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Study of the Effects of Process Parameters on High Shear Wet Granulation

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Abstract: ***In this experimental work, the effect of binder solid concentration and viscosity on the granulation kinetics, physical properties, and flow characteristics, has been examined by conducting experimental runs on high shear mixer granulators. Granulation of Microcrystalline cellulose (MCC) and Lactose monohydrate blend was performed by using a binder solution containing PVPK-30, PVPK-90 and starch paste with 3% and 6% solid concentrations. Granulation batch time was the same for all experimental batches. The granule's growth behaviour and consolidation rate were monitored by the impeller motor current consumption trend. Granule's physical properties and flow characteristics have been evaluated for each experimental batch. Dry granule's Hausner ratio, compressibility index, and angle of repose were calculated to determine the flow characteristics. Binder viscosity has a large influence on particle size, shape, surface morphology, and flow characteristics of the granules. Low viscosity binders help to produce uniform size, snowball structure granules that have a good flow whereas high viscosity binder produces large, irregular granules which can create difficulties for the subsequent process.***

Keywords: Granulation, binder concentration, viscosity, flowability, granule characteristics

1. Introduction

High shear granulation is the most popular and adopted process in pharmaceutical industries. High shear granulation is the size enlargement of the micro-fine powder which provides good flow and compressibility of the particles.. The high shear granulation processes are classified into three major stages namely, dry mixing, wetting & nucleation, and attrition & breakage. The combination of these processes controls the final physio-chemical properties of granules, although the granule's growth and mechanism are dependent on the physical and chemical parameters of formulation and critical process parameters..

The granule growth mechanism depends on intimate contact between the dry powder blend and the binding solution under the impeller agitation. The dry blend of ingredients is wetted by binding solution and then mixed under the exhaustive force by the impeller to form dense agglomerates. However, one of the most important necessities for granulation is to ensure homogeneity of the formulation ingredients, especially in the case of low dosage products..

Impeller motor current measurements during high shear granulation provide meantime information on liquid saturation and granules growth in the mixer. A pendular state occurs when particles hold together by the liquid bridges . When voids are filled with liquid, capillary state occurs. The Binder addition in the granulation process can be done either by adding a liquid binder or by water directly in a dry blend of excipients, API, and solid binder. The selection of binder and its concentration are critical process variables for high shear granulation. In this work, the impact of the effect of polymer binder and its concentration on the granulation performance was studied while fixing the critical process parameters. . This work also attempts to investigate the significance of the selection of binder and its concentration on the physical properties and flow characteristics of the granules.In this study, the effect of starch paste, Polyvinylpyrrolidone K-30, and Polyvinylpyrrolidone K-90 at various concentrations and the effect of various binders on wet granulation have been studied.

2. Materials and methods

2.1 Materials

The materials chosen for this study were Microcrystalline cellulose (MCC) and Lactose monohydrate. The mixture of the above excipients has very high cohesion and poor flow properties which are an ideal dry mix for agglomeration. Aqueous-based Polyvinylpyrrolidone K-30, Polyvinylpyrrolidone K-90, and starch paste were prepared at varying solid concentrations of3% and 6 % respectively. The solid concentration of binder in solution is calculated on a weight basis andviscosity was obtained by Brookfield's viscometer. All relevant properties of these materials are presented in Table ***1***.

2.2 High shear granulation

A laboratory-scale high shear mixer granulator (10 litters) was used for all the granulation experiments. Granulation batches were conducted as shown in Table 1. The impeller motor current values were recorded within 5 seconds interval. Impeller motor current rising trend allowed us to determine saturation stages and granules growth. Granulation time was about 8 min during which the powder bed was homogenized by dry mixing for 2 min before the liquid binder addition was done. Binder addition rate and kneading time were constant for all the experimental batches.

Table 1: Details of the experimental batches

Batches	Name of binder	Binder Concentration in solution (%)	Quantity binder gm	Viscosity cps	Density (kg/cm^3)
E-01	PVPK-30	3	7.5	2.3	1002
E-02	PVPK-30	6	15	4.1	998
E-03	PVPK-90	3	7.5	20	993
E-04	PVPK-90	6	15	33	990
E-05	Starch Paste	3	7.5	270	980
E-06	Starch Paste	6	15	480	970

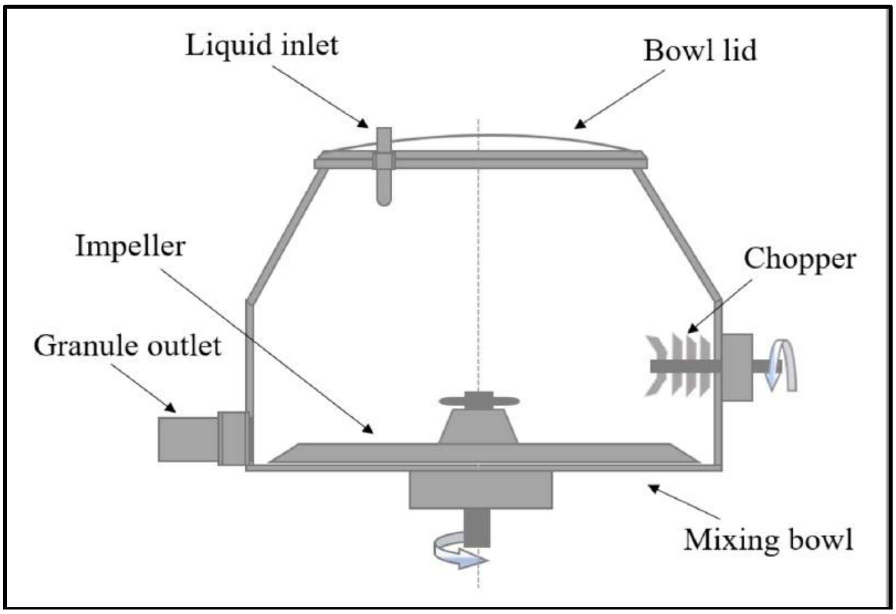


Figure 1: Schematic of high shear mixer granulator

All the high shear granulation runs were conducted with an experimental batch size of 1 kg. Water quantity was varied

Table ***1***. Impeller operated in the dry mixing phase for 2 minutes for each run. During the binder addition phase impeller and chopper both were operated at 150 rpm and 2000 rpm respectively. The binder addition rate was 84 gm/minutes for all experimental batches. In the binder addition phase chopper operated for uniform distribution of binder. In kneading, the phase impeller was kept at 300 rpm with 2000 rpm chopper speed. Formed granules were dried in a tray dryer at a temperature of 70^{o}C till moisture content was reduced below 2% (w/w). Dried granules were immediately analyzed for the study of various granule characteristics.

2.3 Granules analysis and Temperature profiles

The physical characterization of the granules was performed by standard available methods

2.3.1 Granulation Trend

Granules' growth trend was monitored by impeller motor current power consumption values of current are logged in auto-generated batch report with the help of variable frequency drive.

2.3.2 Hausner ratio & Carr's Index

Flow characteristics of granules were determined by the Hausner ratio (HR) and Carr's index (CI). The values of HR ratioand CI were calculated based on the obtained bulk density and tapped densities.

to maintain the solid concentration binder in the solution as shown in

$$HR = \frac{\rho_{max}}{\rho_{min}} \quad (1)$$

$$CI = \frac{\rho_{\max} - \rho_{min}}{\rho_{max}} \times 100 \quad (2)$$

2.3.3 Angle of Repose

The angle of repose was determined by the standard fixed funnel method in which the granule sample of 100 gm sample was.

$$\theta = tan^{-1}\frac{h}{r} \quad (3)$$

3. Results and discussion

3.1 Granulation kinetics

The selections of binder and its concentration is very critical and have greater influence. Properties of binder can affect the final particle size, shape, and flow properties of final granules. The growth kinetics can be monitored by the impeller motor current trend. To monitor the granule's growth, impeller motor current consumption was recorded in real-time at 5-sec intervals through a variable frequency drive.

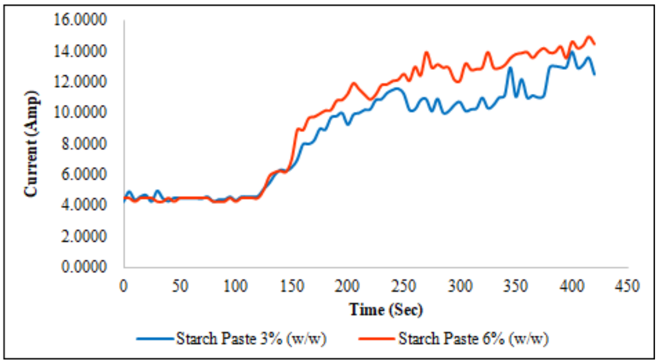


Figure ***2*** shows the torque profiles of the experimental batches. The current consumption fluctuation during the dry mixing phase was very negligible. As binder addition started in a dry powder blend, current consumption increased with wetting and granules growth. At starting of the wet mixing phase, the current consumption increased with the rate of consolidation and granules growth. An increase in impeller motor consumption is an indication of growth. The binder solids concentration and the viscosity have a greater influence on particle size growth. It is directly proportional to the growth rate. Increased solid concentration increases the solution viscosity and thus the particle size within the granulator.

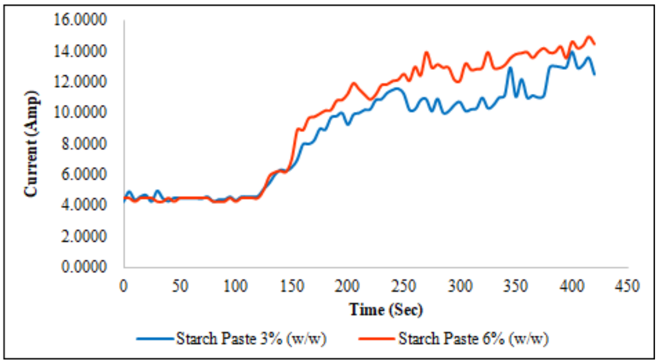


Figure ***2***(a) shows the granulation growth kinetics in terms of impeller motor consumption trend for Polyvinylpyrrolidone K-30 (PVPK-30) with 3% and 6% solid concentration respectively. The motor current consumption trend was linear for granules growth.

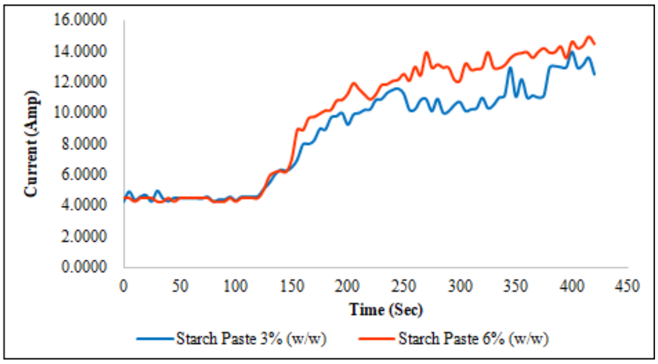


Figure ***2*** (b) shows the current consumption trend for polyvinylpyrrolidone K-90 (PVPK-90) granulation batches. The viscosity of PVPK-90 is higher than the PVPK-30 and thus the granule's growth rate was higher. The current consumption rate indicated the same as consumption was during the binder addition and kneading phase as compared to PVPK-30.

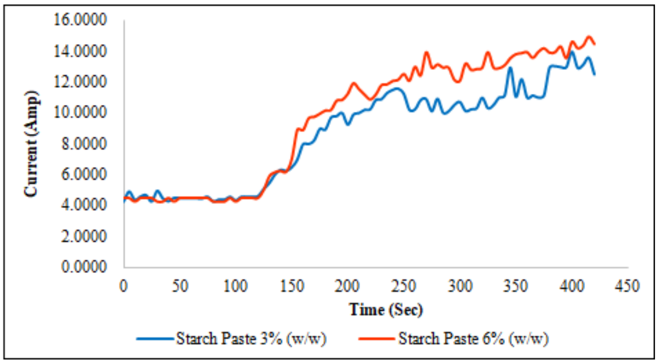
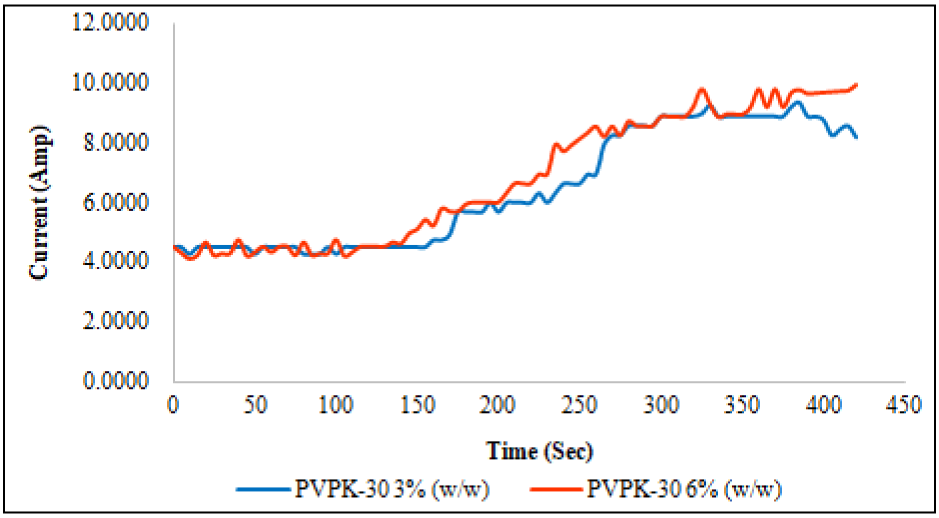


Figure ***2***(c) shows the trend for starch paste with 3% and 6% solid concentration respectively. The granules formed with starch paste are lumpy and have high density and are harder.The current consumption trend was high as compared to previous batches. The large fluctuation in current indicates the uncontrolled growth and formation of lumpy granules.



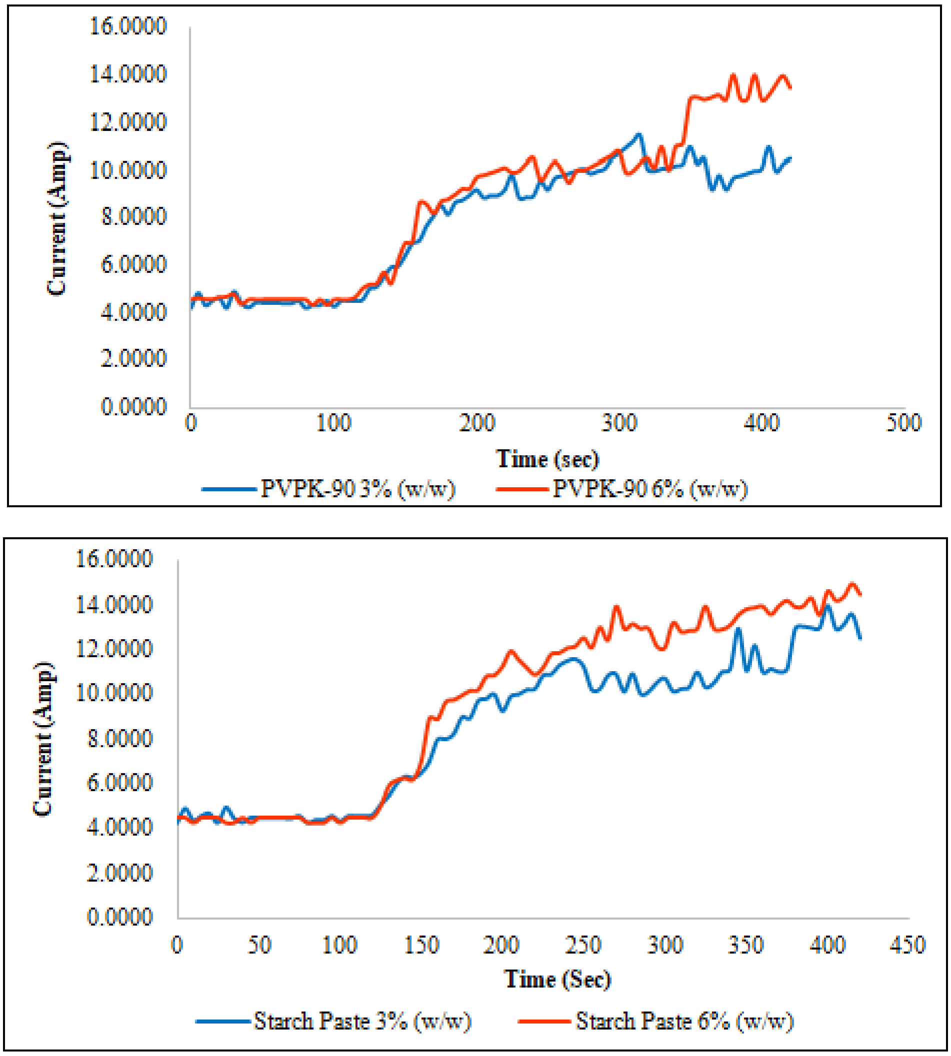


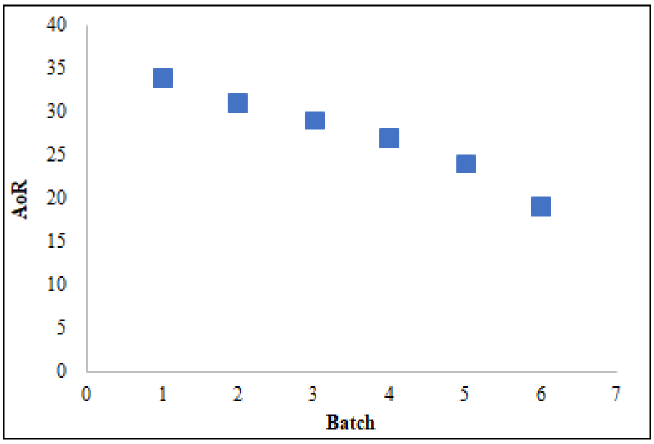
Figure 2: Granulator's current profile (a) PVPK 30 (b) PVPK 90 (c) Starch paste

3.2 Impact on the granules flow characteristics

Flow characteristics of dried granules were measured and analyzed through compressibilityindex (CI), and Hausner ratio (HR) which was determined by the obtained values of bulk density and tapped density of final granules. Theoretically, higher density particles have a good flow. High viscosity binder produces a higher density particle, although granules produced, have an irregular shape. For such granules further sizing would require dry milling and sifting.

It is observed that the binder viscosity hasthe most significant impact on final granules properties and granules growth rate. High viscosity binder produced the high density, harder, and lumpy granules, whereas a low viscosity solution produced narrow, good-quality granules. Granules formed with starch paste have hardness and high density.

The angle of repose is another criterion to define the flowability of dry granules. In this method, dry granules flow through a funnel from a fixed distance. The Diameter and height of the formed pyramid provide the angle of the cone which can be used as a flow parameter. The angle below or 30^{o} is considered to be of very free-flowing characteristics, and the angle above 40^{o} is considered to be of poor flow (cohesive) characteristics. With an increase in the binder concentration, the angle of repose of granules was reduced. Granules formed with PVPK-30, have good flow properties, whereas the granules produced with starch paste have excellent flow.



As shown in Figure ***4***, it can be concluded that the, higher solid concentration solution produces high density and excellent flow characteristics granules as compared to low solid content binders

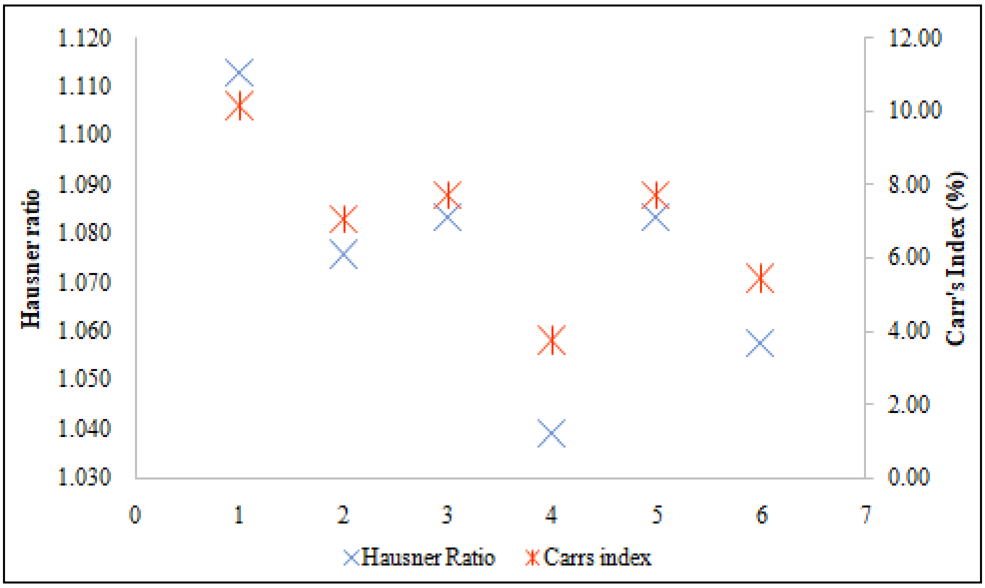


Figure 3: Flow characteristics

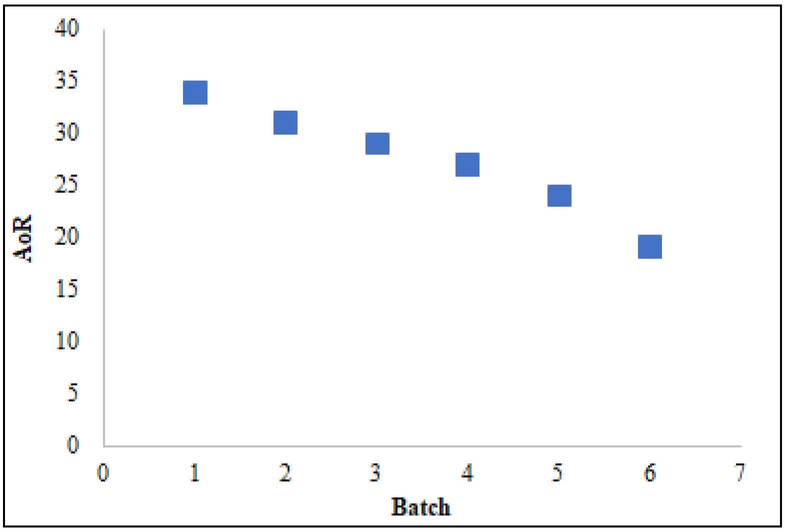


Figure 4: Angle of Repose

4. Conclusion

The effects of the binder solid concentration and viscosity on the granule's growth, and physical properties were investigated in this experimental work. Three types of the binder were used with 3% and 6% solid concentrations which have different viscosity. The results show that it has a greater impact on granules' growth and subsequent processes. These results show that the increase in the viscosity and solid content in the solution leads to a growth in particle size and better flow properties. High viscosity binder produced with starch paste with 3% and 6% solid content has viscosity 270 and 480 Centipoises respectively, produced harder and lump granules which have excellent flow but the shape of formed granules was uneven and irregular. The rate of granule growth is uncontrolled with high viscosity binder and thus it produces larger granules with a minimum time of kneading, whereas exactly opposite phenomena were observed with low viscosity binder. The granules formed with low viscous binder are uniform in size and shape with good flow granules (PVPK-30 and PVPK-90respectively). The current trend also shows the linear growth of granules with low viscosity binders. It can be concluded from the study that, the granules produced with a low viscous and solid content binder produce more uniform and narrow granules which require minimum energy and processing for further applications like milling and sifting. In conclusion, this experimental work provided an initial insight into how the selection of binder along with the solid concentration impacted the granule's growth, physical properties, and critical quality attributes of granules.

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