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FLUIDIZED-BED AGGLOMERATION OF ACETAMINOPHEN; DIRECT COMPRESSION OF TABLETS AND PHYSIOLOGIC AVAILABILITY

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ABSTRACT

A novel process was developed for manufacturing acetaminophen in a free-flowing, directly compressible agglomerated form, involving spray agglomeration of acetaminophen powder with polyvinylpyrrolidone (PVP) in isopropyl alcohol as a bonding agent using a fluidized-bed granulator. Agglomerates prepared with 5% PVP yielded a free-flowing and compressible material. Upon lubrication with 0.5% magnesium stearate, the material was found to be directly compressible into tablets. To improve dissolution and

tableting properties, the agglomerates were compressed into tablets after blending with varying weight ratios of microcrystalline cellulose/pregelatinized starch as a filler/disintegrant combination. The final stable tablet formulation consisted of agglomerates equivalent to 325 mg of acetaminophen, 2.1 mg of magnesium stearate, and the filler/disintegrant in a weight ratio of 70:30 to yield a tablet weight of 425 mg. Physical properties and dissolution profile of these tablets were comparable to those of a commercial acetaminophen tablet. Physiologic availability calculated using the urinary excretion method indicated half-lives of 2.0, 2.1, and 2.2 hours for control (acetaminophen powder), experimental tablet, and a marketed product, respectively.

INTRODUCTION

Unlike aspirin, acetaminophen, a widely used analgesic and antipyretic drug, is claimed to be non-irritant to the gastrointestinal lining (1). It is a white crystalline powder with a low bulk density and meager compressibility due to lack of cohesiveness. The powder acquires static charges while flowing through the hopper and during milling operations which can be neutralized by the addition of colloidal fumed silicon dioxide (2,3). Acetaminophen tablets also undergo elastic deformation during compression, often resulting in a capping problem

(4). Hence, a granulation processing is required before the drug is compressed into tablets. This can be accomplished by fluidized-bed (5) or wet granulation methods.

Direct compression has long been a popular method of tablet production. Salpekar et al. utilized a spray drying process for converting acetaminophen, combined with excipients including stearic acid, into a directly compressible material containing 90% acetaminophen (6). Vogel prepared a product with 90% acetaminophen by spray granulating a blend of acetaminophen and carboxymethylcellulose with an aqueous dispersion of pregelatinized starch (7). Both these acetaminophen compositions are under patent protection.

This paper reports on a process of converting acetaminophen into a directly compressible agglomerated material with 95% drug content using a fluidized-bed technique with the aid of PVP as a bonding agent. To improve tableting and dissolution profiles, the material was blended with directly compressible excipients and tableted. Urinary excretion rate constants of acetaminophen after administration of the experimental tablet and a marketed product were compared.

MATERIALS

Acetaminophen[1] powder, amorphous fumed silica[2], isopropyl alcohol[3] USP; magnesium stearate[3] USP;

methylene chloride[3], microcrystalline cellulose[4], pregelatinized starch[5], potassium phoshate monobasic[6], polyvinylpyrrolidone[7], and vanillin[8] USP were used as received.

METHODS

Manufacture of Acetaminophen Agglomerates. Acetaminophen powder was agglomerated in a fluidized-bed granulator[9] by spraying a bonding solution over a fluidized powder bed using a peristaltic pump[10]. Acetaminophen powder, 200 g, and amorphous fumed silica (to prevent static charges), 1 g, were then charged into the granulating column of the fluidized-bed granulator. As the compressed air was allowed to enter the column by opening the exhaust flap, the powder was converted into a fluidized-bed state. PVP in isopropyl alcohol was sprayed onto the fluidized powder bed from above with an atomizing nozzle attached to a peristaltic pump (25 ml/min). Once the material was converted into a free-flowing granular state, the spraying operation ceased and the product was dried in the fluidized state for 10 minutes.

Acetaminophen powder had been previously agglomerated by this procedure using 200 ml of 2, 3, and 5% aqueous solutions of PVP. The equipment and processing parameters were: column, a granulating container; nozzle orifice, 1.5 mm; exhaust flap opening set at 10; inlet

air temperature, 60 °C; spray rate, 25 ml/min; atomizing pressure, 0.4 bar; yield of 95%. The resultant product was in the form of large agglomerates and granules of undesirable size, and consequently, the solvent was changed to isopropyl alcohol.

PVP, from 2, 3 and 5% in isopropyl alcohol was used to agglomerate acetaminophen according to the above processing parameters. Resulting material was sized by passing through a 20-mesh sieve. The agglomerates prepared with 5% PVP showed acceptable compression characteristic as explained under the results and discussion section. Therefore, a pilot batch was manufactured using 600 g acetaminophen, 3 g amorphous fumed silica, and 600 g acetaminophen, 3 g amorphous fumed silica, and 600 ml of 5% PVP in isopropyl alcohol. The general procedure and operating parameters as described previously were used except that the atomizing pressure was 0.8 bar and the exhaust flap opening was set at 15. To confirm the usefulness of the method, all experiments were performed in triplicate, with similar results.

Physical Properties. Angle of repose, aerated bulk and tapped bulk densities, and compressibility of the agglomerates were ascertained by standard methods (8,9). Loss on drying was done by drying in an oven at 100 °C for 1 hour. The shape and surface topography of acetaminophen powder and the resultant agglomerates were determined with a scanning electron microscope[11].

PVP Analysis. A 10-g sample was shaken with 50 ml of methylene chloride. The mixture was filtered; the filtrate was dried and the PVP content was calculated from weight of the residue.

Formulation Development, Manufacture, and Properties of Acetaminophen Tablets. Batches of one thousand tablets were prepared using the agglomerates either after lubricating or after blending with a filler/disintegrant combination together with a lubricant.

Formulation. Required amount of the agglomerates equivalent to 325 mg of drug per tablet were mixed with 0.5% magnesium stearate in a planetary mixer[12] for 15 minutes and compressed into tablets using a rotary tablet press[13] with 7/16" standard concave punches. The agglomerates containing 2 and 3% PVP were compressed into soft and unsatisfactory tablets. Those containing 5% PVP yielded tablets with 10 kg hardness and they were considered satisfactory from a compressibility point of view. Disintegration time of the latter tablets was 4 minutes compared to less than 1 minute for a commercial product[14]. Therefore, a formulation was developed using the agglomerates containing 5% PVP with the addition of a filler/disintegrant combination, containing the following ingredients per tablet: agglomerates equivalent to 325 mg acetaminophen, 2.1 mg magnesium stearate as a lubricant and varying proportions of

microcrystalline cellulose and pregelatinized starch as a filler/disintegrant combination in a sufficient quantity to yield a tablet weight of 425 mg. Various tablets were prepared utilizing (a) three PVP concentrations in the agglomerates and (b) three blends of microcrystalline cellulose and pregelatinized starch in 30:70; 50:50; and 70:30 proportions. This resulted in 9 different batches of 425 mg tablets shown in Table 1. To eliminate variables other than those listed above, the quantity of active ingredient was kept constant and the weight and thickness values of each tablet were maintained at 426 ± 3 mg and 4.84 ± 0.07 mm, respectively. Ingredients of each of the formulations were blended in the planetary mixer for 15 minutes and compressed into tablets. The formulation containing the agglomerates with 5% PVP together with microcrystalline cellulose and pregelatinized starch in a ratio of 70:30 yielded tablets with most desirable physical properties as described under the results and discussion section. Consequently, a 5,000-tablet batch was manufactured for further studies with a tablet hardness of 7.6 ± 0.3 kg and 0.8% friability.

Physical Properties of the Formulation Blends and Tablets. The angle of repose, aerated bulk and tapped bulk densities of all blends were determined by established procedures (8, 9). Compressibility factor was

TABLE 1

Tablet Formulation with Varying PVP Content and Fillers

	Percent PVP in the Agglomerates								
	2			3			5		
Ingredients (mg per Tablet in the formulation)									
	A	B	C	D	E	F	G	H	I
Drug Agglomerates	330.2	330.2	330.2	331.1	331.1	331.1	338.9	338.9	338.9
Avicel® PH 102	27.8	46.4	64.9	27.5	45.9	64.3	25.2	42.0	58.8
Sta-Rx® 1500	64.9	46.3	27.8	64.3	45.9	27.5	58.8	42.0	25.2
Magnesium Stearate	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1

then computed by Carr's method (10). Tablet weight, thickness, hardness and friability values were determined using an analytical balance, a micrometer, a Stokes-Monsanto tester and a Roche friabilator, respectively.

Dissolution Test. The USP dissolution apparatus 2 was employed using 900 ml of phosphate buffer (pH 5.8) as a dissolution medium at 37 ± 0.5 °C with a paddle speed of 50 rpm. Samples were withdrawn at regular intervals with media replacements. After filtration, the drug content of each sample was determined spectrophotometrically[15] at 241 nm, using the predetermined absorptivity of 55.6 $(g/L)^{-1}$ cm^{-1}.

Stability Study. Stability was determined by storing 100 tablets in 60-ml screw cap amber bottles at room temperature, 37 °C and 45 °C. The tablets were tested after 3 months for the physical properties listed above.

Urinary Excretion Study

Protocol. Five healthy, male subjects gave informed consent to participate in the study. None of the subjects ingested any drugs or alcohol for at least one week prior to the study. Each subject received product A, B or C at one-week intervals in a randomized, crossover design as shown in Table 2.

TABLE 2

Dosing Schedule for Acetaminophen Tablets

Subject	Age (Yr)	Weight (Kg)	Product[a] Taken at Week 1	2	3
1	26	59.1	A	B	C
2	31	61.4	B	C	A
3	27	64.1	C	A	B
4	28	65.9	A	B	C
5	32	56.8	B	C	A

[a] Key: A, Control, acetaminophen powder 650 mg, (Lot # 0048984P847, Mallinckrodt Inc.); B, two acetaminophen tablets, 325 mg each, (Lot # SE0101, McNeil CPC); and C, two acetaminophen tablets, 325 mg each, the experimental product.

Each product was taken with 200 ml water in the morning. The acetaminophen powder was dispersed in 200 ml of water before ingestion. A normal breakfast was eaten half an hour before ingestion of product. Urine samples were collected predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours post administration with ingestion of 200 ml water after each collection. Normal lunch and dinner were taken after 4- and 12-hour urine collections. Total urine volume was recorded and a 20-ml sample of each specimen was stored at -20 °C until analyzed.

Urine Sample Analysis. The procedure of Plakogiannis and Saad (11) was employed with minor modifications. The sample was allowed to reach ambient temperature. In a test tube, 1 ml urine and 4 ml of 1 N HCl were boiled at 100 °C for 1 hour to complete hydrolysis of unchanged acetaminophen and metabolic conjugates to p-aminophenol; which was assayed spectrophotometrically at 395 nm, using the predetermined absorptivity of 20 $(g/L)^{-1}cm^{-1}$. Acetaminophen content was then computed using a molecular weight conversion factor of 1.385.

RESULTS AND DISCUSSION

Acetaminophen Agglomerates. Acetaminophen agglomerated with PVP as a bonding agent in a fluidized state yielded a free-flowing material.

Scanning electron micrographs as portrayed in Figure 1 disclose that the product was in an agglomerated form (Figure 1B) whereas the original acetaminophen crystals were irregular monoclinic prisms (Figure 1A). Data on physical properties of the agglomerates (Table 3) demonstrate that the angle of repose decreased and both bulk and tapped densities increased with an increase in PVP content of the agglomerates. Based on these data and considering the compression characteristic of the agglomerates containing 2, 3, and 5% PVP as presented under the methods section, it was inferred that the agglomerates with 5% PVP would show a desirable flow and compressibility characteristics. This was indeed confirmed during direct compression of formulations when such agglomerates, blended with directly compressible excipients produced the most acceptable tablets.

Acetaminophen Tablet Formulation. The agglomerates prepared with 2 and 3% PVP and blended with 0.5% magnesium stearate as a lubricant produced soft tablets upon compression. However, those prepared with 5% PVP and similarily compressed after lubricating yielded tablets with 10 kg hardness and a disintegration time of 4 minutes.

By blending the agglomerates with two directly compressible fillers and lubricant, compressibility characteristics were improved, as can be inferred from data of Table 4.

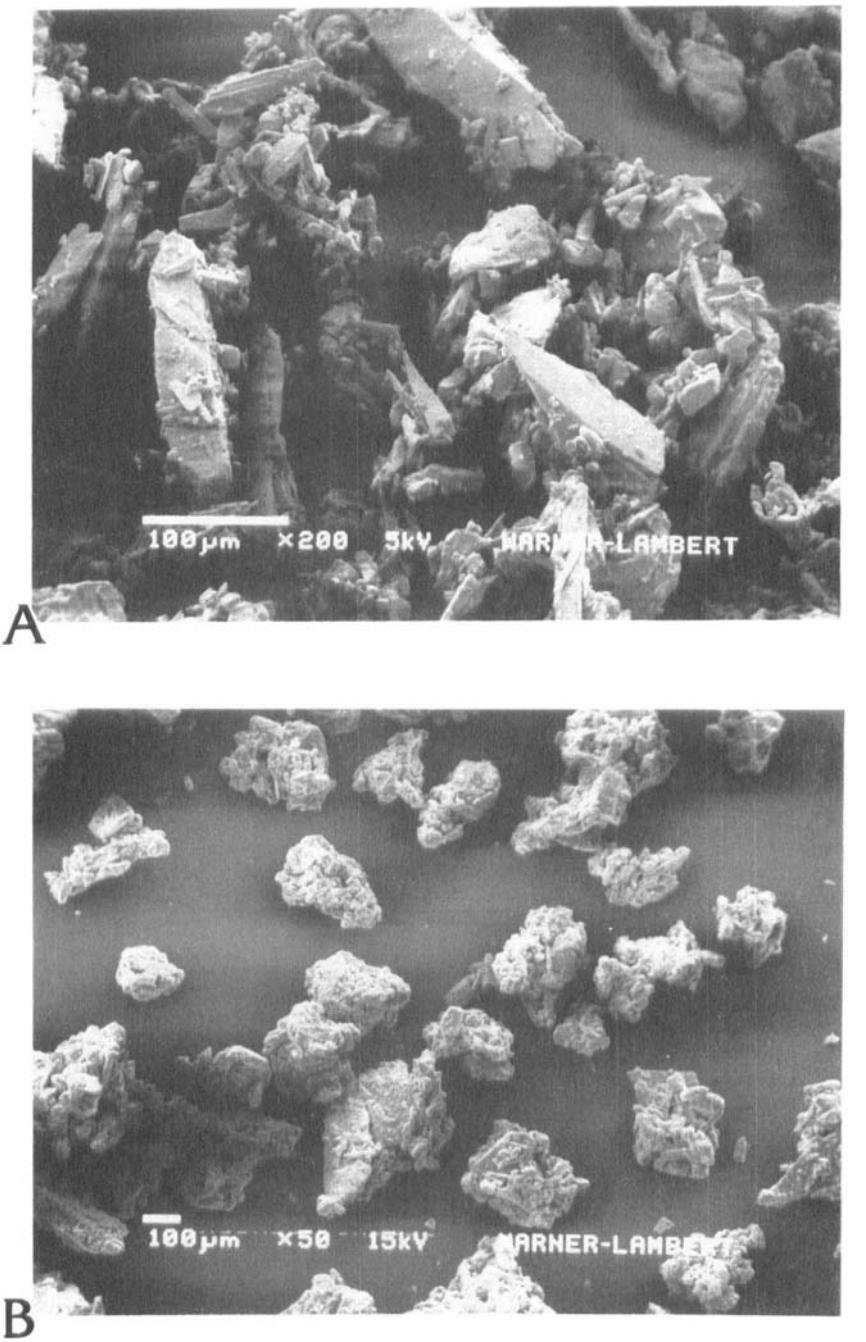

FIGURE 1

Scanning Electron Micrographs of Acetaminophen (A) and Acetaminophen Agglomerates (B).

TABLE 3

Physical Properties of the Agglomerates

PVP %	Angle of Repose	Density, g/ml		Compressibility
		Bulk	Tapped	
0[a]	43°	0.24	0.26	7.7
2	39°	0.26	0.29	10
3	36°	0.32	0.35	8.6
5	29°	0.34	0.38	10

[a]Acetaminophen Powder

TABLE 4

Physical Properties of the Formulation Blends

Formulation[a]	Filler Ratio[b]	Moisture Content	Angle* of Repose	Density*,g/ml		Compressibility, %
				Bulk	Tapped	
A	30:70	1.9	36°	0.32	0.36	11
B	50:50	1.6	39°	0.34	0.39	13
C	70:30	1.4	39°	0.35	0.39	10
D	30:70	2.1	36°	0.40	0.45	11
E	50:50	1.8	36°	0.41	0.47	13
F	70:30	1.7	39°	0.43	0.49	12
G	30:70	2.3	37°	0.39	0.43	9.3
H	50:50	1.8	36°	0.40	0.47	15
I	70:30	1.5	33°	0.41	0.51	20

[a] See Table 1, formulation A to I; [b] Microcrystalline cellulose: Pregelatinized starch; and *The values are the average of three determinations.

Considering the physical properties of the agglomerates (Table 3) and cohesiveness as indicated by a lack of softness of tablets compressed with the 5% PVP-containing agglomerates, the latter agglomerates were selected for the formulation blends of Table 4. Reviewing the angle of repose and compressibility values in Table 4, formulation blend I evidenced a desirable flow and compressibility characteristic. It is to be noted that in going from the agglomerates to formulation I, the angle of repose and compressibility values increased from 29° to 33° and 10 to 20% respectively. As suggested by Carr (10), the lower angle of repose tends to yield a floodable flow. Formulation I with an angle of repose of 33° and compressibility of 20% has been considered suitable for a proper flow of materials through the tablet hopper (10). Usefulness of these properties is shown in Table 5 where it is demonstrated that formulation I was compressed into tablets with the lowest standard deviation values for the tablet weights and thicknesses. This table also shows that formulation I tablets displayed 0.8% friability and a disintegration time of 40 sec. which compare well with those of two lots of Tylenol® tablets. A small variation in the moisture content of the blends (Table 4) can be attributed to the differences in the moisture content of the raw materials. Therefore, formulation blend I was selected for the final tablet formulation.

TABLE 5

Physical Properties of Acetaminophen Tablets

Formulation	Tablet Weight[a], mg	Thickness[a], mm	Hardness[a], kg	Disintegration Time[a], sec	Per Cent Friability
A	424.6 (2.1)	4.6 (0.10)	7.2 (0.3)	28 (4.6)	.[b]
B	427.2 (3.5)	4.7 (0.10)	7.0 (0.4)	23 (2.8)	.[b]
C	427.0 (3.9)	4.7 (0.10)	7.0 (0.4)	27 (3.1)	.[b]
D	428.3 (3.8)	4.6 (0.10)	7.5 (0.3)	41 (5.2)	4.5
E	425.5 (2.7)	4.9 (0.10)	7.4 (0.4)	43 (2.9)	1.8
F	424.6 (3.6)	4.9 (0.04)	7.2 (0.4)	36 (1.8)	1.5
G	424.4 (2.8)	4.9 (0.05)	7.6 (0.3)	33 (3.4)	1.7
H	424.0 (3.2)	5.1 (0.03)	7.4 (0.3)	35 (8.3)	1.2
I	426.3 (1.4)	5.2 (0.02)	7.6 (0.3)	40 (4.2)	0.80
T.T.[c]	415.4 (4.0)	3.9 (0.04)	12.6 (0.9)	95 (18.3)	0.80
T.T.[d]	435.4 (3.6)	4.8 (0.10)	10.0 (0.7)	104 (17.8)	0.40

[a] Each value represents the mean of 20 determinations ± the standard deviation is shown in parenthesis.

[b] Capping and breakage of tablets, [c] Tylenol® tablets Lot SE 0101 and [d] Lot SC 2968.

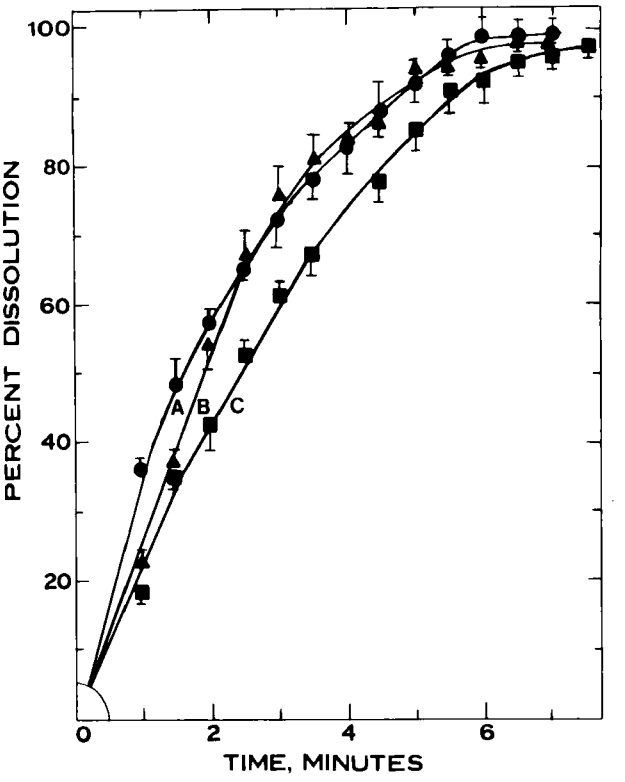

FIGURE 2

Dissolution Rate Data (Mean ± S.D., n = 18). Key: A, Experimental Product; B, Tylenol® Tablet Lot # SE0101; and C, Tylenol® Tablet, Lot # SC2968.

Dissolution Profile. Dissolution rate data of the experimental tablet, as delineated in curve A of Figure 2, are practically superimposible on that of a marketed product (curve B) which was manufactured by the fluidized-bed granulation method[16]. A small but insignificant decrease in the dissolution rate of one of the lots of the marketed product (curve C, Figure 2) may be attributable to the extruder process[16] used in granulation.

Stability Studies. Physical properties of the experimental tablets after 3 months' storage at room temperature, 37 °C and 45 °C are shown in Table 6. Hardness values increased from 7.6 (initial) to 10.5, 10.9 and 11.9 kg at RT, 37 and 45 °C respectively; and after 3 months they are comparable to 10 kg (Lot #SC2968) and 12.6 kg (Lot #SE0101) for commercial tablets. There was a small decrease in percent friability. However, this increase in hardness had no significant effect on the disintegration time and time for 90% drug dissolution from the tablets after 3 months' storage at the 3 temperatures. Hence, the product was considered physically stable.

Physiologic Availability. To assess the relative physiologic availability of acetaminophen from both experimental and marketed products, urinary excretion data were collected. The elimination of acetaminophen follows the one compartment model proposed by Cummings et al. (12) and confirmed by Levy and associates (13) and Miller et al. (14). The elimination rate constant of acetaminophen was determined from the urinary excretion data according to established methods (12, 14) and includes both unchanged acetaminophen and its metabolites. Semilogarithmic plots of unexcreted acetaminophen versus time for the control, the experimental product, and the marketed product are shown in Figure 3. Each point represents the average of

TABLE 6

Physical Properties of Experimental Acetaminophen Tablets After Three Months' Storage at Various Temperatures

Tests	RT	37 °C	45 °C
Percent Friability	0.65	0.54	0.45
Hardness (kg)	10.5	10.9	11.9
Disintegration time (sec)	27.0	27.6	28.0
Time for 90% dissolution (min)	5.0	5.5	5.5

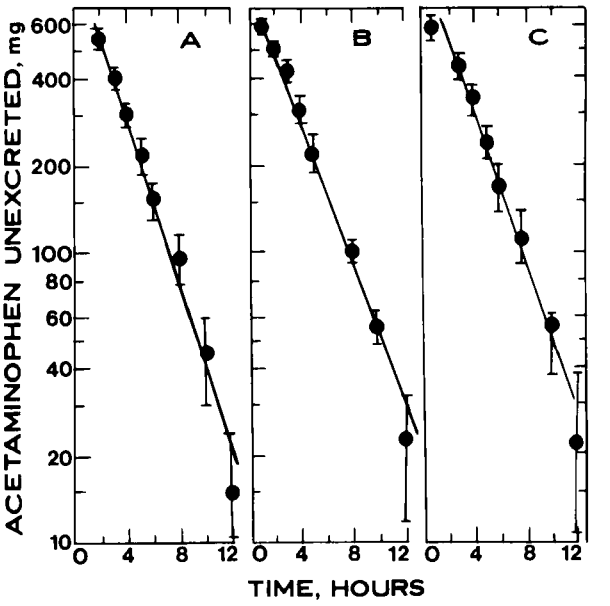

FIGURE 3

Semilogarithmic Plots of Acetaminophen Unexcreted Mean ± S.D., n = 5) as a Function of Time After Oral Administration of 650 mg Dose. Key A, Acetaminophen Powder; B, Experimental Product, and C, Tylenol® Tablet Lot # SE0101.

five determinations and slopes were obtained by least squares regression analysis. The overall elimination rate constants for three products, computed from the slope values of the lines, were 0.35 (line A), 0.30 (line B), and 0.32 hr^{-1} (line C) corresponding to the overall elimination half-lives of 2.0, 2.1, and 2.2 hr respectively. The latter values compare well with those reported by Lowenthal et al. (15). Experimental values of 14- and 24-hr urine collections were excluded from the linear regression because they represented less than one percent

of the dose and would have had a disproportionate influence on the determination of the slope.

The urinary excretion data obtained in this study indicate no significant difference in the availability of acetaminophen from the control, experimental and marketed product.

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FOOTNOTES

[1] Mallinckrodt Inc., St. Louis, MO.

[2] Cab-O-Sil®, Grade M5, Cabot Corp., Tuscola, IL.

[3] Fisher Scientific Co., Manufacturing Div., Fair Lawn, NJ.

[4] Avicel® PH 102, FMC Corp., Philadelphia, PA.

[5] Sta-Rx® 1500, Colorcon Inc., West Point, PA.

[6] Amend Drug and Chemical Co., Irvington, NJ.

[7] Plasdone® K-29/32, GAF Corp., Wayne, NJ.

[8] Sigma Chemical Co., St. Louis, MO.

[9] Aeromatic Strea-1, Aeromatic Inc., Towaco, NJ.

[10] MHRE 200, Watson-Marlow Ltd., Falmouth, UK.

[11] Amray, Model 1200B, Amray Corp., Bedford, MA.

[12] Hobart, Model C-100, Hobart Manufacturing Corp., Troy, OH.

[13] Stoke's Model B-2 Press, Pennwalt Corp., Philadelphia, PA.

[14] Tylenol® tablets, Lots SE0101 and SC2968, McNeil Consumer Products Co., Fort Washington, PA.

[15] Spectronic 200 UV, Shimadzu, Bausch & Lomb, Columbia, MD.

[16] J. Jaffe, McNeil Consumer Products Co., Fort Washington, Personal Communication.

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