DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(11), 1911-1922 (1994)

DIRECTLY COMPRESSIBLE ACETAMINOPHEN COMPOSITIONS PREPARED BY FLUIDIZED-BED GRANULATION

Cheng-Hsiung Liu[1], *Shou-Chiung Chen*[1], *Yung-Chi Lee*[1], *Theodore D. Sokoloski*[2], *and Ming-Thau Sheu*[*1]

[1]*Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, Taipei, Taiwan, R.O.C.*

[2]*Pharmaceutical Sciences, L-913, SmithKline Beecham, P.O. Box 1539, King of Prussia, PA 19406-0939, USA*

ABSTRACT

Polyvinylpyrrolidone (PVP) in aqueous solution was used as a binding agent in a fluidized-bed system to agglomerate acetaminophen powder into directly compressible granules. It was found that a minimal amount of 5% w/w PVP in a concentration of 7.5% w/v or less was needed to produce granules with an acceptable flow and the corresponding tablets having enough hardness without capping. There was a strong correlation between the time for 80% dissolved (T_{80}) and the logarithm of granule volume-surface mean diameter. A directly compressible acetaminophen composition to manufacture tablets having a T_{80} value less than 30 min can be prepared simply by adding an appropriate amount of disintegrant (crospovidone, sodium starch glycolate, or pregelatinized starch) to the agglomerated granules.

INTRODUCTION

Several attempts have been reported to prepare granular acetaminophen that contains all adjuvants required for direct compression. Barlow et al. disclosed the preparation of free-flowing

granular paracetamol containing PVP, soluble starch and potassium sorbate by continuously slurrying the components in water and spray drying (2). Vogel et al. introduced a product containing 90% acetaminophen by spray granulating a blend of acetaminophen and carboxy methylcellulose with an aqueous dispersion of pregelatinized starch (3). Salpekar et al. utilized a spray drying process for converting acetaminophen, combined with excipients, into a directly compressible granule containing 90% acetaminophen (4). In another study Salpekar employed a fluidized-bed process to obtain a directly compressible product containing 90% acetaminophen by spraying an aqueous dispersion of pregelatinized starch onto a blend of acetaminophen and pregelatinized starch (5). Patel et al. reported a fluidized-bed process for manufacturing acetaminophen in a free-flowing, directly compressible agglomerated form employing PVP in isopropyl alcohol as a binding agent (6). This paper summarizes the results of using an aqueous PVP solution as a binding agent to obtain a directly compressible agglomerated acetaminophen granule utilizing the fluidized-bed system.

EXPERIMENTAL

Materials

Acetaminophen (Seven Stars Chem. & Pharm. Co., LTD, Lot No. 8912-AC101) used was mixed with 0.2% Aerosil-200 and screened through an 100 mesh siever. Polyvinylpyrrolidone K-30 (PVP K-30, BASF, Lot No. 12-5424), Crospovidone (GAF Corp., U.S.A.), Pregelatinized starch (National Starch & Chemical Corp., U.S.A.), Sodium starch glycolate (Avebe America, Inc., U.S.A.), Aerosil 200 (Degussa, Inc. U.S.A.), and Magnesium stearate were obtained without any treatment.

Manufacture and Characterization of Acetaminophen Granules

Five hundred grams of screened acetaminophen powder were agglomerated using the fluidized-bed granulator (Glatt Air Techniques Inc., model GPCG-1). Preliminarily, the PVP amount of either 2, 5, or

10% w/w in aqueous solution at a concentration of either 10, 7.5 or 5% w/v was examined. It was found that a minimal amount of 5% w/w PVP at a concentration of less than 7.5% w/v (Table 1) was needed to convert acetaminophen powder into a free-flowing form and the corresponding tablets possessing enough hardness without capping. Subsequently, 5% w/w PVP was employed in a two level factorial experiment design (7,8) to examine the effects of four factors on the properties of resultant acetaminophen granules and tablets made using them. A total of sixteen experimental sets resulted (Table 2). Experiment 2 was performed in triplicate to determine the variation in the granulation process.

The properties studied for the granules included those described in the following. Size distribution was evaluated by the size analysis technique (Tyler Analysensieb, Haver & Boecker, Westfalen). The bulk and tapped density of the granules were measured in an 100 ml graduated cylinder mounted on a mechanical tapping device (Erweka, SVM). The obtained values were used to calculate the compressibility index. The angle of repose was determined by the method of fixed funnel and cones. The water content was obtained by drying the granules in a moisture balance (Ohaus, Model MB200) at 50 ^{o}C.

Formulation and Characterization of Acetaminophen Tablets

Screening out the granules with the size greater than 10 mesh, acetaminophen granules prepared by the several methods described above were used to prepare tablets either by adding the lubricant alone or by blending a disintegrant together with the lubricant. Agglomerates equivalent to 325 mg of drug per tablet were mixed with 0.5% magnesium stearate in a plastic bag for 10 min and then compressed into tablets using a rotary tablet press (Jenn-Chiang Machinery Co., LTD) with 7/16" standard flat punches. The granules produced under Experiment 2 (Table 2) were used to develop a formulation containing the following ingredients per tablet: agglomerates equivalent to 325 mg acetaminophen, 1.63 mg magnesium stearate as the lubricant and varying amounts of disintegrant selected from crospovidone, sodium starch glycolate (both at 1 and 3%) or pregelatinized starch (at 5 and

TABLE 1

Properties of Granules Made Using Varying Amount of PVP Applied from Solutions Having Different Concentrations.

% (w/w) of PVP in Granule	2	10		5		
% w/v of PVP solution used	10	7.5	5	10	7.5	5
Particle size distribution[a] mesh No.						
+20	5.7	21.0	27.6	15.2	33.8	43.0
+40	6.7	37.7	41.9	29.2	74.2	79.8
+60	100.0[b]	58.1	61.2	46.2	86.0	89.2
+80	--	82.6	80.0	65.9	92.1	93.8
Angle of repose (°)	--	--	--	--	39.7[c]	44.1
Bulk density	--	--	--	--	0.40	0.44
Tapped density	--	--	--	--	0.45	0.49
Moisture content (%)	--	--	--	--	0.76	0.83

[a]Cumulative percent retained.
[b]Cannot pass through the siever because of static charge.
[c]Mean (n=3).

TABLE 2

Experimental Design Employed to Evaluate Operational and Equipment Parameters Affecting Acetaminophen Granules

Factors	A	B	C	D	Factors	A	B	C	D
Experiment					Experiment				
1	-	+	-	+	9	-	-	+	-
2	+	-	-	-	10	+	+	-	-
3	+	+	+	-	11	+	+	+	+
4	-	+	-	-	12	+	+	-	+
5	-	+	+	+	13	+	-	-	+
6	+	-	+	+	14	-	-	-	-
7	+	-	+	-	15	-	-	+	+
8	-	-	-	+	16	-	+	+	-

A: Binder solution conc.(%): (+) = 7.5, (-) = 5.0.
B: Spray rate (ml/min.): (+) = 30, (-) = 20.
C: Spray pressure (psi): (+) = 25, (-) = 15.
D: Inlet air temp. (°C): (+) = 60, (-) = 50.

10%). This resulted in six different batches of tablet. The physical properties of the tablets, i.e. tablet weight, thickness, hardness and friability, were determined using an analytical balance (Mettler, AE-240), a micrometer (Vernier Caliper, Mitutoyo, Japan), a gauge-type hardness tester (Model AE-20, Aikho Engineering, ROC.), and a Roche type Friabilator (All-Trans Ent. Corp., ROC.) respectively.

Dissolution Test

USP dissolution apparatus 2 was employed to determine the dissolution rate of acetaminophen using 900 ml of phosphate buffer (50 mM, pH=5.8) as the dissolution medium at 37 ± 0.5 ^{o}C. The paddle speed was 50 RPM. Samples were withdrawn with filtration at predetermined intervals with medium replacement. The drug content in the samples was determined by comparing its UV absorbance to a calibration curve of standard samples at =241 nm. A polynomial equation was generated statistically to describe each dissolution curve and subsequently was used to determine the dissolution time at 80% release using Newton's method. Both curve fitting via the polynomial equation and root solving by Newton's method were run on a computer program written in *TURBO BASIC*. The average dissolution time of five or six tablets for each formulation was calculated and reported.

RESULTS

The properties found for the sixteen batches of granules and the replicates are listed in Table 3. Reproducibility in granule properties and size distribution (Table 3) among replicated batches using granules produced under experimental condition 2 indicates that the granulation process was well controlled. It was found that under most of experimental conditions granules were produced with a repose angle within the desirable working range of 28-42^{o}, except that conditions indicated in experiments 6 and 13 gave a higher value of 47^{o}. However, granules from batches 6 and 13 gave the greatest compressibility of 22.5% and 19.2% respectively. The average size of granules in batch 6 is the smallest at a geometric weight mean diameter of 279 um and the size

TABLE 3

Properties Found for 18 Batches of Acetaminophen Granules.

Experiment No.[a]	1	2-1	2-2	2-3	3	4	5	6	7
Bulk density (g/cc)	0.42	0.39	0.40	0.41	0.42	0.45	0.44	0.31	0.36
Tapped density	0.48	0.44	0.45	0.46	0.47	0.51	0.49	0.40	0.40
Compressibility (%)	12.5	11.4	11.1	10.9	10.6	11.8	10.2	22.5	10.0
Angle of repose (°)	38	40	39	40	39	43	39	47	41
Loss on dry (%)	0.87	0.83	0.73	0.73	0.80	0.83	0.83	0.80	0.83
Particle distribution[b]									
mesh size									
+20	42.5	36.6	36.5	28.2	26.9	48.4	33.1	9.4	21.3
+40	79.2	75.8	74.8	71.9	59.4	83.9	65.4	33.7	57.1
+60	89.0	87.3	86.9	84.1	79.0	92.9	82.0	52.6	71.8
+80	94.2	92.7	93.1	90.4	88.6	97.2	90.5	67.1	80.1
Geometric weight mean (um)	776	724	700	617	519	891	596	279	457
S.D.	2.34	2.34	2.32	2.24	2.34	2.21	2.45	2.34	2.43
d_{VS}[c]	547	494	491	446	362	651	399	196	308

Experiment No.[a]	8	9	10	11	12	13	14	15	16
Bulk density (g/cc)	0.36	0.44	0.43	0.40	0.42	0.38	0.44	0.40	0.45
Tapped density	0.41	0.48	0.48	0.45	0.47	0.47	0.49	0.44	0.50
Compressibility (%)	12.2	8.3	10.4	11.1	10.6	19.2	10.2	9.1	10.0
Angle of repose (°)	43	37	41	39	39	47	44	39	39
Loss on dry (%)	0.80	0.80	0.87	0.83	0.70	0.90	0.83	0.80	1.13
Particle distribution[b]									
mesh size									
+20	29.8	27.5	47.4	22.8	52.9	47.1	43.0	26.5	47.2
+40	68.4	68.7	82.6	54.6	79.3	63.1	79.8	66.1	80.2
+60	78.0	81.4	91.4	65.9	87.5	68.1	89.2	78.3	91.7
+80	86.8	88.2	95.3	72.6	91.9	70.0	93.8	84.7	96.5
Geometric weight mean (um)	519	575	902	427	1023	813	813	556	832
S.D.	2.48	2.29	2.43	2.88	3.98	10.5	2.34	2.51	2.24
d_{VS}[c]	343	408	608	247	480	530	594	368	601

[a]The operational and equipment parameters varied conform to the designations found in Table 2.
[b]Cumulative percent retained.
[c]Volume-surface mean diameter.

distribution in granule batch 13 is the widest with a standard deviation of 10.5 um. All granule batches were easily tabletted after lubrication. The characteristics of these tablets are shown in Table 4. The hardness of all tablets was in a satisfactory range of from 5 Kg to 10 Kg. The friability of most batches was also low; only batch No.13 gave a moderately higher value of 1.15%. Weight variations of all tablet batches comply with the compendia specification of less than 5%; but tablets made with batch No. 13 showed a large standard deviation of 10.7 mg. In comparing the time for 80% dissolved (T_{80}), it is seen that tablets made from batch No. 13 dissolved slowly (average T_{80} of 152 min) while tablets made from batch No.8 dissolved at the fastest rate with an average T_{80} time of 22 min.

DISCUSSION

A directly compressible acetaminophen composite has to be in a free-flowing agglomerated form having properties requisite for successfully tabletting. Stetsko has shown that the usefulness of factorial design experiment in pharmaceutics (7). Therefore, the two-level factorial experiment was designed in this study to examine the effects of operational and equipment parameters on the properties of acetaminophen granules made via a fluidized-bed granulation process aimed at a final PVP amount of 5% w/w applied as an aqueous solution (8).

Upon reviewing the physical properties of the agglomerates produced under different conditions in the fluidized-bed system, it appeared that 5% PVP-containing agglomerates had flow properties that would permit compression into tablets with desirable hardness and low friability. Granules manufactured under different conditions had different properties, which conceivably would affect the physical properties of resulting tablets. As shown in Table 3, granules produced under similar conditions (6 and 13) were some what resistant to flow as evidenced by a repose angle of 47^{o} and it was seen that one batch (No. 13) gave tablets with a high standard deviation in tablet weight. With respect to size distribution, it was noted that these two batches (6 and 13) contained a larger

TABLE 4

Properties of Tablets Manufactured Using the Granules Listed in Table 3 to Which Only Magnesium Stearate Was Added.

Tablet Property	Thickness (mm)	Friability (%)	Hardness (Kg)	Weight[a] (mg)	Dissolution Time(min.)[b]
Experiment No.					
1	3.43	0.1	6.6	328.0(5.3)	139.7
2	3.56	0.0	7.0	328.8(5.0)	51.4
3	3.77	1.0	7.0	342.6(5.1)	63.8
4	3.57	1.1	5.4	333.7(5.5)	112.0
5	3.63	1.1	6.6	332.5(7.6)	68.9
6	3.74	0.0	7.7	345.8(3.2)	100.6
7	3.75	0.0	9.6	353.6(2.1)	53.8
8	3.68	0.7	7.5	331.7(2.4)	22.1
9	3.58	0.2	6.2	332.5(4.1)	82.9
10	3.46	0.1	7.7	333.3(6.3)	127.4
11	3.63	1.0	4.9	337.2(6.9)	43.6
12	3.61	1.1	6.0	329.0(7.7)	63.5
13	3.26	1.5	6.5	326.5(10.7)	152.0
14	3.50	0.5	6.0	331.7(7.0)	110.6
15	3.69	0.6	9.0	341.2(1.2)	51.3
16	3.59	0.6	8.1	341.6(4.4)	125.9

[a]Mean(Standard Deviation,n=15).
[b]The time for 80 percent dissolved.

fraction of granule sizes smaller than mesh No. 80 when compared to other granules made. Moreover, batch 13 showed a wider distribution (standard deviation value 10.5 mg) than batch No.6 (and others). It seems natural that a wide distribution in granule size would lead to a larger weight variation in tablets.

As shown in Table 2, batches 6 and 13 were manufactured under similar conditions except for the spraying pressure used. Basically, there was a lower water input to the fluidized-bed system when the PVP concentration was high and the spraying rate low : this led to a higher drying efficiency by inlet air. Droplets with smaller size, formed under high spraying pressure, can be spray-dried easily but make granulation impossible and also lead to small granule size (No.6). On the other hand, a low spraying pressure results in droplets of binder solution that are distributed unevenly. Not only is there a high probability for droplet fractions having small size to be spray-dried, but larger sized

droplets may form larger granules resulting in a wider distribution (No. 13). Thus, the proper control of experimental conditions to minimize differences in granule size would be a way to reduce weight variation in acetaminophen tablets formed with granules produced in a fluidized-bed system.

The estimates of each effect was run using the STATGRAPHICS statistical program. The significance of each effect was tested by plotting the estimate of the effect on normal probability paper as suggested by Daniel (9). It is concluded that factor D (inlet air temperature) is not a significant parameter. The design then becomes 2^3 factorial in A, B and C with two replicates. The result of analysis of variance for the data using this simplifying assumption concluded that the effect of factor B and C are significant, as is the AC interaction. Then the estimated geometric mean diameters at the vertices of the design are given by the following equation, where 668.9 um is the average response and X_a, X_b, X_c take on the value +1 or -1 according to the sign for A, B and C. The accuracy of the model was validated based on the randomization of residuals by plotting as a function of predicted value.

$$\ddot{y} = 668.9 + \frac{153.75}{2} X_b - \frac{277.5}{2} X_c - \frac{167.5}{2} X_a X_c$$

A possible correlation between the time for 80% dissolved (T_{80}) and the average granule size was investigated as potentially useful screening method. The volume-surface diameter (d_{vs}) was calculated via the Hatch-Choate Equation (10). Fig. 1 shows the result when T_{80} is regressed with respect to log d_{vs} as determined by least squares. There appears to be a strong correlation between T_{80} and the logarithm of d_{vs} with both intercept and slope significantly different from zero at the 5% ($r = 0.8074$). The data corresponding to batches No.13 and 6 were rejected because they were proved to be probable outliers. An abnormal size distribution in both batches as rationalized above might be the reason. On the other hand, this correlation indicates the increase of T_{80} with increasing log d_{vs}. It implies that the dissolution of acetaminophen is dominantly controlled by the size of granules after

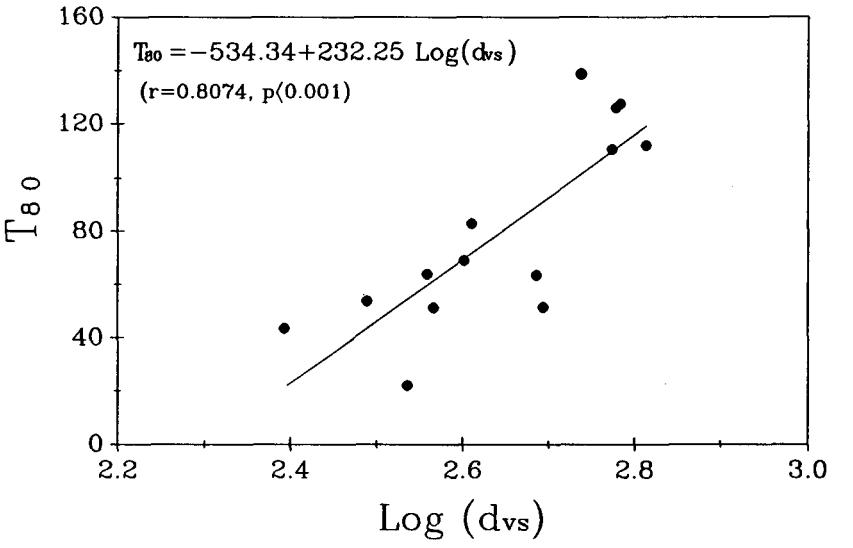

FIGURE 1

The Correlation of T_{80} with Respect to the Logarithm of Volume-surface Mean Diameter for a 2^3 Factorial Design.

disintegration. A similar result of a correlation existing between dissolution and disintegration rate constant has been reported (11). Based on the correlation between T_{80} and log d_{vs}, controlling granule size makes it possible to produce (or monitor) acetaminophen tablets that conform to the USP dissolution specifications.

In the preceding discussion, tablets were made using only agglomerated acetaminophen and magnesium stearate. To study the desired amount of disintegrant needed, three disintegrants at two levels were added to the granule batches manufactured under condition 2 (Table 2). The tablets so made all possess enough hardness and low friability. The dissolution profile of acetaminophen tablets with and without disintegrants are shown in Fig. 2. The addition of disintegrants does not change flowability and compressibility of granules but does significantly improve dissolution rate to an extent of dissolving 80% within 20 minutes. Moreover, there is a difference in effect among the

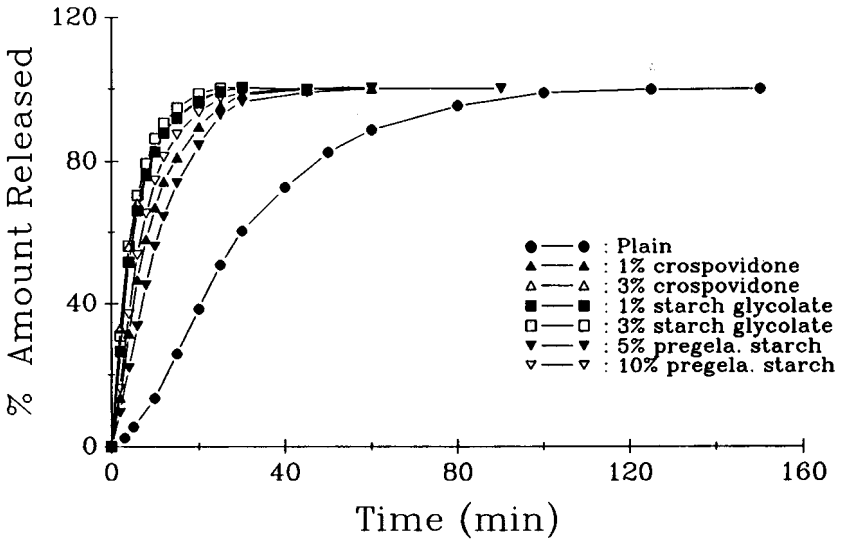

FIGURE 2

The Dissolution Profiles for Acetaminophen Tablets with or without Added Disintegrants.

disintegrants. Both crospovidone and sodium starch glycolate enhance dissolution rate at the 1% or 3% level. On the other hand, pregelatinized starch improves dissolution rate only at higher levels (5% or 10%). A similar result was reported by Visavarungroj et al. in evaluating the potential use of several disintegrants (12).

CONCLUSIONS

This work shows that the free-flowing form of acetaminophen granules was possibly prepared in a fluidized-bed system employing 5% w/w PVP in an aqueous concentration of 7.5% w/v or less. These granules were compressed directly into the tablets with enough hardness. There also exists a correlation between T_{80} and the logarithm of volume-surface mean diameter, which is useful as an in-process control parameter. However, The agglomerated compositions must be blended with a suitable amount of disintegrant to improve their dissolution profile.

ACKNOWLEDGMENTS

This work was supported by the National Sciences Council of the Republic of China (NSC 79-0412-B038-01).

REFERENCES

1. D. S. Phadke and N. R. Anderson, Drug Dev. Ind. Pharm., 16, 983 (1990).

2. C. G. Barlow and J. W. Harrison, British Patent 1,390,032 (1975).

3. S. H. Vogel, U.S. Patent 4,439,453 (1984).

4. A. M. Salpekar, S. R. Freebersyser and D. A. Robinson, U.S. Patent 4,600,579 (1986).

5. A. M. Salpekar and L. E. Denton, U.S. Patent 4,757,090 (1988).

6. N. K. Patel, N. R. Poola, A. Babar and F. M. Plakogiannis, Drug Dev. Ind. Pharm., 15, 1175 (1989).

7. G. Stetsko, Drug Dev. Ind. Pharm., 12, 1109 (1986).

8. D. C. Montgomery, 2 and 3 factorial design, Design and analysis of experiments, 2nd ED, John Wiley & Sons, New York, pp. 273-281 (1984).

9. C. Daniel, Technometrics, 1, 311, (1959).

10. A. Martin, J. Swarbrick and A. Cammarata, Micromeritics, In Physical Pharmacy : Physical chemical principles in the pharmaceutical sciences, Lea&Febiger, Philadelphia, pp. 501 (1983).

11. N. Najib and I. Jalal, Int. J. Pharm., 44, 43 (1988).

12. N. Visavarungroj and J. P. Remon, Int. J. Pharm., 62, 125 (1990).