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MANIPULATION OF NAPROXEN PARTICLE MORPHOLOGY VIA THE SPHERICAL CRYSTALLIZATION TECHNIQUE TO ACHIEVE A DIRECTLY COMPRESSIBLE RAW MATERIAL

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ABSTRACT

Crystals of naproxen were modified by the spherical crystallization technique to improve the compression and flow characteristics of the drug substance. A naproxen:acetone solution was added to water, and the crystals were agglomerated with either hexanol, octanol, or toluene. The resulting agglomerates were compact spherical aggregates of plate shaped crystals, regardless of the agglomerating solvent used. The quantity of the agglomerating solvent and the temperature of the solvent system were critical process parameters, probably due to their effect on the drug solubilization. Crystal agglomeration sufficiently improved the intrinsic compressibility and flow characteristics of naproxen that the agglomerated material was directly compressible.

INTRODUCTION

In the production of tablets it is both quicker and less expensive to avoid the wet granulating and drying steps, and instead use materials that are directly compressible. However, the crystal morphology of many drug substances causes them to have extremely poor flow characteristics, thereby eliminating the possibility of a direct compression process for formulations with high levels of drug. Crystal morphology can also significantly impact a material's compression characteristics, and many formulations with a high percentage of drug substance do not lend themselves to direct compression due to poor compressibility. Kawashima et al's work[1-8] indicates that the spherical crystallization technique has the potential of improving the flow and dissolution characteristics of drug materials. This technique manipulates the drug substance during the crystallization process.

The crystal agglomeration process may also have the potential of improving the intrinsic compressibility of drug substances. This creates the possibility of directly compressible formulations for tablets that previously could only be manufactured with the aid of a binder during a wet granulation process. In this study we prepared crystal agglomerates of naproxen via the spherical agglomeration process while varying the agglomerating solvent, the amount of solvent, and the temperature of the solvent system. The spherical agglomerates were then compressed into tablets and the tablet hardness was examined. Naproxen was used as a model drug because it forms plate shaped crystals that exhibit both exceptionally poor flow characteristics and low intrinsic compressibility.

METHODS

Materials - The naproxen (Syntex, Inc.) was USP grade. The acetone, hexanol, octanol, and toluene were reagent grade. The water was deionized.

Spherical Crystallization - The drug was first dissolved in acetone heated to 25-30°C, while being stirred with a Lightnin Mixer. The acetone/drug solution was then mixed into a larger volume of room temperature water (quantities are specified in Table 1) for one minute. A third solvent (kept at room temperature) was then added (the "agglomerating solvent") and the mixture was stirred for 5-10 minutes (except Batch 5, which was mixed for only a half minute to avoid oversolubilizing the drug), leading to agglomeration. The agglomerates were filtered using a Buchner funnel, the filter cake was gently broken apart with a spatula, dried in an oven at 65°±5°C (85°±5°C for Batches 7 - 9), and passed through a 14 mesh screen.

Intrinsic Compressibility - The intrinsic compressibility of the powders was determined utilizing a Carver Press equipped with a 3/8 inch standard concave punch and die set. Three tablets were compressed per level of pressure using a fixed fill volume (the unagglomerated naproxen had to be weighed and hand packed into the die cavity because of it's poor flow characteristics).

Flow - Due to the small quantities of powder available, the flow characteristics were subjectively judged by visual examination.

Hardness - Tablet hardness was determined immediately after compression using an instrument (model HT-300, Key International, Inc.) that utilized the principal of strain-gauge linear force.

RESULTS AND DISCUSSION

A trisolvent system was utilized to produce the spherical agglomerates. The drug was first dissolved in acetone, in which it was highly soluble (140 mg/ml). The acetone/drug solution was then mixed into a larger volume

TABLE 1

Formulations Used to Produce the Naproxen Spherical Agglomerates. Units are Grams for Naproxen and Milliliters for Solvents.

Batch Number:	0	1	2	3	4	5	6	7	8	9
Ingredient										
Naproxen	6.0	6.0	6.0	20.0	20.0	20.0	20.0	60.0	60.0	60.0
Acetone	50	50	50	150	150	150	150	450	450	450
Water	250	250	250	750	750	750	750	2250	2250	2250
Agglomerating Solvent:	None									
Octanol		9.0	4.5						50	
Hexanol				13.0	20.0	30	40	50		
Toluene										200

of water (quantities are specified in Table 1). Naproxen is relatively insoluble in water (<1 mg/ml), consequently it precipitated as crystals. A third solvent was then added while stirring, which will be referred to as the "agglomerating solvent," which was immiscible with the second solvent (water), but which had limited naproxen solubility. The agglomerating solvent preferentially wetted the naproxen crystals causing them to become tacky, leading to agglomeration. Previous work with aspirin in an ethanol, chloroform, and water solvent system successfully produced crystal agglomerates[1]. The solubility of aspirin in these solvents is about

TABLE 2

Solubility Data for the Agglomerating Solvents with Respect to Naproxen and Water.

Solvent	Naproxen Solubility (mg/ml)	Water Solubility (wt %)[10]
Hexanol	30	0.55
Octanol	23	0.0586
Toluene	6	0.0492

200:24:0.25 (in mg/ml). Therefore, agglomerating solvents were selected that would give roughly the same ratio of solubility for naproxen, and that would also be immiscible with water. Another criterion for the solvents examined in this study was that they should not be known carcinogens. Table 2 exhibits the solubility data for the selected solvents, hexanol, octanol, and toluene, that were found to be in the appropriate solubilization range for naproxen and were not miscible with the precipitating solvent.

Batches 1 and 2 utilized 6 grams of naproxen to examine if spherical agglomerates of naproxen could be produced on a small scale. The batch size was increased to 20 grams in Batches 3 - 6, and was scaled up to 60 grams in Batches 7 -9. A control batch (Batch 0) of plain crystalline naproxen was manufactured. Octanol was the first agglomerating solvent studied. A 3:100 ratio of octanol:water+acetone was used in Batch 1. This resulted in oversolubilized crystals. Large, soft, semi-melted agglomerates that closely

resembled small curd cottage cheese were produced, and they coalesced during drying. Therefore, the amount of octanol was decreased by 50% in Batch 2. Batch 2 resulted in a fine, free flowing powder.

Hexanol was studied as the agglomerating solvent in Batches 3 - 6. This solvent produced some satisfactory spherical agglomerations, depending on the amount of hexanol used. The size of the agglomerates were about 250 microns in Batch 3, and their size increased as the amount of toluene was increased. In Batch 6, a single viscous mass was produced upon hexanol addition. Further, after screening it was seen that the Batch 3 material had better flow properties, being fairly free flowing, than Batches 4 - 6. The process was next scaled up to a 60 gm batch size with Batch 7. Approximately 83% of the drug was recovered in the form of agglomerates. The level of improvement in the flow properties of this batch, compared to the unagglomerated crystallized drug, was similar to that of the smaller batches. X-ray diffraction indicated that Batch 7 was identical to the original naproxen, demonstrating that this process was not inducing polymorphism.

Batch 8 showed that the process utilizing octanol as the agglomerating solvent could also be scaled up to the 60 gm batch size, and resulted in approximately 93% of the drug being recovered. The improvement in the flow characteristics of this batch, compared to the unagglomerated crystallized drug, again resembled those of the smaller batches.

Batch 9 utilized a third agglomerating solvent, toluene. Some preliminary work determined a desirable quantity of agglomerating solvent. Batch 9 produced satisfactory crystal agglomerates with moderately good flow properties. The effect of temperature on the spherical agglomeration process was examined by manufacturing two additional batches (Batches 9A and 9B). In Batch 9A, the temperature of the water prior to use was lowered to

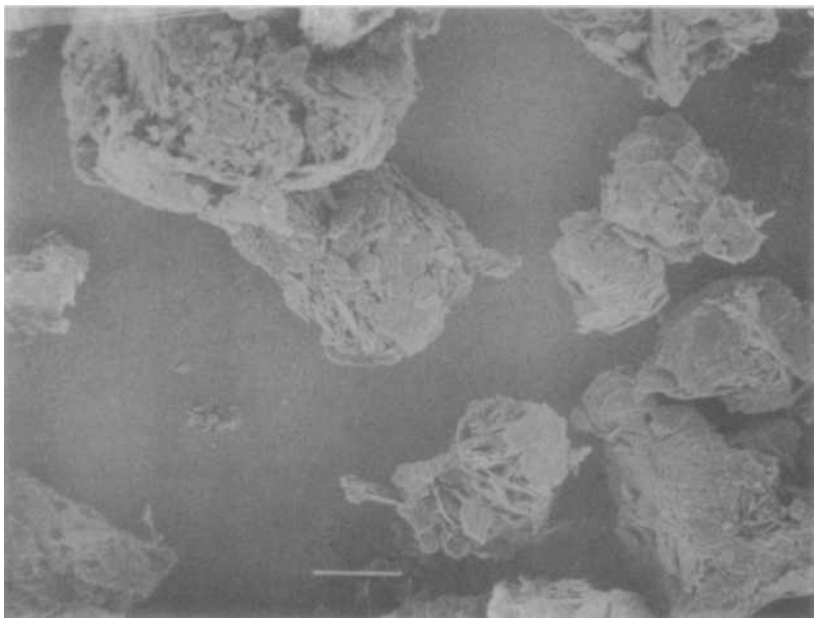

FIGURE 1
Scanning Electron Photomicrograph of the Batch 8 (Octanol) Crystal Agglomerates, Magnified 100 Times.

10°±3°C, and the solvent/water mixture was subsequently maintained at that temperature. The result was that no agglomeration occurred, even after prolonged mixing, possibly due to the decreased solubility of the drug in the agglomerating solvent at this lower temperature. Less solubilization of the drug would cause reduced wetting (and hence tackiness) of the drug particles, and therefore, decreased agglomeration. In Batch 9B, the temperature of the water prior to use was raised to 50°±2°C. This resulted in very large agglomerations being formed as well as a lowering of the amount of recovered drug (to 45%), probably due to the increased solubility of the

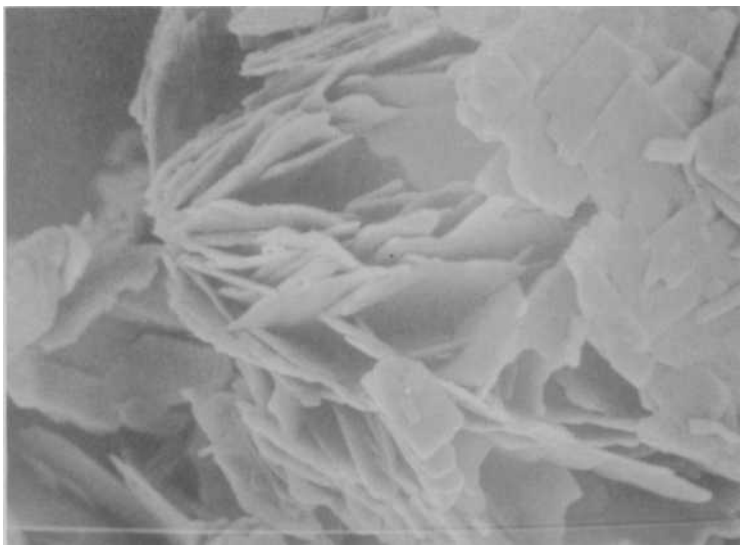

FIGURE 2

Scanning Electron Photomicrograph of the Batch 8 (Octanol) Crystal Agglomerates, Magnified 700 Times.

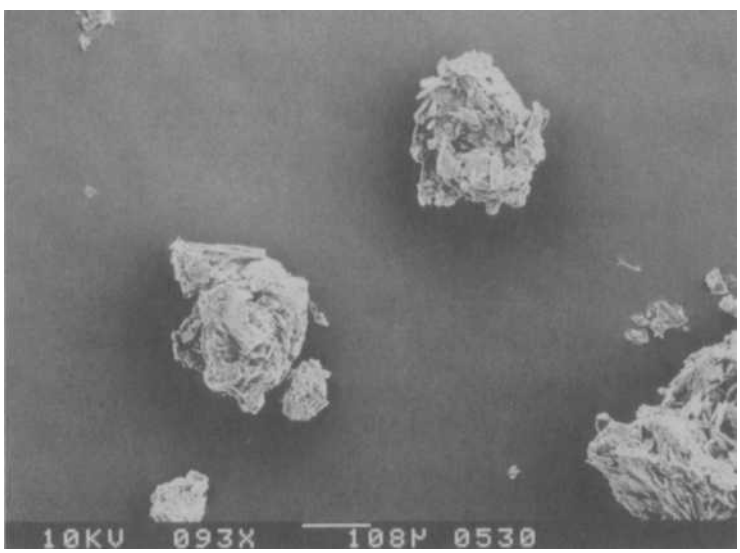

FIGURE 3

Scanning Electron Photomicrograph of the Batch 9 (Toluene) Crystal Agglomerates, Magnified 93 Times.

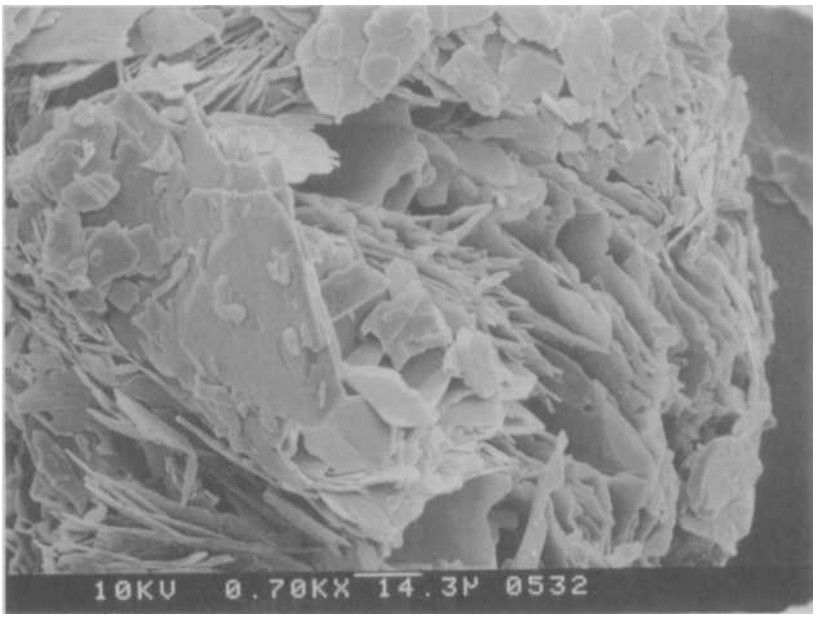

FIGURE 4
Scanning Electron Photomicrograph of the Batch 9 (Toluene) Crystal Agglomerates, Magnified 700 Times.

drug at this temperature. It is therefore apparent that solution temperature is an important process parameter.

Figures 1 and 2 are scanning electron photomicrographs of the Batch 8 crystal agglomerates, magnified 100 and 700 times, respectively. Figures 3 and 4 are scanning electron photomicrographs of the Batch 9 crystal agglomerates, magnified 100 and 700 times, respectively. These representative batches demonstrate that the agglomerates were compact, spherical aggregates of plate shaped crystals.

TABLE 3

The Intrinsic Compressibility of Nonagglomerated (Control) Naproxen and of Spherically Agglomerated Naproxen Batches, with the Column Heading Noting the Agglomerating Solvent Used.

	Batch 0 (Control)		Batch 7 (Hexanol)		Batch 8 (Octanol)		Batch 9 (Toluene)	
Compression Pressure (Lbs)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)	Tablet Weight (Mg)	Tablet Hardness (Kp)
1000	300 + 3	3.0 + 0.7	307 + 3	10.3 + 1.5 [1]	359 + 1	3.3 + 0.4	278 + 4	11.3 + 2.0 [1]
1500	-	-	302 + 4	13.6 + 1.3	357 + 7	5.2 + 0.4	269 + 3	14.9 + 1.1
2000	299 + 1	4.8 + 0.5	301 + 2	13.9 + 2.0 [1]	360 + 8	7.7 + 0.4 [1]	265 + 10	11.4 + 0.4 [1]
2500	-	-	302 + 3	10.5 + 0.5	362 + 7	8.7 + 1.9	259 + 3	8.5 + 0.9
3000	299 + 4	6.3 + 0.6	304 + 3	9.7 + 1.5 [1]	368 + 6	8.3 + 0.8	271 + 4	9.7 + 0.6 [1]

[1] Statistically significantly different from the control batch, using a Student's t test at the p=0.05 level.

Having established that spherical agglomerates had been formed, and that the agglomerates flowed much better than the nonagglomerated crystalline material, Batches 7, 8, and 9 were examined to see if the spherical agglomerates evidenced improved compressibility versus unagglomerated crystalline drug. Table 3 demonstrates that the intrinsic compressibility of the drug was consistently improved in a statistically significant fashion at the p=0.05 level after the crystal agglomeration process was employed with either hexanol or toluene utilized as the agglomerating solvent. When octanol was used as the agglomerating solvent compressibility was significantly improved for only one of the three compression pressures. The order of compressibility was generally
unagglomerated drug<Batch 8<Batch 9~Batch 7.

CONCLUSION

The results of this study suggest that the spherical crystallization process can be utilized to improve the flow characteristics and the compressibility of drug raw material. This improvement is due to the modification of the morphology of the drug substance particles. The fact that each of the three agglomerating solvents chosen for study were effective may indicate that this is a fairly robust technique. The quantity of solvent used and the solvent temperature were demonstrated to be critical process parameters. The effects of varying these parameters are probably due to their influence on the amount of drug solubilization. The data indicates that the spherical crystallization technique increases drug compressibility to the degree that a directly compressible formulation is feasible.

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