Influence of Operational Variables on Properties of Piroxicam Pellets Prepared by Extrusion-Spheronization: A Technical Note

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INTRODUCTION

Extrusion-spheronization is the most commonly used method for pellet production.[1] Suitable excipients and fillers can be used to produce pellets with the desired characteristics.[2] Spherical pellets possess many advantages, including a low surface area–to-volume ratio, good flow properties, and uniformity in packing.[3] This ideal shape of pellets makes them excellent substrates for coating as desired for aesthetic purposes or to control the release of active ingredients.[4] Microcrystalline cellulose (MCC) is the most commonly used excipient in extrusion-spheronization. It leads to the formation of round spheres with desirable characteristics.[5] During spheronization, the moisture entrapped in the MCC microfibrils adds plasticity to the extrudates and helps to round the short extrudates into spherical pellets.[6]

The pellet properties can be affected by many operational variables during the extrusion stage, the spheronization stage, or the drying stage. Both drying technique and drying temperature have a considerable effect on the pellet structure and properties. The variables that affect the final pellet qualities are screen pressure[7]; screen hole diameter[8]; extruder type and speed[9]; type of friction plate; and spheronization time,[10] speed, and load.[11] There is considerable interaction between spheronization time and spheronization load. With small and large spheronization loads, the yield of large pellets increases with longer spheronization time, an effect that is exacerbated by faster spheronization speed. Unsuitable processing parameters lead to pellets with poor qualities.

The objective of this study was to prepare pellets using extrusion-spheronization with Avicel PH 101 and Avicel PH 302 and to study the influence of operational variables like drying conditions, spheronization time, and spheronization speed on various pellet properties such as size and size distribution, shape, densities, flow properties, friability, and drug release.

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MATERIALS AND METHODS

Materials

Piroxicam was a generous gift from Lark Laboratories (New Delhi, India). The Avicel grades used for the study, Avicel PH 101 and Avicel PH 302, were obtained from FMC Corporation (Philadelphia, PA). Hydrochloric acid was procured from SD Fine Chemicals (Mumbai, India).

Methods

Preparation of Pellets

Operational variables may affect several important pellet properties,[13] which can render a pellet either suitable or unsuitable for use. In the current study, the different process variables used for the preparation of pellets were drying method, drying temperature, spheronization time, and spheronization speed. Pellets were prepared using Avicel PH 101 and Avicel PH 302. The amount of water used in all the formulations was kept constant at 80% wt/wt on a dry basis. The drug (piroxicam) concentration in the pellets was also kept constant at 5% of the total pellet weight. Exactly 50 g of the powder mass was extruded through a Caleva extruder 25 (Caleva, Dorset, England) and subsequently spheronized (Caleva spheronizer 120). The batches ET1, ET2, E1, ET3, and ET4 were prepared using Avicel PH 101 at a medium spheronization speed with 2 minutes of spheronization time and were subjected to different drying conditions, that is, at room temperature (in a desiccator), 37°C, 50°C, 65°C (in a tray dryer fitted with fan [Narang, New Delhi, India]), and –20°C (in a freeze dryer [Edward, Crawley, UK]), respectively, for 24 hours. The batches ES1, E4, ES2, ES3, ES4, and ES5 were prepared using Avicel PH 302 at a medium spheronization speed with a constant drying temperature of 50°C (in tray dryer) and subjected to different spheronization times (ie, 1, 2, 3, 5, 7, and 10 minutes, respectively). Batches ESS1, and ESS2 were prepared using Avicel PH 302 at different spheronization speeds (ie, low and high, respectively), with a constant drying temperature of 50°C (in tray dryer) and a spheronization time of 2 minutes.

Size Analysis

Size analysis of the pellets was performed with the help of sieve analysis. A sieve shaker (Nippon, New Delhi, India) was used for 20 minutes to separate the pellets into various size fractions. The mass median diameter and span were employed to characterize the pellet size and size distribution. The modal class fraction was the size fraction obtained from sieving with the highest weight of pellets.

Shape Analysis

At least 20 pellets from each batch were randomly selected for shape analysis from the modal class fraction obtained from size analysis by sieving. The pellets were mounted on a light microscope fitted to a camera lucida, and the images of the pellets were drawn manually on graph paper. The area of the images and the maximum and minimum radii were calculated, and from these the various shape factors were calculated, as reported by Koo and Heng.[1]

Densities, Angle of Repose, and Friability

Densities (bulk, tapped, and granule densities), angle of repose, and friability were determined in triplicate for piroxicam pellets by standard methods. The Hausner ratio and the Carr index were calculated.[14]

Dissolution Studies

Exactly 400 mg of the pellets (equivalent to 20 mg of drug) of 18/25-mesh (1000-710 μm) fraction were used for the drug release studies. A constant sieve fraction of the pellets was used for each batch so as to minimize the effect of change in total surface area of the pellets upon dissolution rate. USP dissolution apparatus type I was used for the studies at 50 rpm. Simulated gastric fluid (without pepsin) was used as the dissolution media, and samples were withdrawn after predetermined time intervals and were analyzed by UV spectrophotometer at a λ_{max} of 333.0 nm. The dissolution studies were conducted in triplicate, and the average drug release ± SD was calculated.

Results and Discussion

Size Analysis

The results of the size analysis data of the pellets as a function of the different drying conditions and spheronization times are shown in Table 1. The pellets dried at room temperature (ET1) had the highest pellet size, followed by the pellets that were freeze dried (ET4), but there was no remarkable variation in their size. After drying in a tray dryer at 37°C and 50°C, the pellets showed no shrinkage, but drying at a higher temperature of 65°C caused a decrease in the particle size. This finding corroborates the hypothesis that pellets shrink on drying at a higher temperature.[15] This may be due to a decrease in pellet porosity, which is also evident from these formulations' drug release profiles, in which the drug release rate fell with a reduction in porosity. Mehta et al[2] reported similar findings. No relationship could be found between the span values of these pellets.

Not much difference in mean pellet diameter or pellet size distribution could be observed by varying the spheronization time. Contrary to the findings of a previously published report (where it was observed that the pellet size increased with an increase in spheronization time),[14] it was observed that spheronization time did not contribute to the differences in mean pellet size in this study's experimental conditions. This difference in the results could be ascribed to the fact that in our study, at 7 and 10 minutes of spheronization (ES4 and ES5), a few large spheres (on the order of millimeters in diameter) were obtained and were excluded from the size analysis data.

Shape Analysis

The shape analysis of the pellets obtained at different drying conditions is shown in Table 1. The different shape parameters—circularity, elongation, and rectangularity—did not change much for pellets dried in different conditions. As discussed in the previous section, pellets shrink on drying at a higher temperature. The pellet shrinking might have occurred uniformly throughout the pellets, thus leaving the shape unaffected by the drying conditions.

The pellet shapes were, however, highly affected by their retention time in the spheronizer during manufacture. As can be seen from Table 1, the pellets became rounder with an increase in spheronization time. At 1 and 2 minutes of spheronization (ES1 and E4) the pellets were dumbbell shaped (Figure 1A and 1B), and the pellets became rounder when spheronized for 3 and 5 minutes (ES2 and ES3) (Figure 1C and 1D). However, a further increase in spheronization time did not considerably affect the pellet shapes. At 5 minutes of spheronization, the circularity of the pellets was 0.902, whereas for 7 and 10 minutes of spheronization (ES4 and ES5) (Figure 1E and 1F), the circularity values were 0.913 and 0.911, respectively, which indicates that the roundness did not increase after 5 minutes of spheronization. Thus, a spheronization time of 5 minutes was found to be optimum for Avicel PH 302. The increase in roundness with time was obvious as the extrudates got more attrition force for their rounding, and after an optimum time of spheronization, the pellets became compact enough so that no attrition forces could act upon them anymore. This finding corroborates the results reported by many researchers. Gouldson and Deasy[12] have reported that the greatest change in circularities of pellets occurred during the initial 3 minutes of spheronization.

Table 1. Size and Shape Analysis of Pellets Obtained by Different Drying Conditions, Spheronization Times, and Spheronization Speeds

Formulation Code	Arithmetic Mean Diameter (μ)	Span	Circularity	Elongation	Rectangularity
ET1	707	0.576	0.853 ± 0.076	1.242 ± 0.101	0.826 ± 0.069
ET2	638	0.361	0.823 ± 0.056	1.253 ± 0.097	0.831 ± 0.074
E1	662	0.619	0.832 ± 0.067	1.250 ± 0.089	0.830 ± 0.063
ET3	613	0.371	0.819 ± 0.073	1.258 ± 0.106	0.833 ± 0.071
ET4	704	0.575	0.859 ± 0.083	1.244 ± 0.096	0.827 ± 0.080
ES1	669	0.646	0.763 ± 0.069	1.413 ± 0.083	0.837 ± 0.085
E4	664	0.646	0.767 ± 0.064	1.406 ± 0.071	0.837 ± 0.087
ES2	655	0.623	0.833 ± 0.079	1.256 ± 0.091	0.828 ± 0.083
ES3	671	0.641	0.902 ± 0.068	1.142 ± 0.078	0.788 ± 0.081
ES4	673	0.691	0.913 ± 0.080	1.127 ± 0.093	0.785 ± 0.094
ES5	691	0.643	0.911 ± 0.078	1.128 ± 0.086	0.786 ± 0.063
ESS1	—	—	0.765 ± 0.068	1.411 ± 0.083	0.836 ± 0.077
ESS2	—	—	0.801 ± 0.063	1.356 ± 0.069	0.831 ± 0.065

— indicates that parameters were not determinted.

Similarly, other researchers found that the maximum sphericity was achieved within 60 seconds in the spheronizer.[16]

The pellet shapes were also affected by the rotational speed of the plate inside the spheronizer. With an increase in the plate speed, the circularity of the pellets increased (Table 1, Figure 1B, 1G, and 1H). But in the studied range of plate speeds, the increase in circularity was not as great as it was when the spheronization time was increased. The highest circularity obtained with an increase in spheronization speed was 0.801 (ESS2) (Figure 1H). This value was even less than that of ES2 (circularity 0.833, Table 1,) where 3 minutes of spheronization was performed at a lower speed. It can be concluded that increased retention time in the spheronizer even at a lower speed imparts a greater attrition force and causes more rounding of the pellets than does performing the spheronization for less time, even at a higher speed.

Densities, Angle of Repose, and Friability

The densities of pellets obtained at different drying temperatures (room temperature [ET1], 37°C [ET2], 50°C [E1], and 65°C [ET3]) and by different drying methods (drying in a tray dryer [E1, ET2, ET3], drying in a desiccator, and drying in a freeze dryer [ET4]) are shown in Table 2. Drying at a higher temperature, as compared with drying at room temperature (ET1), led to an increase in densities (tapped and granule). Perez and Rabiskova[15] reported a similar finding. The Hausner ratio and Carr index were more or less the same in all the batches, which might have been due to a similar size distribution (Table 2).

Little difference in density (tapped or granule) was found among the pellets obtained by spheronizing for different time periods (Table 2), perhaps because, due to similar particle size and size distribution, the packing properties of pellets did not change. Like differences in spheronization time, differences in spheronization speed did not cause much change in the densities of the pellets, which corroborates the results of other researchers.[17]

The flow properties were less satisfactory when the pellets were dried in a tray dryer. An increase in the drying temperature in the tray dryer improved the flow properties, but this improvement was very slight. Freeze drying of the pellets (ET4), however, caused the lowest angle of repose and the highest flow rate.

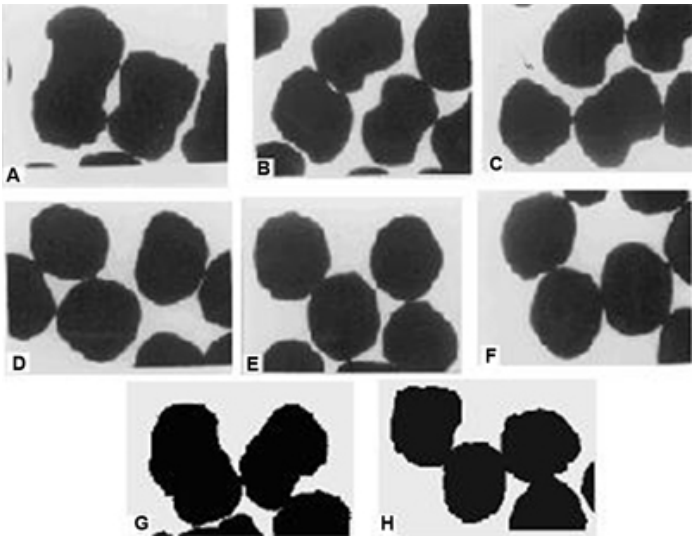

Figure 1. Photomicrographs of modal class fraction (passed through sieve #18 BSS and retained on #25 BSS) of pellets prepared by (A) 1 minute (ES1), (B) 2 minutes (E4), (C) 3 minutes (ES2), (D) 5 minutes (ES3), (E) 7 minutes (ES4), and (F) 10 minutes (ES5) of spheronization, and (G) lower spheronization speed (ESS1) and (H) higher spheronization speed (ESS2). BSS indicates British Standard Specifications.

Table 2. Densities, Flow Properties, and Friability of Pellets Obtained by Different Drying Conditions, Spheronization Times, and Spheronization Speeds*

Formulation Code	Tapped Density	Granule Density	Hausner Ratio	Carr Index	Angle of Repose	Flow Rate (g/sec)	% F
ET1	0.823 ± 0.016	1.104 ±.0.102	1.141	0.124	27.804 ± 1.011	1.629 ± 0.026	0.69
ET2	0.885 ± 0.009	1.381 ± 0.013	1.149	0.130	30.117 ± 0.847	1.537 ± 0.017	0.58
E1	0.881 ± 0.015	1.377 ± 0.019	1.145	0.129	29.858 ± 0.926	1.537 ± 0.021	0.56
ET3	0.890 ± 0.011	1.399 ± 0.017	1.150	0.130	29.303 ± 0.913	1.562 ± 0.029	0.39
ET4	0.806 ± 0.015	1.108 ± 0.011	1.133	0.118	26.814 ± 0.877	1.633 ± 0.023	0.74
ES1	0.943 ± 0.011	1.473 ± 0.046	1.069	0.065	27.616 ± 0.637	1.379 ± 0.029	0.89
E4	0.949 ± 0.008	1.462 ± 0.071	1.078	0.073	27.622 ± 0.525	1.385 ± 0.037	0.93
ES2	0.940 ± 0.013	1.476 ± 0.059	1.077	0.071	27.535 ± 0.681	1.381 ± 0.038	0.91
ES3	0.944 ± 0.013	1.483 ± 0.077	1.061	0.054	25.091 ± 0.713	1.908 ± 0.044	0.67
ES4	0.938 ± 0.009	1.463 ± 0.033	1.039	0.037	25.026 ± 0.673	1.903 ± 0.021	0.68
ES5	0.938 ± 0.008	1.496 ± 0.075	1.045	0.043	25.031 ± 0.599	1.916 ± 0.043	0.64
ESS1	0.963 ± 0.010	1.441 ± 0.051	1.091	0.083	28.131 ± 0.688	1.369 ± 0.027	0.89
ESS2	0.944 ± 0.014	1.463 ± 0.069	1.059	0.056	26.988 ± 0.599	1.386 ± 0.041	0.86

*%F indicates percent friability.

The flow properties of the pellets depended on the spheronization time (Table 2). An increase in spheronization time increased the circularity of the pellets (Table 1). As expected, increased circularity rendered the pellets more flowable.

When the spheronization speed was varied, the results were similar to those obtained with changes in spheronization time. An increased speed of spheronization improved the flow properties (Table 2) of the pellets, mainly by increasing the circularities (Table 1).

The influence of drying conditions on pellet friability is shown in Table 2. The friability of all the batches was below 1%. As the drying temperature increased, the percent friability decreased. At the higher temperatures, the pellets might have become more hardened and less friable because of reductions in porosities and shrinkage.[13] Freeze drying of pellets (ET4) resulted in almost the same percent friability as that obtained by drying the pellets at room temperature (ET1).

The spheronization time seems to have affected the percent friability of the pellets (Table 2), even though the change in pellet friability was less pronounced with small increases in spheronization time (ES1, ES2, and E4). The friability of ES1, ES2, and E4 did not differ considerably, but when the spheronization time was further increased, the percent friability decreased. This may be explained by the fact that, at lower spheronization times, the attrition forces in the spheronizer became insufficient for the compaction of the high-density Avicel PH 302. This lack of compaction resulted in light masses, but when the duration of spheronization was increased, hard masses were formed, which led to a reduction in pellet friability. Also, at short spheronization times, the pellets were dumbbell shaped (Table 1) with protruding surfaces, which became more prone to forces during friability testing.

In the studied range of the speed of the spheronizer plate, no considerable differences in the percent friability of the pellets were found (Table 2). This increased spheronization speed might not have been able to exert as much force as spheronization time did, producing loose compacts with higher and more similar friability indices.

Dissolution Studies

The drying conditions notably changed the pellets' drug release profiles (Figure 2). An increase in the temperature of drying reduced the percent release of the drug. This may have been due to a reduction in porosity of the granules during drying at higher temperatures,[15] because of greater shrinkage. Freeze drying (ET4) resulted in a very high drug

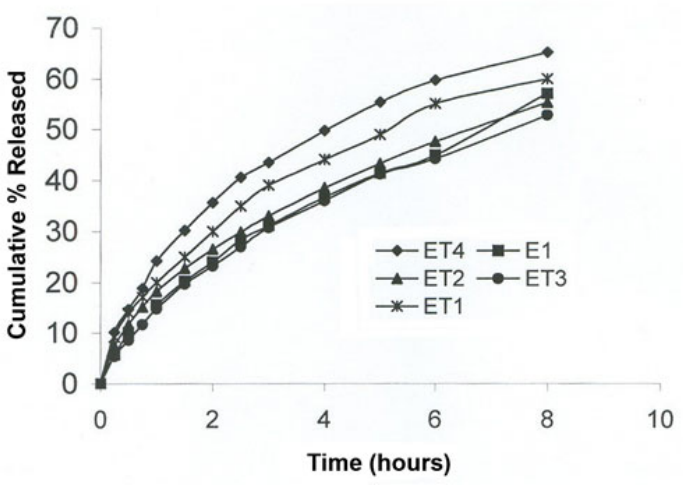

Figure 2. Time vs cumulative percent released of drug from pellets obtained by different drying conditions: drying at room temperature (ET1), drying in a tray dryer (at 37°C [ET2], 50°C [E1], 65°C [ET3]), and drying in a freeze dryer (ET4).

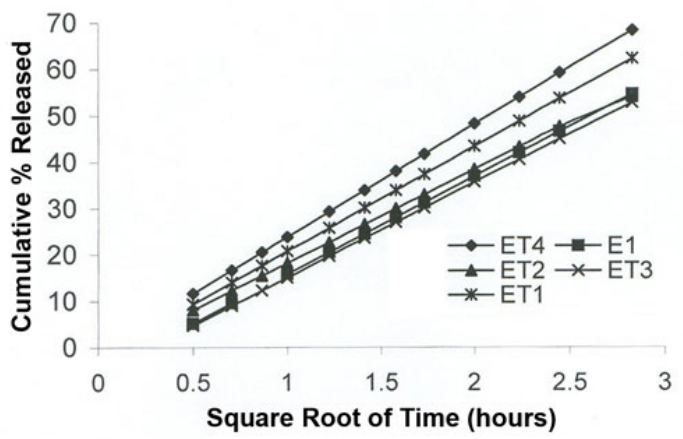

Figure 3. Square root of time vs cumulative percent released of drug from pellets obtained by different drying conditions: drying at room temperature (ET1), drying in a tray dryer (at 37°C [ET2], 50°C [E1], 65°C [ET3]), and drying in a freeze dryer (ET4).

release profile because of the formation of very porous pellets. Drying at room temperature (ET1) also increased the percent drug release, but the increase was not as pronounced as that obtained by freeze drying. All the batches showed a Higuchian drug release profile (square root of time model) (Figure 3).[18]

Summary and Conclusion

The processing conditions had a pronounced effect on the pellet properties. Drying conditions influenced the mean size and the drug release of the pellets. Because of the shrinking of the pellets upon drying at higher temperatures, the pellets also showed increased densities. Freeze drying almost prevented shrinking and thus led to the highest drug release. With an increase in the temperature of drying, the drug release rate decreased.

Both spheronization time and spheronization speed affected the shapes of pellets, and the changes in shapes then affected the pellet flow properties. Within the studied range, the circularity of the pellets was affected more by the spheronization time than by the spheronization speed. Drying conditions influenced pellet friability, which decreased with an increase in drying temperature, indicating the formation of more dense structures at higher temperatures. The same result was obtained with spheronization time. With an increase in spheronization time, the friability decreased, because of the formation of more compact masses at higher spheronization times. Mean size was not affected by spheronization time or spheronization speed.

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