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Research Article

Agglomeration Tendency in Dry Pharmaceutical Granular Systems During Blending: De-Agglomeration Modeling Approaches

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Abstract

Efficient blending of powders is of critical importance in the manufacture of a wide variety of industrial products, including pharmaceuticals, foods, plastics and agrochemicals [1, 2]. This study determined the influence of geometry of blenders (double cone blender and V-blender), blending speed and time. The blend composed of diclofenac sodium, lactose, magnesium stearate and talc. It was subjected to homogeneity assessment, size analysis, drug-excipient analysis and dissolution studies.

Fourier transform infrared spectroscopy (FTIR) analysis of the blend showed that there was no chemical interaction. Then the blend was added separately to the two blenders and tested at 25,50rpm and 75 rpm at 5, 10, 15 and 20mins. For testing the homogeneity (uniform distribution of diclofenac sodium), content of diclofenac sodium was determined and was found that it ranged from 65.2-74.3% at low speed to 85.4-96.7% at high speed. The dissolution profiles showed an unusual flat asymptote indicating incomplete extents of dissolution (54-65%) with blending at low energy rates and short mixing times (5-10 min at 25 rpm) possibly caused by agglomerates that did not readily disperse in the dissolution medium. The study showed that increasing both speed and time of mixing (15-20 min at 75 rpm) enhanced the extent of dissolution (91-96%). Mixing speed and time had much greater influence on the extent of dissolution which was controlled by de-agglomeration than on the initial dissolution rate, which in turn was related to the dispersed diclofenac sodium. The V-blender appeared to operate intermittently combining splitting and merging, while the double-cone appeared to operate continuously, with a nearly constant flow of particles in a more uniform surface layer. This resulted in significantly more rapid mixing in the V-blender than in the double cone. Nevertheless, both exhibited reproducible and rapidly occurring segregation patterns.

The blending conditions influenced the mixing quality of agglomerate characteristics. The use of particle sizing approaches to construct de-agglomeration profiles and their interpretation using modeling approaches provided parameters representing agglomeration and de-agglomeration rate constants.

Keywords: Diclofenac sodium; V-cone blender; Double cone blender; Homogeneity; Dissolution.

Introduction

A more critical blending step often occurs at the final stages of a process prior to packaging the final mixture. This is especially true in pharmaceutical manufacturing where 80% of the medicines produced are in the form of tablets, where the drug content uniformity is heavily scrutinized by regulatory agencies. Powder and granule mixing are the most important operations in the pharmaceutical industry during the preparation of solid dosage forms (Fig 1). The blending operation is to give the best homogenization of two or more components. But difficulties appear due to the diversity of products in terms of size (particles, granules or lumps), shape (spheres, pellets, flakes, filaments, blocks, crystals or irregularly shaped particles), moisture (dry product, wet product or paste) and surface nature (cohesive or non-cohesive powder). As particles become smaller, cohesive effects grow larger. At some point, agglomeration tendencies become very significant. The critical factor in achieving homogeneity becomes the shear rate, which is dependent on both speed and time. This

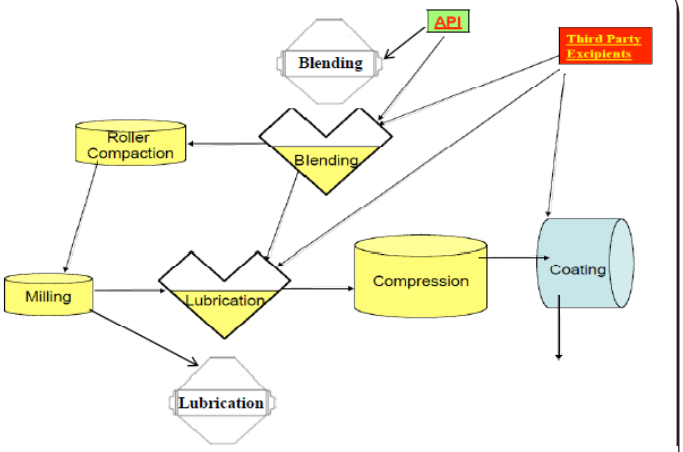

Fig 1: Sequence of operations of tablet manufacture

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problem is common in direct compression applications, but has been rarely identified primarily because of the small number of samples typically used to characterize blends. The homogenization procedure always occurs in competition with segregation or de-mixing process and this secondary phenomenon prevents perfect mixing from being obtained. The V cone blender is most commonly used in the pharmaceutical industry for mixing powders and granular materials. The primary mechanism of blending in a V-Blender is diffusion. Blender movements increase the mobility of the individual particles and thus promote diffusive blending. Diffusion blending occurs where the particles are distributed over a freshly developed interface. In the absence of segregating effects, the diffusive blending will in time lead to a high degree of homogeneity. The double cone blender is also efficient and versatile for homogeneously mixing the dry powder and granules by shear and diffusion. These blenders are immensely demanded by pharmaceutical, food, chemical and cosmetic industries [1, 2].

Materials

Diclofenac sodium, lactose, Magnesium stearate, Talc, Simulated Gastric Fluid (pH 1.2).

Methods

Preparation of blends

Mixing was performed in V and double cone blender (Fig 2) (All purpose model; VJ Instruments, Hyderabad, India). For all experiments, diclofenac sodium was blended with directly compressible lactose and addition of magnesium stearate and talc to enhance the flow properties. All quantities used were accurately weighed using Shimadzu balance. The V cone and double cone blenders (Fig 2) used in this study was of 200 mm diameter with a cone angle of 50 having a capacity of 3.75 liters. The blends were charged into V cone and double cone blenders. The blenders were charged to about half its capacity, the total weight of the mixture being 1.5 kg with the blending speed maintained at 25, 50 and 75 rpm. Samples were taken at the end of 5, 10, 15 and 20 mins and was analyzed spectrophotometrically. Samples were taken separately in the axial and radial directions for each mixing time.

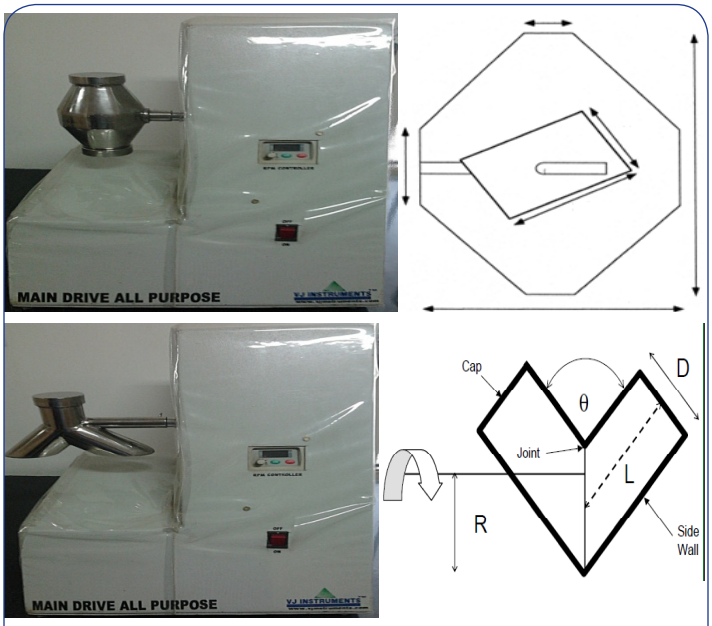

Fig 2: Top Left. A) Double cone; Top Right. B) Double cone drawing; Bottom Left. C) V cone blender; Bottom Right. D) V cone blender drawing

Size analysis of the blend

The size distribution of diclofenac sodium blend in both V cone and double cone blenders were determined using sieve analysis. When sieve shaking of different opening sizes, i.e., 18 (1000 µm), 20 (840 µm), 30 (590 µm), 25 (707 µm), 35 (500 µm), 40 (420 µm), 45 (354 µm), 50 (297 µm), 60 (250 µm), 70 (210 µm) and smaller sized meshes, the particles and agglomerates were gently separated and distributed according to their size. The agglomerates retained at the surface of the screens are weighed and converted to percentage.

Homogeneity assessment

Homogeneity assessment was performed to test the efficiency of the mixing process. Eight diclofenac sodium blends were selected and 20 samples containing drug equivalent to 50 mg were randomly removed from each of the mixtures. Samples were then added to 100 ml of phosphate buffer (pH 7.4) in volumetric flasks and vigorously shaken prior to sonication for 20 min in a sonicator. Aliquots removed from the sonicated solutions were added to 100 ml volumetric flasks with the volume being made up using SGF (pH 1.2). Diclofenac sodium in each of the samples was then analyzed via the validated UV spectrophotometric method. Averages (20 samples), standard deviations and percent CV (coefficient of variation) for each blend were calculated.

Dissolution study of the blends

Dissolution studies were conducted in dissolution apparatus consisting of 8 vessel constant temperature water bath (Electro lab 0T8, India). Simulated Gastric Fluid (SGF; pH 1.2) was used as the dissolution medium to simulate in vivo conditions and was degassed prior to use was equilibrated to 37.0±0.5 °C. Samples of the blend with dose equivalent to 50 mg were added to the dissolution apparatus in series and filtered samples were assayed at 5, 10, 20 and 30 mins. USP basket method was used at a rotational speed of 100 rpm.

Spectrophotometric analysis

Spectrophotometric analyses were performed using scanning ultraviolet-visible spectrophotometer (Analytical Instruments, India). Beer's Law calibration plots were obtained in phosphate buffer (pH 1.2) at 276 nm for the homogeneity assessment and in SGF for the dissolution studies. Absorbance of lactose was insignificant in the dissolution studies and was small (<0.05) which accounted in the homogeneity determinations.

Agglomerates determination

The information present in the size distribution of diclofenac sodium

dispersions were used to determine the state of agglomeration of diclofenac sodium after its addition to dissolution media blended in V cone and double cone blender at 25, 50 and 75 rpm. The blends of diclofenac sodium were added to SGF under non sink conditions, the size of the resulting dispersions of dispersed particles and agglomerates were determined. Observation of the distribution of the size over a 30 min period was examined. Using the amount retained, the percentage of agglomeration was determined and the de-agglomeration profile was constructed.

De-agglomeration modeling

The de-agglomeration modeling profiles for the diclofenac sodium mixtures were fitted to the following exponential equations [3].

$$C_a = C_{oa} e^{(-kat)}; C_a = C_o + C_{oa} e^{(-kat)}$$

a - apparent volume percentages as agglomerates at time t; C_o - apparent volume percentage as non-dispersible agglomerates; C_{oa} - initial apparent volume percentage as dispersible agglomerates; K_a - deagglomeration rate constant.

Results and Discussion

Influence of mixing speed and time in V cone and double cone blenders on the size distribution of the blend

When diclofenac sodium-lactose blend from V cone and double cone blenders at 25, 50 and 75 rpm at 5, 10, 15 and 20 mins were placed on the sieves, different sizes of diclofenac sodium were observed. The size ranged from 10 µm to 1000 µm. With increase in speed and time (Fig 3, 4, & 5) in both blenders, the size was drastically reduced. It is suggested that when V cone and double cone blenders are rotated, powders succumb to compaction forces, thus allowing the formation of agglomerated "chunks" of powders [4]. These "chunks" are broken down into smaller units by the blender's mixing mechanism (Shear and diffusion), the stress of the free powder mass and collisions between them and the equipment walls. This transforms the chunks into "balls" of higher density. Free balls are found on the surface of the powder mass, rolling along the slope while simultaneously increasing in size. The phenomenon of powder accumulation on the surface of ball is similar to that of creating a snowball by rolling it down a snow-covered hill. Kaye [5] has stated that the more the powder is tumbled around with a stearate, the larger are the spontaneously formed agglomerates. From (Fig 3, 4 and 5), it is clearly evident that the size in both V cone and double cone blenders blended at 25 rpm at all time points, 40% of the size is near to 1000 µm. In contrary to that at 50 and 75 rpm, majority of the size ranged from 100 - 300 µm which shows that the blending speed had a great impact on the size variations in both V cone and double cone blenders.

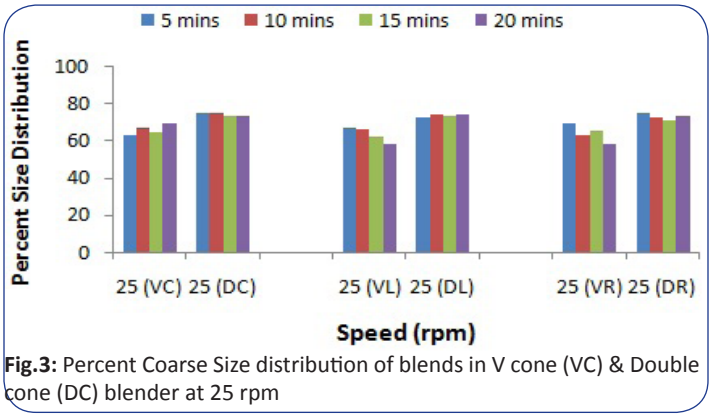

Fig.3: Percent Coarse Size distribution of blends in V cone (VC) & Double cone (DC) blender at 25 rpm

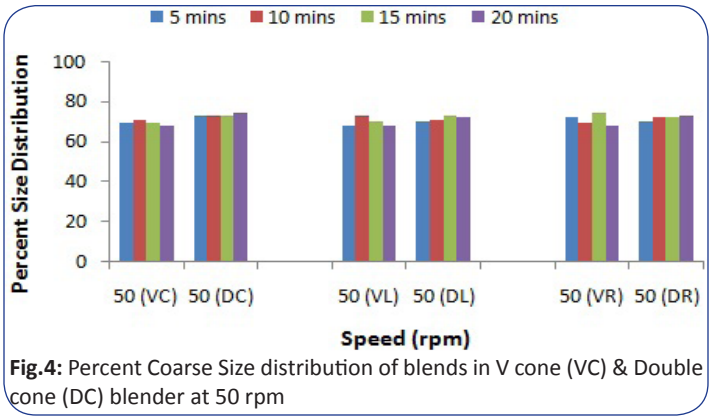

Fig.4: Percent Coarse Size distribution of blends in V cone (VC) & Double cone (DC) blender at 50 rpm

Effect of speed on blending performance

The effect of rotational speed on the homogeneity of diclofenac sodium (Fig 6 & 7), illustrate the observed change in the percent drug content in the free-flowing material as the rotation speed in V cone and double cone blenders increased from 25 to 75 rpm. It is observed that at 25 and 50 rpm from 5 mins to 15 mins, the content was found to be less indicating poor mixing phenomena. But at 75 rpm at all time points in both the blenders, almost 95% of the drug content was observed reflecting uniformity in mixing. This clearly shows that high speed is required for achieving homogeneity during mixing. Initially, at very low speed, the bed's surface is flat and cascades slowly with surface curvature evolving as the speed increases. The curvature of the flowing region increases the surface area, hence the overall volume of the cascading region of the flow increased. At 25 rpm, the surface flow is made up of discrete avalanches of powder that do not slide from one end of the blender to the other, but rather dissipates shortly. At 50 rpm, the frequency of avalanches per rotation increases, nevertheless remaining discrete in time. As reported by [6], the powder located at the highest region of the sloping surface simply slides down the

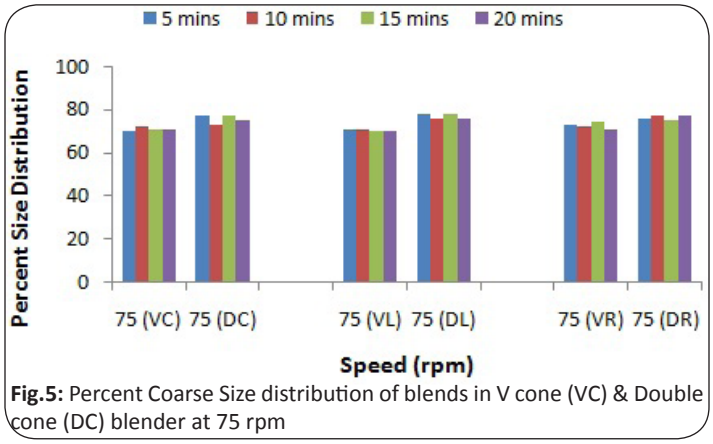

Fig.5: Percent Coarse Size distribution of blends in V cone (VC) & Double cone (DC) blender at 75 rpm

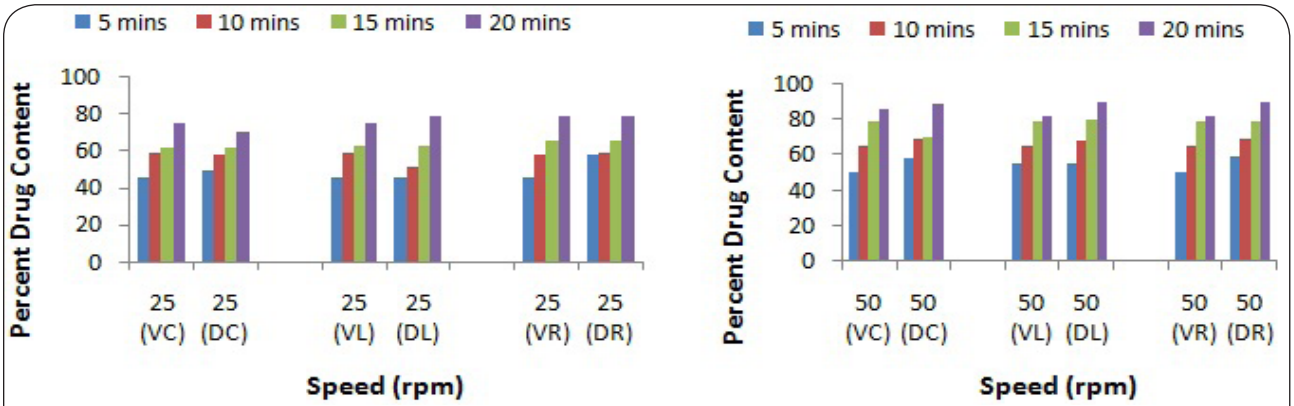

Fig 6: Content of Diclofenac sodium (DFS) in Double cone (DC) and V cone (VC) blender at Left) 25 Right) 50 rpm

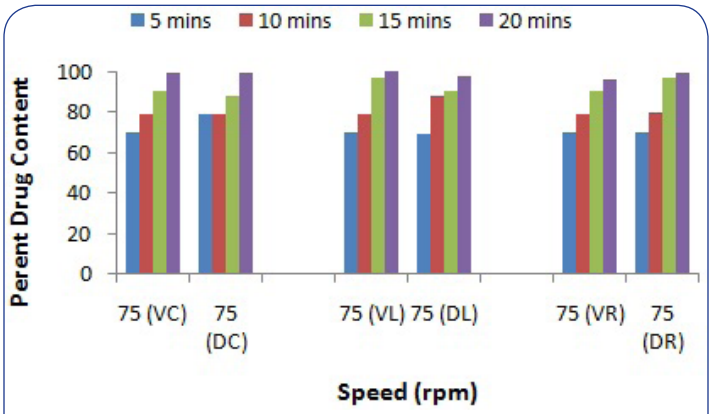

Fig 7: Content of Diclofenac sodium (DFS) in Double cone (DC) and V cone (VC) blender at 75 rpm

entire slope to the opposite walls of the blenders, in larger 'glacier like' avalanches, and exhibits fewer avalanches per time than 25 and 50 rpm case. Therefore in the number of avalanches per revolution signified a higher dispersive rate of mixing observed after 75 revolutions, while fewer avalanches of larger powder portions resulted in a greater radial (convective) mixing component after 50 revolutions.

Influence of blending speed and blending time on the extent of dissolution

Mixtures comprising diclofenac sodium and lactose along with magnesium stearate and talc were blended in V cone and double cone blenders at 25, 50 and 75 rpm. Influence of mixing speed and time on the dissolution of diclofenac sodium was assessed. For each speed, samples were removed at 5, 10, 20 and 30 min and the dissolution profiles of diclofenac sodium in the samples were obtained (Fig 8 and Fig 9). Diclofenac sodium dissolution profiles demonstrating typical changes at different blending speeds (25, 50 and 75 rpm) for the dissolution conducted for 30 mins. The variability seen with similar speeds at different locations (center, left and right side of the V cone and double cone blenders) was likely due to sampling from the mixer and errors associated with the dissolution measurement. Error bars have been excluded from the dissolution profiles obtained for the mixtures prepared at 25, 50 and 75 rpm to facilitate visualization and discrimination between the resultant dissolution profiles. In general, observation of the dissolution profiles demonstrate that both increase in mixing speed and increase in mixing time produce mixtures that dissolve more completely during the time of dissolution (Fig 10). The dissolution profile asymptotes for the mixtures prepared at a rotational speed of 25 rpm for 5 to 20 min were close to 100% dissolved, while those prepared at 25 rpm reach asymptotes at about 55% dissolved. For those prepared at 50 rpm, the only mixture to approach an asymptote of 65% is that sampled at 20 min. The initial dissolution profiles do not provide a clear distinction between the mixing conditions. The initial dissolution of all mixtures prepared at 25 rpm seen similar, while there is an increase in dissolution with increased mixing time for those prepared at 75 rpm. Overall, observation of the dissolution profiles seems to show a clear relationship between the mixing speed and time.

Monitoring of agglomeration of diclofenac sodium blend in the dissolution media

Size analysis was performed on diclofenac sodium blend mixtures prepared at various time and speed conditions. The resulting distributions allowed concentrations of dispersed agglomerated diclofenac sodium to be determined at the beginning of the dissolution process, facilitating comparisons of the state of diclofenac sodium particles in the mixtures at different mixing conditions. (Fig 11-12) shows the comparison of the average size distributions determined for the mixtures of diclofenac sodium without error bars prepared at the different mixing durations for 25, 50 and 75 rpm in V cone and double cone blenders with the fully dispersed, average distribution obtained for diclofenac sodium. Firstly, at 25 and 50 rpm in both the blenders, partial combination of the agglomerate occurred with a resultant decrease in agglomerate size which was not complete dispersion, but insufficient to give complete diclofenac sodium dissolution in the 30 mins time period for the low mixing energy conditions. Secondly, at 75 rpm in both the blenders, complete de-agglomeration might be occurring, but diclofenac sodium re-agglomerated either by forming new agglomerates by networking on the lactose surface or by re-agglomerating through individual inter-particulate interactions off the lactose surface and this mechanism coincides with a previous study [7, 8]. The first of these is most likely to occur; however, in

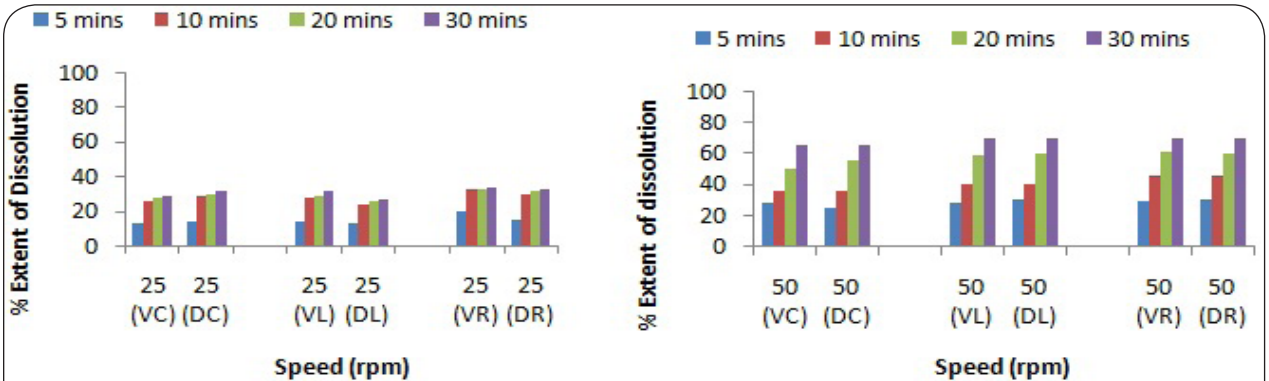

Fig 8: Extent of dissolution of DFS from blend in Double cone (DC) and V cone (VC) at 25 and 50 rpm

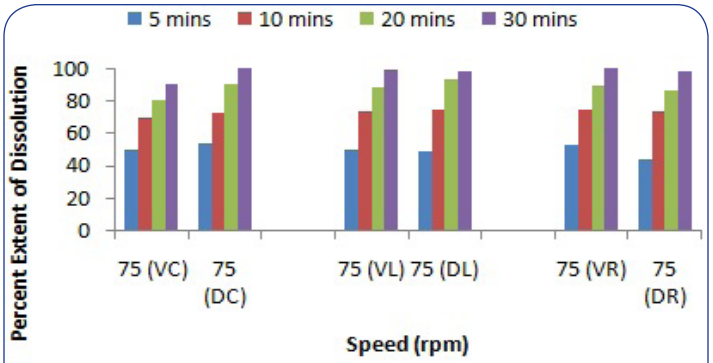

Fig 9: Extent of dissolution of DFS from blend in Double cone (DC) and V cone (VC) at 25 and 50 rpm

either case, the full extent of dispersion was achieved resulting in complete dissolution.

Influence of blending speed and blending time on de-aggregation parameters

The de-aggregation profiles demonstrated effect of blending speed and time on degree of particle dispersion in SGF as the dissolution medium. The shape of the de-agglomeration profiles revealed differences used in this study reflecting differing mechanisms of agglomeration perhaps related to the drug's physical properties, surface adhesion and packing. The de-agglomeration profiles demonstrated less dispersion blended at 25 rpm, however, there were significant differences in the de-agglomeration at 50 and 75 rpm. Observation of the profiles showed differences in the rate of de-agglomeration and the initial degree of agglomeration. The de-agglomeration curves were best modeled by using the two and three parameter single exponential decay equation and the estimated parameters are shown in Table 1. The assessment of goodness of the fit showed that the R2 values of the blend were 0.998 and 0.973, respectively. These statistics indicated a good fit of the data to the three-parameter exponential equation. The results in Table 1 show the influence of speed on the estimated parameters of C0, C0a and ka for the blends of diclofenac sodium. A change in the speed and time affected both the apparent volume percentage as dispersible and non-dispersible agglomerates, but was more significant for the dispersible agglomerates. At the highest speed (75 rpm), the apparent volume percentages as dispersible agglomerates was nearly 90%, however, non-dispersible agglomerates were only about 10%. The apparent volume percentage as dispersible agglomerates (C0a) was much higher for the blends at 75 rpm. The blends also demonstrated time dependent agglomeration particularly for the apparent volume percentage as dispersible agglomerates (C0a). Dissolution profiles for the blends prepared at 25, 50 and 75 rpm in both V cone and double blenders showed an increasing trend in the extent of dissolution as a function of mixing duration (5, 10, 15 and 20 mins). This can be attributed to an increased exposure of diclofenac sodium and lactose to shear forces during powder mixing causing greater de-agglomeration of diclofenac sodium.

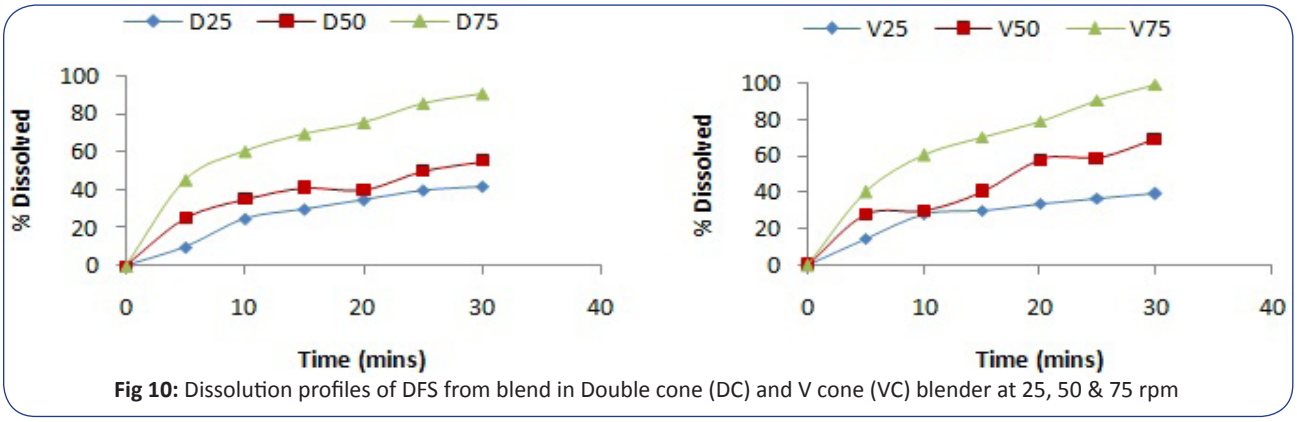

Fig 10: Dissolution profiles of DFS from blend in Double cone (DC) and V cone (VC) blender at 25, 50 & 75 rpm

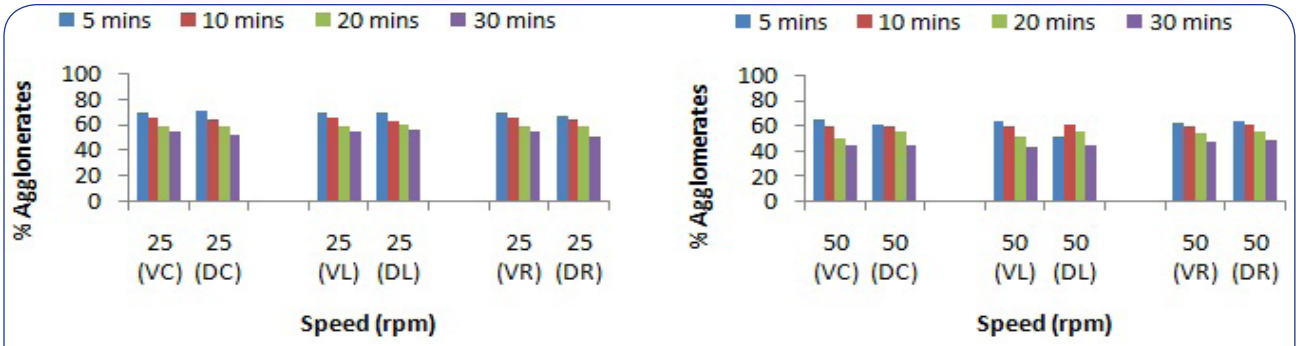

Fig 11: Agglomerates of diclofenac sodium blend in V cone (VC) and Double cone (DC) blender at Left) 25 rpm Right) 50 rpm

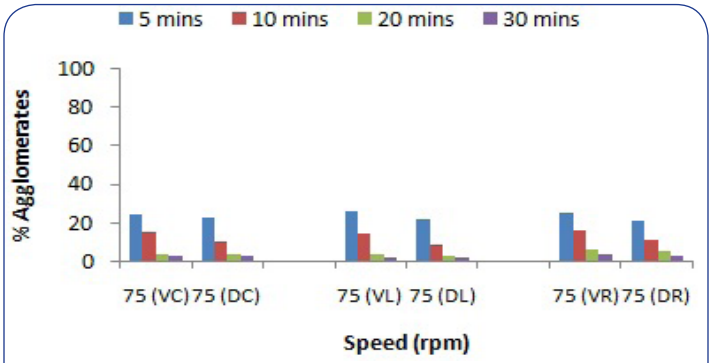

Fig 12: Agglomerates of diclofenac sodium blend in V cone (VC) and double cone (DC) blender at 75 rpm

At 25 rpm, the extent of dissolution as a function of mixing time were small with incomplete deagglomeration, showing asymptotes around 80% for all mixtures which is indicative of weak shear forces generated under these mixing conditions. A failure of these forces to overcome cohesive, intra-agglomerate bonds was manifested by the lack of significant change in extent of dissolution with longer mixing times. The inability of low energy mixing processes to disperse drug agglomerates, with a resultant slow dissolution process due to the suspension of these aggregates in the medium was also noted in a previous study [9]. It was also observed that the mode of the agglomerate distribution was shifted slightly to lower particle size with increasing time of mixing. However, the prevalence of the agglomerate distribution at 20 min of mixing indicated failure of shear forces generated at 25 rpm to cause complete de-agglomeration.

The performance of the V cone blender was correlated to the mechanisms of segregation patterns generated in the V cone blender at various speeds as previously as reported [10]. The curved path lines of particle movement in a V-blender segregate into several robust and sharply defined patterns. From (Fig 13) it is evident that the differences in the motions of the small and large particles cause a general movement of small particles toward the concave side of curved path lines and large particles toward the convex side. The change in particle distribution within a single blender revolution is not prominent, but through repeated exposure to the same low patterns, highly segregated regions develop. Variations in the blender rotation speed at 25, 50 and 75 rpm cause the blend to switch between distinct Patterns (Fig 13). When run at lower rotation speeds, the segregation patterns that form are symmetric with respect to the blender geometry and the pattern within one shell of the blender is a mirror image of the other. However, at

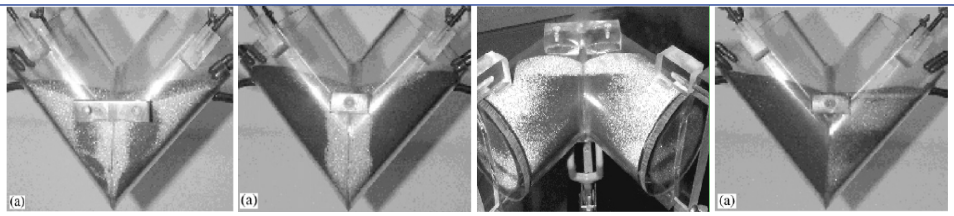

Fig 13[10]: Seggregation patterns in V cone blender

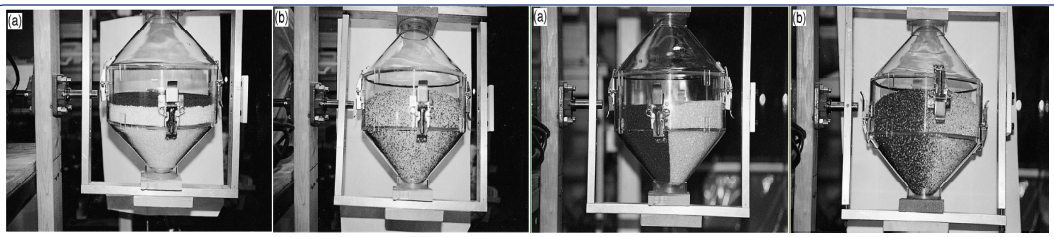

Fig 14[11]: Seggregation patterns in double cone blender

Parameters		V Cone Blender											
Blending speed		25 rpm			50 rpm				75 rpm				
Time (mins)		5	10	15	20	5	10	15	20	5	10	15	20
Two Parameter	Coa	1.4	1.8	2.1	2.5	2.7	2.8	3.2	3.5	3.8	3.9	4.1	4.3
	Ka	0.004	0.007	0.008	0.009	0.010	0.012	0.013	0.015	0.016	0.017	0.018	0.019
Three Parameter	Co	39	36	32	31	25	18	12	10	9	7	6	4
	Coa	2.5	3.2	4.1	4.6	5.2	6.5	7.2	8.1	8.5	9.2	9.1	9.6
	Ka	0.025	0.027	0.029	0.035	0.038	0.041	0.048	0.061	0.067	0.075	0.086	0.095
Parameters		**Double Cone Blender**											
Blending speed		**25 rpm**			**50 rpm**				**75 rpm**				
Time (mins)		5	10	15	20	5	10	15	20	5	10	15	20
Two parameter	Coa	1.1	1.3	1.6	1.7	1.9	2.2	2.5	2.6	2.8	3.5	3.8	4.2
	Ka	0.002	0.003	0.004	0.007	0.009	0.013	0.014	0.016	0.017	0.019	0.019	0.023
Three Parameter	Co	41	37	31	30	28	19	15	13	11	8	5	3
	Coa	2.8	4.4	5.3	6.4	7.3	7.5	8.6	9.1	9.7	10.2	10.1	10.7
	Ka	0.021	0.024	0.031	0.034	0.035	0.046	0.051	0.056	0.059	0.079	0.088	0.096

Table 1: de-agglomeration modeling of the data of diclofenac sodium blend in v cone blender and double cone blenders using two and three-parameter single-exponential decay equations

higher rotation rate, the symmetry of the system is broken and each half of the blender becomes dominated by the presence of one component of the mixture. This behavior is accentuated by slight imperfections in the symmetry of the experimental apparatus, but also appears spontaneously. The performance of the double cone blender was correlated to the mechanisms of segregation patterns (Fig 14) generated in the double cone blender at various speeds as previously as reported [11]. The main barrier to mixing in a standard double-cone blender is flow of particles across the plane of symmetry. The rate of both axial and radial mixing within one half of the blender is 20-30 times faster than the rate of axial mixing across the plane of symmetry. For free-flowing materials, decreasing the fill percentage from 60% to 40% decreases mixing time by about one third per bath. Changing the rotation rate between 8 and 24 rpm has little effect on the mixing rate, indicating the existence of a regime in which scale-up can be based solely on the number of blender revolutions. Above 30 rpm, inertial effects begin to influence motion inside a double-cone blender, and it is likely that the vessel speed will have additional effects on the mixing rate.

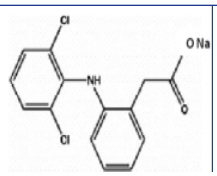

Fig 15: Structure of diclofenac sodium

FTIR studies

Diclofenac sodium is used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. Its pharmacological effects are thought to be related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are the mediators of the inflammatory processes [12]. The diclofenac sodium strucure (Fig 15) and its spectrum (Fig 16) showed the aromatic ring stretch split bands from 1604.7 to 1388.7 cm^{-1} assigned to the substituted phenyl groups. The 1452.87-1449.79 cm^{-1} and 869.8-621 cm^{-1} bands indicate a dihalogenated substituted benzene ring, as the presence of three adjacent hydrogen atoms resulting from the hygroscopic form of the sodium salt. Bands at 771.5-740.3 cm^{-1}, assigned to the presence of three adjacent hydrogen atoms in the ring, are mostly weak, yet relatively stable in position. The 1604.7-1550.8 cm^{-1} bands is assigned to an ortho-disubstitution. The 1, 2-substitution in the second ring is shown at 1234.4-1201.6 cm^{-1} and at 682.8-416.6 cm^{-1} frequencies. The neutralized entity of the carboxylic acid ranges from 1610-1554.5 and 1409.9-1292.2 cm^{-1} (Table- 2). Indicating that there are no drug excipient interactions.

Conclusion

Particle size, Aggregation patterns and dissolution profiles for free-flowing blends in V-cone blenders and double cone blenders have been shown to vary with changes in rotation rate and time. The mechanisms that drive pattern formation appear to depend on particle velocities in two specific regions of the blenders. The blenders

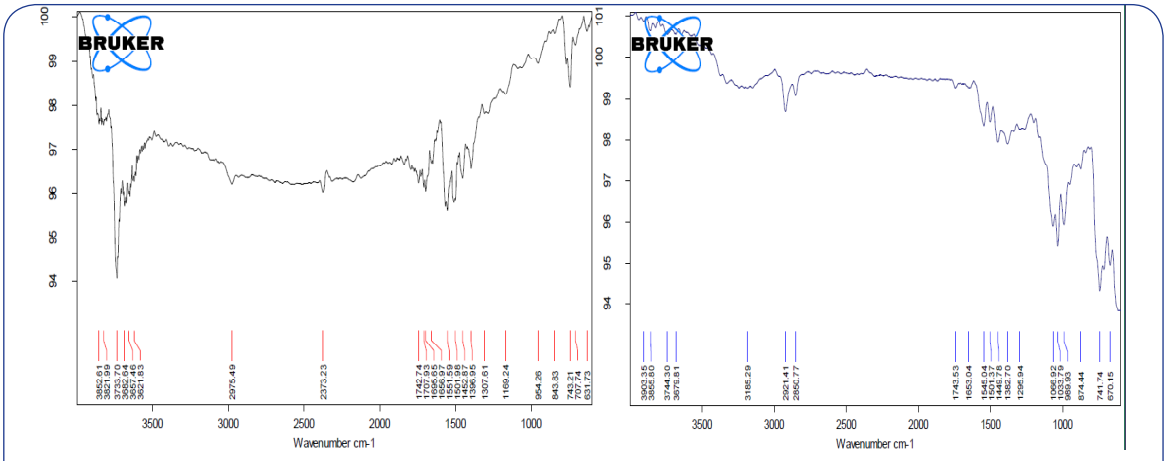

Fig 16: Left) FTIR spectra of Diclofenac sodium Right) FTIR spectra of Diclofenac sodium blend

Functional Groups (cm^{-1})	Diclofenac sodium (cm^{-1})	Blend (cm^{-1})
V (Char)	2975.49	2941.41
V (COO^-)	1551.59	1545.04
δ (disubst.cl-ϕ)	1452.87	1449.78
δ(COO^-)	1307.61	1295.94
δ(1,2,3-subst.ϕ)	1169.24	1066.92
(disubst.cl-ϕ)	631.73	670.15
(3 adj.H atoms)	743.21	741.74

Table 2: Selected IR absorbance bands for diclofenac sodium and the blend

used in this study are laboratory models which are relatively small than industrial or pilot-plant sized vessels and that these patterns will only appear for strongly segregating free-flowing materials. When run at lower rotation speeds, the segregation patterns are symmetric with respect to the blender geometry. However, at higher rotation rates, the symmetry of the system is broken and each half of the blender becomes dominated by the presence of one component of the mixture. High initial agglomeration, slow de-agglomeration rates and high non-dispersible agglomeration would indicate significant potential formulation problems with dissolution and perhaps bioavailability of poorly water soluble drugs in a formulation. The "V" Blender is an efficient [13] and versatile blending machine for mixing and lubrication process of dry powders homogeneously. The primary mechanism of blending in a V-Blender is diffusion. Diffusion blending is characterized by small scale random motion of solid particles. Blender movements increase the mobility of the individual particles and thus promote diffusive blending. Diffusion blending occurs where the particles are distributed over a freshly developed interface. V-Blenders are therefore preferred when precise blend formulations are required. They are also well suited for applications where some ingredients may be as low as five percent of total blend size. Normal blend times are typically in the range of 5 to 15 minutes depending on the properties of material to be blended.

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