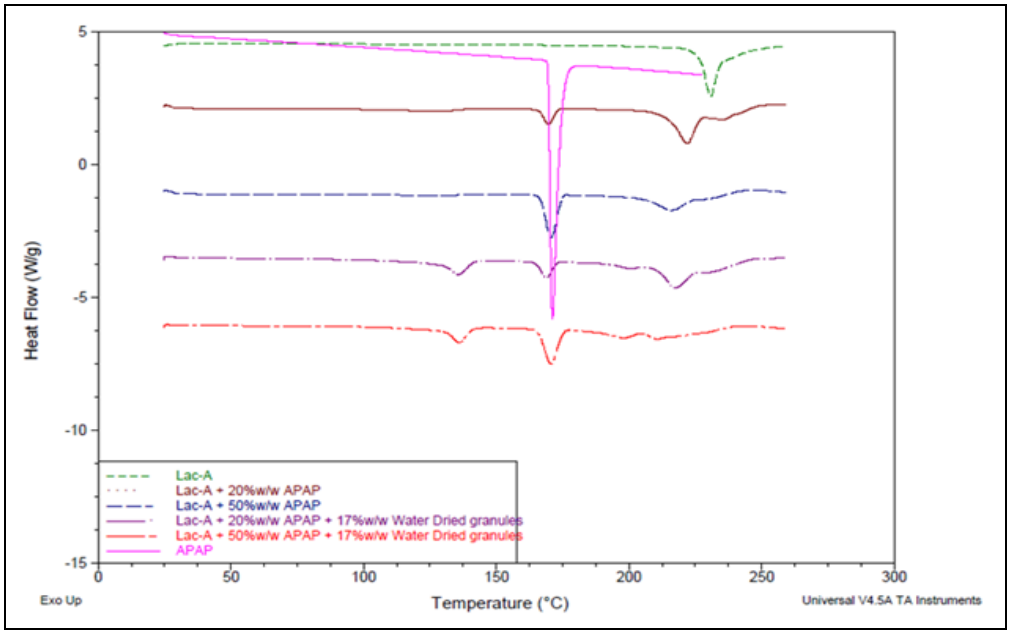


FIG. 10B: DSC THERMOGRAMS OF LACTOSE ANHYDRATE AND APAP

Thermal analysis using DSC indicates that there was absence of any interference between APAP and Lactose in powder blends and wet granulation. This implies that both form of Lactose are compatible with Acetaminophen.

CONCLUSION: The study shows the significance of the selection of appropriate crystalline forms of the excipient with API. An attempt was made to understand a well established technique of wet granulation in a different way to understand the changes in the excipients properties with successive addition of API undergoing granulation process. With the determination of end point of wet granulation using a new real time off-line PAT tool and conducting further investigation with rheological, thermal and mechanical properties of various processes and final products help characterizing the overall selection of excipient for particular API.

Upon wet granulation, the DSC thermogram indicated the conversion of anhydrous form of Lactose to monohydrate, however, the rheological properties indicate that the dried granules of Lac-A with APAP were higher in bulk density and permeability as compared to Lac-M with APAP.

These results corroborate the evaluation of % compressibility of the dried granules. The dried granulation crushing strength for Lac-A reduces with increasing concentration of APAP as compared to Lac-M. The clear distinctions in powder properties were observed. Use of this approach immediately following pre-formulation studies and early on formulation design phase will result into appropriate selection of forms of excipients for the formulation. This will in turn save time, API consumption and will prove to be cost-effective.

ACKNOWLEDGEMENT: The authors would like to thank Division of Pharmaceutical Sciences, Long Island University to provide support in conducting the research.

DECLARATION OF INTEREST: The authors declare that they have no competing interests.

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How to cite this article:
Trivedi MR, Patel HKH and Dave RH: To evaluate physicochemical characteristics of granulation for lactose and acetaminophen by utilizing rheological and thermal tools. Int J Pharm Sci & Res 2018; 9(1): 382-92. doi: 10.13040/IJPSR.0975-8232.9(1).382-92.