# INFLUENCE OF PROCESS VARIABLES ON PHYSICOCHEMICAL PROPERTIES OF THE GRANULATION MECHANISM OF DICLOFENAC SODIUM IN FLUID BED GRANULATION

**Tejas B Patel[*1], Dr. L. D. Patel[2], Timir B Patel[1], Sunil H Makwana[1], Tushar R Patel[1]**
[*1] Faculty of Pharmacy, Dharmsinh Desai University, Nadiad-387001, Gujarat, INDIA
[2] C. U. Shah College of pharmacy & Research, Wadhwan City, Surendranagar, Gujarat, INDIA
***Email:** tejaspatel264@gmail.com

**ABSTRACT**

The fluid bed granulation is a fairly complex process that can be divided in three steps : (1) Wetting and nucleation, (2) consolidation and growth and (3) breakage and attrition. Process parameters and physicochemical properties of the binder and granule substrate can have significant impact on these rate process and consequently the physical properties of the granule formed. This study investigated the influence of process variable and PVP K-30 binder physicochemical properties on binder atomization process with special attention to the relationship between wetting and the granule growth profile. Special attention was given to how fluid bed process parameters, such as binder addition rate, atomizing pressure, and binder concentration, impact the granule growth process and the final physical characteristics of the granules.

**Keywords:** Fluid Bed Granulation, Process variables, PVP-K 30, Diclofenac Sodium

## INTRODUCTION

Fluid bed granulation is a process, which forms small particles into aggregates or granules using a liquid binder sprayed onto the fluidized bed or particles. The granulation process can generally be viewed as a combination of three-rate process:

(1) Wetting and nucleation

(2) Consolidation and growth and

(3) Breakage and attrition.

The process parameters like atomizing air pressure, inlet and out let temperature, inlet air humidity, binder addition rate etc, the physicochemical properties of the binder liquid and the material particles and their relationship, rules each of them. Consequently, fluid bed granulation is considered a fairly complex process[1].

In fluid bed granulation, a finely divided binder is sprayed onto fluidized particles. As a result of collision and coalescence between the surface wetted powder particles, liquid bridges are formed and nucleation of particles occurs leading to the growth of granules. The availability of the liquid binder at or near the granule surface is thus of great importance in the formation of liquid bridges between particles. Whether or not the liquid binder spreads on the granule surface, evaporates or is imbibed into the porous powder structure, as well as its ability to migrate to the surface upon collision with other granules, will greatly impact on the granulation mechanism and the granule growth profile[2].

The present investigation examined the granulation mechanism of Diclofenac sodium in fluidized bed granulator using PVP K-30 solution at different concentration as a liquid binder. Special attention was given to relationship between wetting profile and granule growth profile of the granules especially how fluid bed process parameters, such as binder addition rate, atomizing pressure, and binder concentration, impact the granule growth process and the final physical characteristics of the granules.

## MATERIALS AND METHODS

### Materials

Materials were used in this study as such obtained from the various locations. PVP K-30, starch, HPMC 15cps and carbopol 934p was used as binders of laboratory grade of (*S.D Fine Chemicals, Mumbai).* Lactose used as diluent (*S.D Fine Chemicals, Mumbai*). Diclofenac sodium was used as received (*Lincoln pharmaceutical ltd, Ahmedabad*) as gift sample. Other equipment used included: fluid bed granulator (*Cronimach Machineries, Ahmedabad*), sieve shaker (*Kevlab*), IR moisture balance (*Hicon, Delhi*).

### Experimental Test Matrix

The experimental test matrix was set up in order to study the binder spray rate, atomizing air pressure and the binder concentration which are known to affect the granule growth mechanism and the physicochemical characteristic of granules (Table 1). The experimental matrix allowed the isolation of each parameter for the evaluation of its effect on the granulation mechanism and the final product characteristics.

### Preparation of Granules

Granules of Diclofenac sodium were prepared using fluid bed granulation technique.25gm of Diclofenac sodium and 75 gm of lactose were blended in a mini mass mixer (Hardik Engineering, Ahmedabad) for 10 mins. The blend was transferred to fluid bed granulator and granulated using different concentration of binder (Table 1). Binder solution was made using water. There was spraying of

binder solution through the nozzle on to the fluidized bed of granulating material. The nozzle was located in the upper port above the bed, facing downward. The total quantity of solution added varied with the binder concentration. Batch size for fluid bed granulation technique was 100grams. Spray rate, atomizing air pressure for preparation of granules in fluid bed granulation technique was as per Table 1. The inlet air temperature was set to 65 $^0$c and the inlet air humidity was not controlled and generally constant. The inlet air temperature was monitored throughout the granulation process. Samples were taken at regular intervals in order to measure the granule growth and the bed moisture content as the granulation progressed.

**Table 1:** Experimental Test Matrix

| Experiment run | Binder Concentration (%W/W) | Binder spray rate (ml/min) | Binder Atomizing Pressure (kg/cm2) | Inlet air temperature ($^0$C) |
|---|---|---|---|---|
| 1 | 2 | 3 | 0.15 | 65 |
| 2 | 5 | 3 | 0.5 | 65 |
| 3 | 8 | 3 | 0.15 | 65 |
| 4 | 8 | 5 | 0.5 | 65 |
| 5 | 5 | 5 | 0.15 | 65 |
| 6 | 2 | 5 | 0.5 | 65 |

**Characterization of Granulation Process:**

**Granule growth profile**

The granule growth profile was obtained by plotting the geometric mean diameter ($D_{50}$) of each sample taken during the granulation process versus time. The geometric mean diameter was determined on a 15 gram of sample using sieve shaker (*Kevlab*) and the sieves no used were 10, 20, 40, 60, 80, 100.

**Granulation wetting profile**

The IR moisture balance (*Hicon, Delhi*) was used to measure the moisture content of each sample taken during the progress of the granulation run. The moisture level was plotted against time to provide the wetting profile of the granulation process.

**Final granule- size distribution and friability**

Using sieve shaker (*kevlab*) and a set of 6 sieves (10, 20, 40, 60, 80, 100), a 50 gm of the final product was shaken for 10 min to obtain the size distribution and the geometric mean diameter. To determine the friability of granules, sieves are shaken for an additional 20 min and change in mass percentage of fines was measured. For the Diclofenac sodium lot used in this study, a geometric mean diameter ($D_{50}$ µm) was measured 100 µm and the corresponding $D_{95}$ µm was 150 µm. Hence particles that were smaller than 150 µm were considered non-granulated Diclofenac sodium and reported as fines for the friability measurements.

**Bulk and tapped densities**

Granules were gently poured into 50 ml graduated cylinder. The granule weight and volume were used to calculate the bulk density. Using automatic tapper, the cylinder was tapped 500 times and the new volume was used to calculate the tapped density. The bulk and tapped densities were used to determine the Carr's index, and Hausner ratio. The Carr's index and Hausner ratio value was used to categorized the powder flow. The Carr's index was calculated according to equations (4.1) and (4.2).

$$\text{Carr's index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{Tapped density}}$$

$$\text{Hausners ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**RESULTS AND DISCUSSION**

**Granule Wetting and Growth Rate**

**Effect of Binder Concentration**

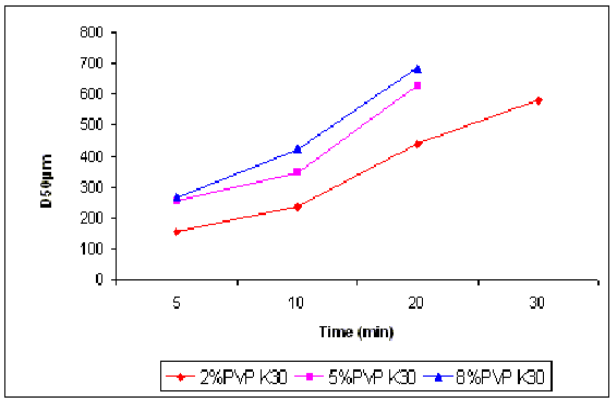


**Figure 1:** $D_{50}$ versus time for different binder concentration

Figure 1 presents Diclofenac sodium granulation when PVP K-30 solutions of various concentrations were added to the fluidized bed of particles. The shape of the curves suggests that the granulation proceeded through an induction period of little growth, followed by a period of rapid growth. This granulation behavior indicated an induction growth mechanism, where saturation pores is not the main factor affecting the granule growth rate, but

rather the availability of binder at the surface of the particle[3]. The increase in the PVP K-30 binder concentration decreased the duration of the nucleation period (Figure 1). This was the predictable behavior as greater PVP K-30 binder solution on the surface allowed formulation of strong bonds that resisted the breaking forced encountered during fluidization of particles. Moreover, granulation manufactured with 5% w/w, and 8% w/w PVP K-30 solutions showed similar wetting profile. The granulation remained relatively dry. This suggested that the solution did not imbibe the particles and partial evaporation occurred which correlated well with the induction growth observed.

These results also indicate that the growth of the granules was dictated mainly by the amount of PVP K-30 binder solution sprayed independently of the PVP K-30 solution concentration. As above observed for granulation manufactured with 5% w/w and 8% w/w PVP K-30 binder solution growth was similar when amount of PVP K-30 solution added was considered (Figure 2).

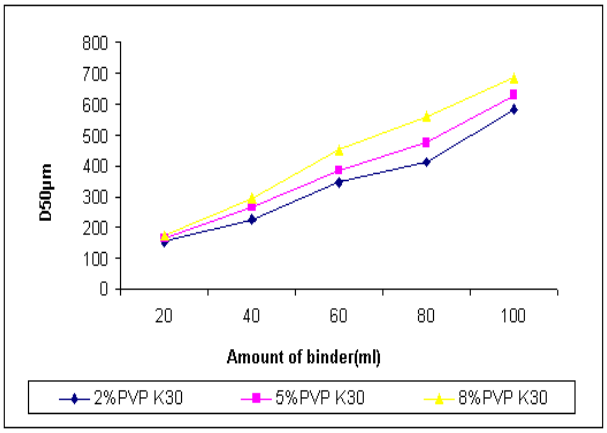


**Figure 2:** $D_{50}$ versus pvpk30 added for different binder concentration

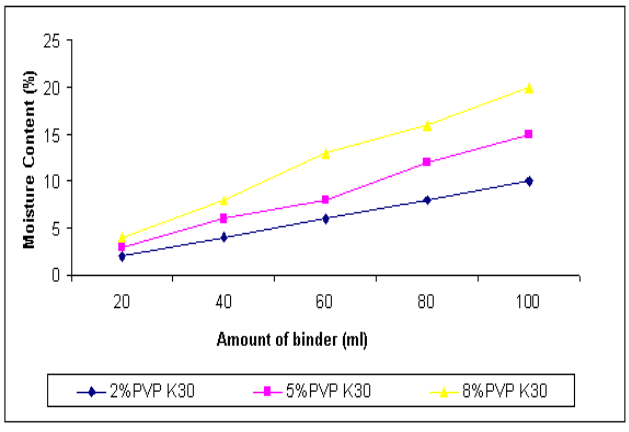


**Figure 3:** Moisture content as function of pvpk30 added for different binder concentration

Moisture level had less impact on the growth profile of the granules in this situation. The deviation observed for the 2% w/w PVP K-30 solution was ascribed to improve penetration of the less viscous solution into the powder resulting in the reduced availability of the PVP K-30 binder solution on the surface[4]. The increased penetration rate explains the significant increase in wetting profile observed when the granulation was performed with the 2% w/w PVP K-30 solution (Figure 3). As a result of the reduced process time, the effect of growth rates easier, 5% w/w PVP K-30 binder solution was used for the remainder of the work.

**Effect of Binder Addition Rate**

Using the 5%w/w PVP K-30 binder solution addition rates of 3 and 5 ml/min were tested in this experimental section. At the slower addition rate (3 ml/min), it was observed that effective evaporation of the solvent was obtained such that there was little influence on the moisture levels (Figure 4). At these low wetting levels, the granule growth was primarily controlled by the amount of PVP K-30 added (Figure 5). At the higher addition rate (5ml/min), wetting profile of the granules was much more apparent however it was not reflected in the growth kinetics and the addition of the PVP K-30 controls granule growth (Figure 5). This granulation behavior was consistent with the induction growth mechanism observed earlier, where saturation of pores was not the main factor affecting the granule growth rate, but rather the binder availability at the surface[5,6].

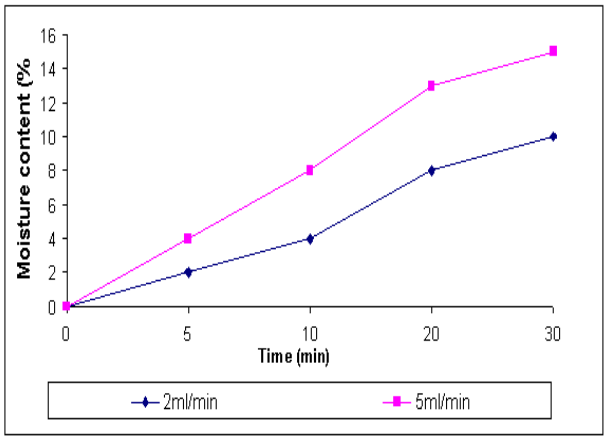


**Figure 4:** Moisture content versus time with different spray rate for 5% w/w pvpk30 binder concentration

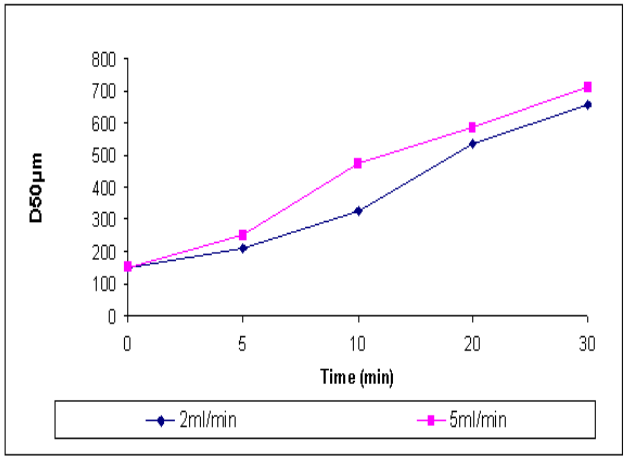


**Figure 5:** $D_{50}$ versus time with different spray rate for 5% w/w pvpk30 binder concentration

**Effect of Atomization Pressure**

Binder droplets have been reported to impact on nucleation and growth of granules. Specially, two nucleation mechanisms were identified as a function of the

droplet and particle size ratio and enhanced moisture penetration into the granule: the immersion mechanism, where binder droplets are bigger than the particles to granulate, and the distribution mechanism where binder droplets are smaller than the particles. The letter mechanism is generally dominant in fluid bed granulation because of binder atomization, which leads to the formation of nuclei by collisions between the surface wetted powder particles[7,8,9]. Since the growth of the Diclofenac sodium granules with PVP K-30 binder solution had shown an inductive granule enlargement behavior, little effect of the binder atomization pressure was expected on the granulation growth rate. The larger droplets being compensated by a larger no of smaller droplets.

Figures 6 and 7 present the wetting and granulation profiles, respectively, for a granulation prepares at 5 ml /min and atomization pressure of 0.15 kg/cm$^2$ and 0.50 kg/cm$^2$. It could be observed that while atomization pressure had significant influence on the wetting profile of the granules. It had little influence on the granulation mechanism and the growth profile remains unaffected by atomization pressure or droplet size. The change in wetting behavior could be related to the droplet size. For a given binder solution, the larger droplet size enhance the moisture penetration into granule, therefore hindering the evaporation. Lesser the atomization pressure the larger the binder droplet size was observed[10].

At a reduced binder addition spray rate of 3 ml/min, the situation was somewhat reversed, i.e., atomization pressure or droplet size did not have a significant influence on the wetting profile, due to efficient drying, but the increase in pressure was shown to produce a somewhat smaller granule particle size (Figure 7). As it had already been established that wetting has no influence on the granule growth at binder spray rate varying from 3 ml/min to 5 ml/min, it was believed that the effect of the atomization pressure observed at lower spray rate was not related to wetting of the granules but rather to the increase in shear force provided by the atomization air accentuating breakage and affecting the granulation growth rate.

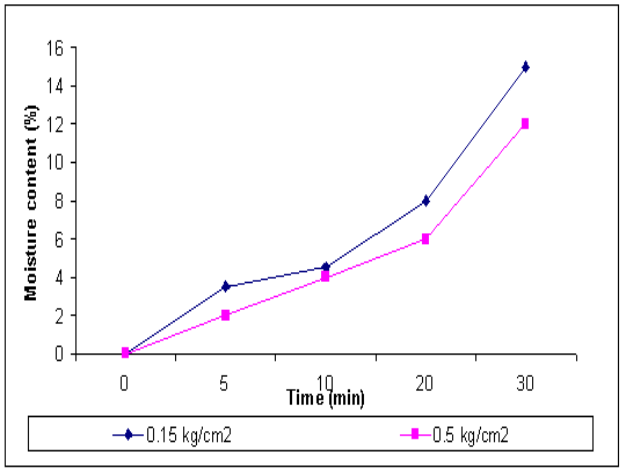


**Figure 6:** Moisture content versus time for different atomization pressure

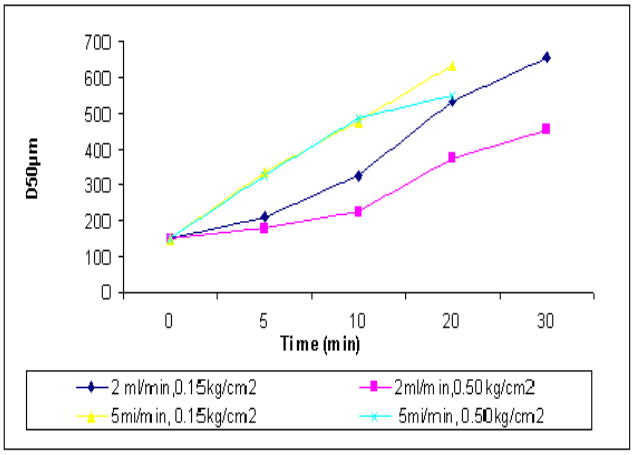


**Figure 7:** $D_{50}$ versus time for different atomization pressure at different spray rate

Moisture levels in the granulation affect the collision of the granules and the balance the contribution of the granule breakage to the granule growth. Liquid penetration increases the plasticity and the hardness of the granule thereby reducing the agglomerates tendency to fracture up to critical liquid saturation, where moisture creates a lubrication effect to increase the breakage of the granules by attrition[11].

**Breakage of Granules on Drying**

Granules can break and wear due to either particle - particle walls collisions or compaction. Jet grinding bubbling and splashing of ejected particles is additional factors contributing to breakage of granules in fluid bed granulation Table 2 shows level of breakage of granules on drying (after the addition of binder solution was terminated) for different granulation runs. Increasing in the atomization pressure from 0.15 kg/cm$^2$ to 0.50 kg/cm$^2$ had a clear effect with the breakage of granules increasing from 13.14 % to 20.44 %. Lower spray rate decreased the availability of binder to form liquid bridges between particles, which imply weaker cohesive force involved in forming the granules, and promote breakage.

**Effect of Processing Parameters on Final Granules Characteristic**

**Friability**

Granules must be strong enough to survive handling. One measure of granule strength is friability. Since granule strength tends to increase with the formation of more liquid bridges conditions that favor the formation of liquid bridges should reduce friability. From experiments described in Table 2, it could be seen that an increase in binder spray rate, a decrease in atomization pressure and an increase in PVP K-30 binder concentration were important factors that contribute to reduce friability of the granules.

**Flow Behavior**

The Carr's index value provided some indication of the flow of behavior of the various granulations obtained during this investigation. Granule having high Carr's index values shows the relatively poor flow than the lower the Carr's index. This was also observed and proved by

measuring the angle of repose of different granulations. Experiments 2, 3, 4, shows higher values of angle of repose as well as Carr's index so it was observed that binder concentration, atomization pressure and binder spray rate affect the flow behavior of the granules and granules that maintained at lower binder spray rate and atomization pressure during granulation had improved flow characteristics.

**Table 2:** Summary of Granulation Physical Characteristics for the Different Processing Test

| Batch | Granule size wet (µm) | Granule size dried (µm) | Breakage on drying (%) | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner ratio | Angle of repose | Friability (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 685 | 565 | 17.52 | 0.5 | 0.58 | 13.79 | 1.16 | 30.52 | 1.25 |
| 2 | 583 | 496 | 14.92 | 0.52 | 0.66 | 21.12 | 1.26 | 36.45 | 0.68 |
| 3 | 656 | 575 | 12.35 | 0.55 | 0.71 | 22.53 | 1.29 | 38.56 | 0.45 |
| 4 | 456 | 396 | 13.16 | 0.56 | 0.72 | 22.22 | 1.29 | 39.65 | 1.1 |
| 5 | 635 | 584 | 8.03 | 0.54 | 0.68 | 20.59 | 1.26 | 28.96 | 0.46 |
| 6 | 550 | 459 | 16.55 | 0.52 | 0.62 | 16.13 | 1.19 | 27.86 | 0.66 |

## CONCLUSION

The growth mechanism depended on the interrelated contribution of the binder added and bed moisture content. The amount of binder added via solution mainly controlled the nucleation and the growth process, while the moisture content level was important in reducing the breakage and attrition during both the granulation phase and the drying phase. It is believed that the granulation process is almost controlled by the amount of binder added; suggesting increasing the binder concentration of the solution without producing significant variations in the granulation growth rate and final product characteristics can reduce the processing timer. Atomization air pressure also affects the granule breakage and flow properties of granules.

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