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NAPROXEN CONTROLLED RELEASE MATRIX TABLETS: FLUID BED GRANULATION FEASIBILITY

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...; 2) high inlet temperature decreased granule particle size; 2) granule geometric median diameter correlated directly with the polymer fraction sprayed onto the granulation; 3) granulations with high bulk density and per cent fines generally produced much more friable and softer tablets due to the relatively small polymer fraction used in the spray solutions; 4) a small fraction of polymer sprayed onto the powder had resulted in a poor flowing granulation, delamination and capping during tableting, and subsequently a faster dissolution rate (USP Paddle Apparatus). With certain conditions, CR tablets can be produced from fluid bed granulations which show adequate dissolution, hardness, and friability.

INTRODUCTION

Fluidization techniques have been used in a variety of industries for some 30 years(1). However, only in recent years has a great deal of work been published by the pharmaceutical industry related to the use of fluid bed technology for granulating and agglomerating. Because GMP regulations governing dosage form manufacture have become so stringent, there is a need to cut production costs. Fluid bed granulating (FBG) is amenable to these regulations because powder blends can be mixed, granulated, and dried in a single operation, thereby avoiding cross-contamination of several manufacturing pieces of equipment. FBG also offers the advantage of freeing up conventional mixing equipment. Furthermore, manpower savings and processing costs can be implemented by computer automation of the fluid bed granulation equipment.

An article examining scaleup factors (2) and a review article describing the effect of various processing and formulation parameters on the final product have been published (3). Among the parameters evaluated include inlet air temperature, binder concentration/viscosity and quantity, and powder hydrophobicity. Despite the number of papers evaluating the previous parameters there is very little reported literature evaluating the effect of high molecular weight polymers on the physical properties of a fluidized product granulation and resultant tablet. Hence the purpose of this work is to investigate the feasibility of granulating a hydrophobic, poorly water soluble active agent with a high molecular weight (Mn=120000) polymer to prepare a large dosed tablet.

EXPERIMENTAL

Naproxen, USP was supplied from Syntex (Palo Alto, California). Hydroxypropyl methylcellulose 2208, USP; magnesium stearate, NF; and F. D. & C. Yellow #6 were supplied by Dow Chemical (Midland, Michigan), Mallinckrodt (St. Louis, Missouri) and Kohnstamm (New York, New York), respectively.

Manufacturing Equipment

The equipment used in this work is given in Table 1.

Fluid-Bed Granulation Procedure

The granulating solution was prepared by heating the purified water to 90°-100°C, dissolving the F.D.&C. Yellow #6, then dispersing the appropriate amount of hydroxypropyl methylcellulose (HPMC) 2208 in the boiling water. If

TABLE 1

Listing of Process Equipment Used for Experiments.

Process	Range	Equipment
Moisture Analyzer	3 g sample	Computrac® MA-5A
Hardness Tester	1-30 Kp	Key HT-300
Friabilator	20 tablets	Vanderkamp 10809
Particle Size Distribution	10 g sample	Allen-Bradley Sonic Sifter®
Tablet Dissolution	6 tablets	HP-8451A Diode Array Spectrophotometer
Granulation Characteristics Tester®	-----	Hosokawa Powder Characteristics
Tabletting	50 tablets/min. 1000 tablets/min.	Stokes F-4 (single station) Manesty Beta-Press® (16-station)
Granulator/Dryer	15 kg/5 kg	Vector Flo-Coater® FLF-15/5
Milling	-----	Erweka Oscillator AR-400
Blending	16 qt. capacity	Patterson-Kelly®
Viscosity	0 - 500 cps 1600 - 8000 cps	Cannon-Fenske® #350 Cannon-Ubbelohde® #500

the granulating solution contained no HPMC then the heating step was eliminated. After the HPMC was dispersed, the solution was cooled to room temperature, allowed to sit overnight, and the evaporated water replaced.

Viscosities of the 0.50% w/w, 0.75%, and 1.25% w/w HPMC solutions were determined to be 50 cps, 250 cps, and 1700 cps, respectively, which is less than the 2000 cps viscosity limit recommended by the gear pump manufacturer.

A series of preliminary spray studies were performed to optimize spray rate and spray pattern. A spray rate of 50 ml/min/gun was chosen as the standard rate and the spray pattern was altered by using main air pressures of 1.5, 3.0 and 4.5 kg/cm in conjunction with various spray gun atomization and

TABLE 2

Naproxen Controlled Release Matrix Tablet Fluidized Bed Granulating Parameters

	Independent Granulation Variables			
Granulation Lot #	Inlet Temp.(°C)	Polymer Sprayed (%)	Spray Soln. Conc. (%)	Spray Time (min.)
A	55	40	1.25	71
B	70	40	1.25	74
C	55	40	0.5	177
D	55	10	1.25	20
E	55	25	1.25	50
F	70	25	1.25	45

Inlet Temp. - refers to the temperature of inlet air to the Flo-Coater®.

Polymer Sprayed - refers to the HPMC used in the granulating solvent expressed as % of the total HPMC used.

Spray Soln. Conc. - refers to the Polymer Sprayed expressed as % of the granulating solvent.

Spray Time - refers to the actual total time it required to spray the appropriate amount of granulating solvent onto the powder bed.

pattern air settings. An optimal pattern was determined by spraying the colored granulating solution onto white paper. The optimal settings were a flow rate of 50 ml/min/gun (2 guns), 100 Standard Liters Per Minute (SLPM) atomizing air and 75 SLPM pattern air.

The appropriate amount of HPMC and naproxen to make a five kilogram batch was then placed in the fluid bed granulator, the powder bed fluidized with 50°C air, then the appropriate solution (Table 2) sprayed on to the powder bed. After all granulating solution was added, the granulation was dried to a target L.O.D. moisture content of 0.5%.

Granule Preparation and Tabletting

All granules were milled through an 8-mesh screen using an oscillator. Magnesium stearate was blended with the milled granules for 5 minutes in a

V-blender. The lubricated granules were then compressed to a thickness of 0.33" using capsule-shaped punches (0.75" x 0.35") on a Stokes F-4 single station tablet press. The appropriate tablet thickness was determined by compressing all the granulations on a Carver Press Station at 3500 lb.

Characterization of Granulation

All granulations were evaluated for aerated bulk density, angle of repose, compressibility, uniformity, angle of spatula, particle size distribution, and the geometric median diameter. Compressibility (expressed as %) is a numerical term of 100 times the difference in packed and aerated bulk densities, divided by the packed bulk density. Uniformity is the ratio of screen sizes (in microns) passing 60% of the granulation, to that passing 10% of the granulation. The flowability index is the sum total of the arbitrary indices assigned to the compressibility, angle of repose, uniformity, and angle of spatula. The geometric median diameter is a central value of the particle size distribution (by mass) assuming Gaussian distribution.

Dissolution

Tablet dissolution was monitored using a Hanson dissolution apparatus. Nine hundred mL of deaerated dissolution media, pH 7.5 $\pm$ 0.05 simulated intestinal fluid without enzymes, maintained at 37 $\pm$ 0.5°C was used as the dissolution media. The USP Paddle Dissolution method was employed at a rotation speed of 60 rpm. Release of the naproxen was monitored at a wavelength of 332 nm by using an automated sampler interfaced with an HP-8451A Diode Array UV spectrophotometer.

RESULTS AND DISCUSSION

All granulations were characterized by determining their particle size distribution, geometric median diameter, bulk density, compressibility, angle of repose, uniformity, and angle of spatula. The major differences among each granulation are shown in Table 3.

The geometric median diameter of the granulations ranges from 326 μ to 1044 μ and is directly related to the percent polymer sprayed onto the granulation (4-6). Specifically, the greater the polymer mass sprayed onto the powder bed, the larger the granule median diameter. The particle size distributions for the granulations are also significantly different (Figure 1). Granulations D and F contained the greatest percentage of fine particles. The low geometric median diameter and high percentage of fines in D demonstrates

TABLE 3

Physical Properties of Fluidized Bed Granulations

	Batch Number					
	A	B	C	D	E	F
Geometric Median Diameter (microns)	1044	1032	612	326	889	610
% Fines (< 106 microns)	3.5	3.8	18.0	63.7	18.4	36.3
Aerated Bulk Density (g/cc)	0.35	0.33	0.37	0.43	0.39	0.41
Packed Bulk Density (g/cc)	0.41	0.39	0.44	0.56	0.44	0.49
Compressibility (%)	14.6	15.4	15.9	23.2	12.8	19.5
Angle of Repose (degrees)	42	41	37	46	40	44
Uniformity	2.1	1.9	2.1	2.9	14.2	20.2
Angle of Spatula (degrees)	38	36	41	62	48	59
Flowability Index	80	81	79	65.5	70.5	62

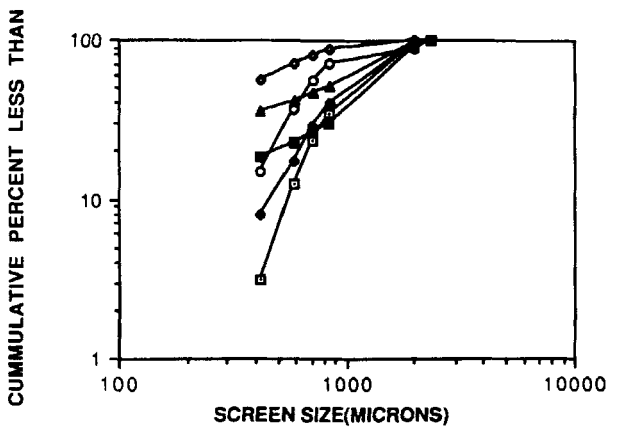

FIGURE 1.

Log-log Plot of Fluidized Bed Granulation Particle Size Distributions Versus Screen Size (Microns): A-(⊡), B-(◆), C-(○), D-(◇), E-(■), and F-(▲)

the adverse effects of not using adequate polymer (binder) in the granulating solution. Granulation F shows that increasing temperature appears to decrease the particle size. This result, which has been reported in the literature (7), is due to lack of wetting and agglomeration as a result of more rapid solvent evaporation. Furthermore, this result could be envisioned as being a result of the polymer being spray dried onto the drug particles. Granulation C exhibited a rather uniform particle size distribution and a small median diameter which was due to the increased spraying time which allowed for more uniform polymer application. The particle size characteristics of granulation C were probably due to the increased attrition due to the lengthy fluidization process.

In general, large particles are advantageous for a free flowing granulation. Hence as observed in Table 3, granulations A, B, and C contained a high percentage of particles in the 840-2000 μ size range which gave these granulations good flow properties. This qualitative observation was also confirmed by the flowability index which is the sum total of the arbitrary indices assigned to the compressibility, angle of repose, uniformity, and angle of spatula. For instance, the best flowing granulations were A, B, and C, which had flowability values of 80, 81, and 79, respectively.

Although large particles are advantageous to granulation flow properties, large particles also have the potential to be porous. Granulations D, F, and B demonstrate the extremes of this phenomena. For instance in Table 3, it can be seen that the two former granulations had a high percentage of fines which filled the void spaces among large granuales thereby increasing bulk density. At the other end of the spectrum was granulation B which had large particles and a set of bulk densities which were 77% and 70% of the aerated and packed bulk densities of D, respectively.

High bulk densities are important for tablet manufacture since the die fill limit corresponds to the maximum punch stroke length. The maximum punch stroke therefore determines the maximum tablet weight of a granulation with a given bulk density. It is important that a formulation undergoing compression avoid using a punch stroke near the maximum for a large tablet, hence the need for a high granulation bulk density. Avoiding the maximum punch stroke will further prevent tableting problems which could occur when there is batch to batch granulation density variations. Fluid bed granulations tend to produce porous granulations, but by increasing agglomerization, a granulation with increased bulk density and reduced porosity could be produced. Although not evident from this data, it may be possible to densify the granulation using more viscous solutions if the appropriate pumping system were available. Certainly one other viable method is the use of rotary fluid bed granulators

TABLE 4

Physical and Chemical Properties of Tablets Compressed from Fluidized Bed Granulations

Batch	Hardness (Kp)	Friability (%)	Composition (% L.S.)
A	25.8	0.24	98
B	26.6	0.18	102
C	26.8	0.33	97
D	13.3	0.98	100
E	25.7	0.14	100
F	20.0	0.70	99.

(8). This is advantageous to granulation production, but this could also unfortunately result in an oversized granule fraction larger than desired and a reduced compressibility as the granulation approaches its true density.

Unfortunately, all granulations possessed such low bulk densities that they could not be tableted on a high speed, 16-station Manesty Beta-Press®. Therefore, tablets were made on the single station Stokes F-4 press. Results of tablet characteristics are given in Table 4.

Granulations D and F produced tablets which were much more friable than any of the other 4 granulations. Some delamination and capping was also observed with these two batches, which could be ascribed to the poor compression characteristics of the active and inadequate binder concentration. The tablet hardness of these batches was 51% and 76% of the average values for the other 4 batches. This may be due to: 1) the increased number of fine particles which do not allow for sufficient bonding, 2) smaller fractions of the hydroxypropyl methylcellulose being sprayed onto the powder blend as a binder, and 3) lack of an intimate polymer-drug particle interaction.

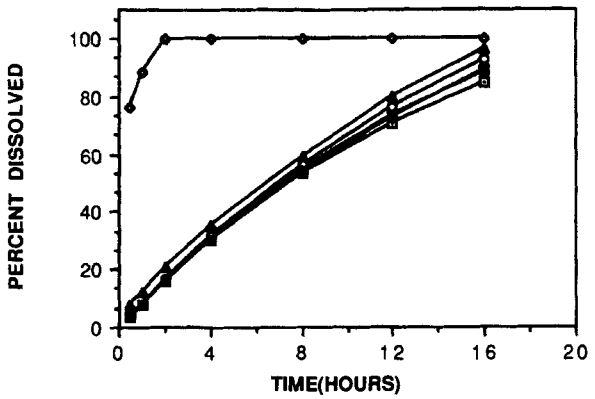

FIGURE 2.
Dissolution Profiles of Naproxen CR Matrix Tablets:
A-(◻), B-(◆), C-(○), D-(◇), E-(■), and F-(▲)

Dissolution results are graphically presented in Figure 2. Since delamination and capping were observed in the tableting of batch D and F, it may be postulated that this caused the dissolution for batch D to be much faster than expected and F is slightly faster than the rest of the batches. The cracks (from delamination and capping) allowed water to enter the tablet and cause tablet swelling before a gel layer could be established. The swelling phenomena caused the tablet to disintegrate slightly, increasing the available surface area for drug dissolution, which resulted in the faster dissolution rates observed. Therefore, batch D would not behave as a reliable controlled release dosage form. Hence batch F shows that increasing the spray temperature is not of nearly as much consequence on dissolution as reducing the polymer fraction added in solution.

CONCLUSION

Tablets were compressed from fluid bed granulations which showed adequate dissolution, hardness and friability. Therefore, very good potential exists for a fluid bed granulated form of naproxen controlled release tablets. Although process parameters which exemplify optimal conditions have not been isolated, this feasibility study emphasizes the importance of adding sufficient binder in solution and, to a less extent, spray temperature of the binder solution. Thus, a good direction has been provided for further study of larger sized batches.

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