

Table III—Disintegration Rates of Sulfamethoxazole Tablets Containing 3% of Various Grades of Carboxymethylcellulose Sodium

Grade	Degree of Substitution	Degree of Polymerization	Disintegration Time, sec	
			Simulated Gastric Fluid	Simulated Intestinal Fluid
—	Control	—	>1800	>1800
IVH	0.4	High	30	30
IVM	0.4	Medium	90	300
IVL	0.4	Low	>1800	>1800
VIII	0.7	High	90	600
VIIM	0.7	Medium	100	900
VIII	0.7	Low	>1800	>1800
IXH	0.9	High	100	900
IXM	0.9	Medium	>1800	>1800
XIIM	1.2	Medium	>1800	>1800

carboxymethylcellulose sodium with a degree of substitution of 1.2 and a low degree of polymerization would be a poor disintegrating agent. The results are summarized as follows:

1. The highly polymerized grades of carboxymethylcellulose sodium are good disintegrating agents. The preferred disintegrant has a high degree of polymerization together with a low degree of substitution. Type IVH is preferred over VIIIH, which is preferred over IXH (Fig. 1).

2. The medium-polymerized carboxymethylcellulose sodium with a degree of substitution of 0.7 or less has moderate disintegrant properties; but as substitution increases from 0.7 to 1.2, the medium-polymerized grades of carboxymethylcellulose sodium are not as effective as tablet disintegrants. Thus, medium-viscosity carboxymethylcellulose sodium with a degree of substitution of 0.4 or 0.7 has moderate disintegrant properties. Those with a higher degree of substitution, such as 0.9 or 1.2, are poor disintegrants (Fig. 2). Highly substituted carboxymethylcellulose sodium can only be used as a disintegrant when the degree of polymerization is high.

3. With the same degree of substitution, the higher the degree of polymerization, the better are the disintegrant properties. The disintegrant efficacy improves directly with an increase in polymerization. Thus, VIIIH is a better disintegrant than VIIM, which is better than VIII (Fig. 3).

4. Carboxymethylcellulose sodium with a low degree of polymerization is a poor disintegrant irrespective of the degree of substitution. Thus, low-viscosity carboxymethylcelluloses with degree of substitution values of 0.4, 0.7, 0.9, and 1.2 are poor disintegrating agents.

5. The dissolution rate of the sulfamethoxazole tablets correlated with

Table IV—Minimum Viscosities for Good Disintegration Properties

Degree of Substitution	Minimum Viscosity of 2% Aqueous Dispersion at 25° Using Propeller-Type Mixer, cps
0.4	>150
0.7	>200
0.9	>1500
1.2	>3000

the disintegration times of the tablets.

6. There was no significant difference in disintegration time and in dissolution rate between the two experimental formulas.

The minimum viscosity required for effective disintegration properties for the various grades of carboxymethylcellulose sodium is shown in Table IV. Aqueous dispersions of carboxymethylcellulose sodium with a degree of substitution of 0.4 should have a viscosity above 150 cps to have good disintegration properties. Similarly, the higher substituted carboxymethylcellulose sodium should meet the requirements for minimum viscosities to be considered a good disintegrant. Whenever a high degree of polymerization is mentioned, the viscosity will be much greater than the minimum stated in Table IV. Carboxymethylcellulose sodium with a low degree of polymerization will exhibit viscosities less than the minimum value in Table IV.

Further studies are in progress to evaluate the effect of carboxymethylcellulose sodium in solid dosage forms for: (a) disintegrants in tablets containing weak acids, weak bases, or neutral drugs; (b) comparisons with other presently available disintegrants; and (c) alteration of drug delivery systems through the utilization of the appropriate grade.

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Rotary Press Utilizing a Flexible Die Wall

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Received March 31, 1980, from *The Upjohn Company, Kalamazoo, MI 49001*. Accepted for publication November 7, 1980.

Abstract □ A die with a flexible wall was constructed and evaluated on a specially modified instrumented rotary tablet press. The design permits an inward deflection of the die wall by a side punch, which rolls past a side compression roll during compression-decompression. The side compression roll is instrumented to monitor the applied side compression roll forces. On decompression, return of the die wall to its original position permits release of residual die wall pressure. The decreased residual die wall pressure can decrease fracture and capping of tablets for problem formulations. The performance was tested on three experimental formulations. For these formulations, tablets made in a conventional die exhibited severe capping problems. However, most tablets compressed in the special die were superior. With proper adjustment of punch and

die wall compression forces, excellent tablets could be manufactured. The merits of the special die and modified tablet machine are substantiated, although this initial design did not provide adequate die wall pressure for all formulations. Further engineering efforts could result in practical production equipment.

Keyphrases □ Tableting machine—tablets produced from modified tableting machine with flexible die wall compared with those compressed conventionally □ Tablets—compressed with modified tableting machine compared with those conventionally compressed □ Compressed tablets—produced from modified tableting machine with flexible die wall, compared with tablets produced conventionally

It is generally accepted that bonding in a compressed tablet is the result of establishing and maintaining sufficient true areas of contact between particles. Lamination

or capping of tablets, therefore, may seem unexplained since significant portions of a laminated or capped tablet remain densely packed after compression-decompression.

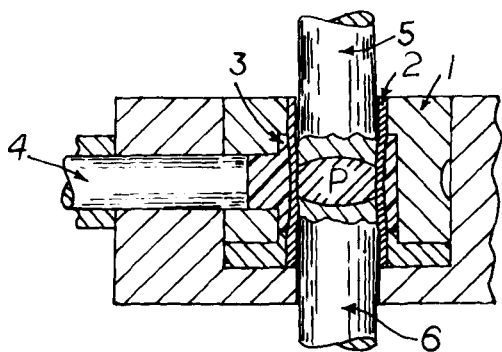


Figure 1—Schematic diagram of specially designed triaxial die.

A sufficient true area of contact apparently is established in these regions to bond ingredients together, yet the bonding is not sufficient to prevent fracture.

BACKGROUND

Fracture is thought to be the result of inadequate plastic flow, resulting in highly stressed regions within the compact. A previous report (1) demonstrated that the die wall pressure for several materials is limited by the shear strength of the compacted material and that it changes with time (viscoelastic effects). Furthermore, it was concluded that the dynamic shear strength is exceeded over much of the compression-decompression cycle. When the shear strength is exceeded, either permanent deformation *via* plastic flow or fracture occurs.

Fracture need not occur if plastic flow occurs before stresses are high enough to cause fracture by crack propagation. Very brittle materials such as phenacetin, methenamine, and acetaminophen cannot relieve local stresses as easily as other materials by plastic deformation. Since high die wall pressure results, fracture is more likely to occur in compacts of these materials. These fractures may occur on decompression or on ejection where the die edge may concentrate stress and cause capping.

A decrease of die wall pressure (either by allowing the die wall pressure to decay with time or by relieving the pressure mechanically) should decrease the likelihood of fracture. A specially designed die was reported (2) that allowed the simultaneous release of punch and die wall pressure. The special square die, split along its diagonal, was placed in a frame holding the two halves together with a hydraulic cylinder. By fluid coupling of this hydraulic cylinder with the cylinder on the hand press that pushes the punches together, the die wall and punch pressures could be reduced simultaneously during decompression. In this manner, intact compacts of materials known to laminate on decompression or ejection (e.g., phenacetin, erythromycin, methenamine, and acetaminophen) could be made.

Success with this split die led to the circular die with the flexible die wall reported in this investigation. The die was mounted into a modified rotary press. A specially designed side compression roll (3) and side punch permit pressure to be applied to the die wall, which contracts under compression. In this way, die wall pressure can be released as the die wall returns to its original shape during decompression. Three direct-compression formulations were studied, and the capping tendencies of tablets formed in the special die were compared with those prepared in a conventional die on the same machine.

Apparatus—The special die is shown in cross-section in Fig. 1. The internal wall of the die, 1, is lined and defined by a sleeve, 2, made of thin steel to provide slight radial flexibility. The sleeve is surrounded by a pressure-transmitting material, 3, such as rubber, which evenly distributes pressure around the sleeve. Application of pressure through the side punch, 4, permits a slight (one thousandth or two thousandth inch) inward deflection of the steel sleeve. Proper timing of the movement of the radial punch and axial punches, 5 and 6, permit the simultaneous three-dimensional or triaxial compression of powders. Release of the side punch pressure, which is simultaneous with axial punch pressure release, permits the steel sleeve to return to its original position.

The side compression roll, 7, and mounting block are shown attached to the rotary press in Fig. 2. The side compression roll is positioned such that pressure is applied simultaneously to the upper, lower, and side punches by the upper, 8, lower, 9, and side compression roll. Appropriate measures were taken to prevent overloading of the machine parts due to the excessive stress conditions. Side compression roll pressure was

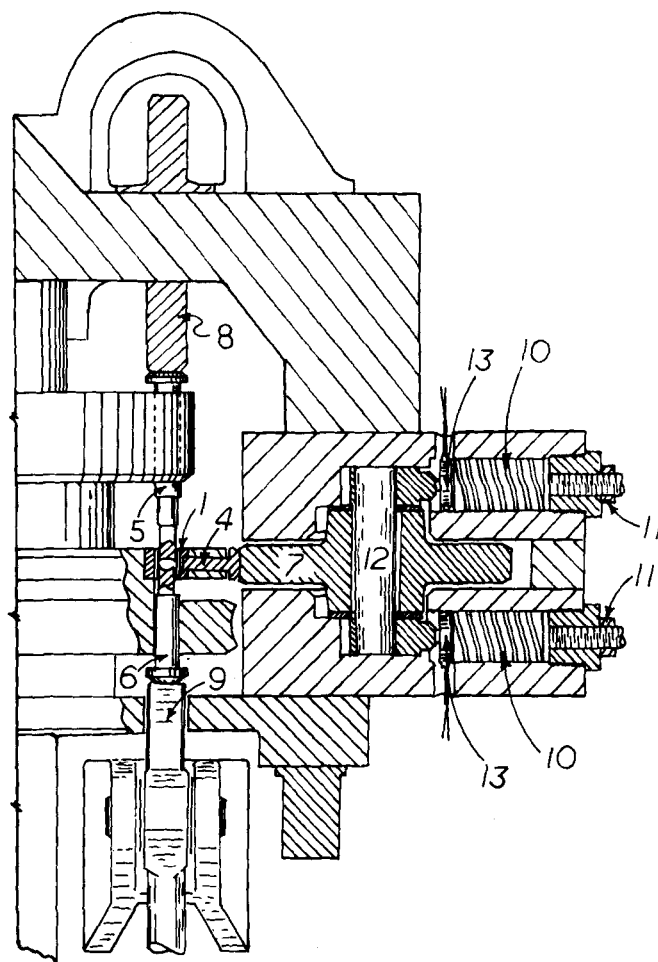


Figure 2—Schematic diagram of modified rotary press showing details of the side compression roll.

adjusted by incorporating two springs, 10, and adjusting nuts, 11, which apply pressure to each end of the side compression roll pin, 12. Strain-gauge sensors, 13, permit monitoring of the side compression force. Adjustable stops incorporated within the mounting block prevent application of excess pressure to the side punch when the die is empty.

The modified rotary press¹ is shown in Fig. 3. For the following experiments, only two of the 16 stations were used. One station consisted of a set of round 1.111-cm ($\frac{7}{16}$ -in.) concave (0.075-cm deep cup) punches and die. On the opposite side of the table was the specially designed die. Similar round 1.106-cm ($\frac{7}{16}$ -in.) concave punches were used in the special die. These punch diameters were reduced by 0.005 cm to allow enough clearance between the collapsed die wall and the punch during compression. The two types of tablets can be separated as they come off the machine, and direct comparisons can be made between them.

The axial punch pressure was monitored by a strain gauge attached to the lower roll support and calibrated with a known load. During operation, all three strain gauges were monitored so that the compression forces were known for both die types and the die wall-punch forces were known for the triaxial die.

Limitations in Design—Technical requirements placed important restrictions on the design and construction of the special die, particularly in the amount of die wall pressure that could be released by die wall flexing. Maximum flexing of the die wall on compression is desired to allow adequate die wall pressure release on decompression. However, the contraction of the die wall radius is limited by the upper and lower punches in the die. At the same time, an excessive gap between the punch and die wall is not acceptable since large weight variation due to powder slipping past the lower punch might occur.

Excessive powder between the punch and die wall also could cause sticking of the punches in the die and failure of the die wall to contract correctly. For these reasons, the punch diameters for the triaxial die were

¹ Model B2, F. J. Stokes Corp., Division of Pennwalt Corp., Philadelphia, Pa.

Table I—Composition of the Three Direct-Compression Formulations Used to Test the Modified Rotary Tablet Machine

Formulation	Composition, %
Ascorbic acid	
Ascorbic acid USP	42.9
Compressible sugar NF	46.3
Microcrystalline cellulose NF	4.2
Starch USP	2.5
Orange oil NF	2.6
Magnesium stearate USP	0.8
Colloidal silicon dioxide NF	0.7
Phenacetin	
Phenacetin USP	42.9
Compressible sugar NF	46.3
Microcrystalline cellulose NF	4.2
Starch USP	5.1
Magnesium stearate USP	0.8
Colloidal silicon dioxide NF	0.7
Acetaminophen	
Acetaminophen	41.4
Lactose USP	47.4
Microcrystalline cellulose NF	8.4
Starch USP	2.2
Colloidal silicon dioxide NF	0.12
FD&C Blue No. 2 Aluminum Lake	0.04
Magnesium stearate USP	0.44

reduced by 0.005 cm to permit this amount of flexing of the die wall. It was felt that this change would provide sufficient die wall radius contraction and, at the same time, minimize the amount of powder slipping past the lower punch. This limited flexibility of the special die, unlike the split die that allows complete release of the die wall pressure, is expected to release only a portion of the residual die wall pressure during decompression.

The present design requires enough side compression roll pressure to flex the steel die wall sleeve inward; therefore, the actual force applied to the compact is not equal to the side compression roll force. However, the observed values for the side compression roll force should be approximately proportional to the actual applied force in the radial direction. The efficiency of the pressure-transmitting material within the die at transferring the pressure from the side punch to the die wall and the elastic properties of the compression roll and mounting block also influence the actual pressure applied to the die wall.

Only one design, the initial effort, was used in these studies. Because the force for die wall contraction in the presence of powder in the die and of small amounts of powder between the die wall and punch could not be evaluated in advance, the choice of spring sizes and load cells for the die compression was conjecture. The experimental results indicate that the springs and load cells were somewhat undersize, which restricted the amount of die wall pressure that could be applied. Some of the experimental results may have been due to this limitation. This limitation results from the arbitrary choice of capacities and is not inherent in the application of the principle.

EXPERIMENTAL

Materials—Ascorbic acid USP², phenacetin USP³ (passed through a No. 64 tensile bolting cloth), and acetaminophen⁴ were used as the primary ingredient in each formulation. Other excipients included microcrystalline cellulose NF⁵, colloidal silicon dioxide NF⁶, starch USP⁷ (cornstarch passed through a No. 105 tensile bolting cloth), compressible sugar NF⁸, FD&C Blue No. 2 Aluminum Lake⁹, lactose USP¹⁰ (hydrous spray process), and orange oil NF¹¹. Magnesium stearate USP powder, food grade¹², was used as a lubricant.

Methods—Three direct-compression formulations were prepared as shown in Table I. The ascorbic acid and phenacetin formulations were

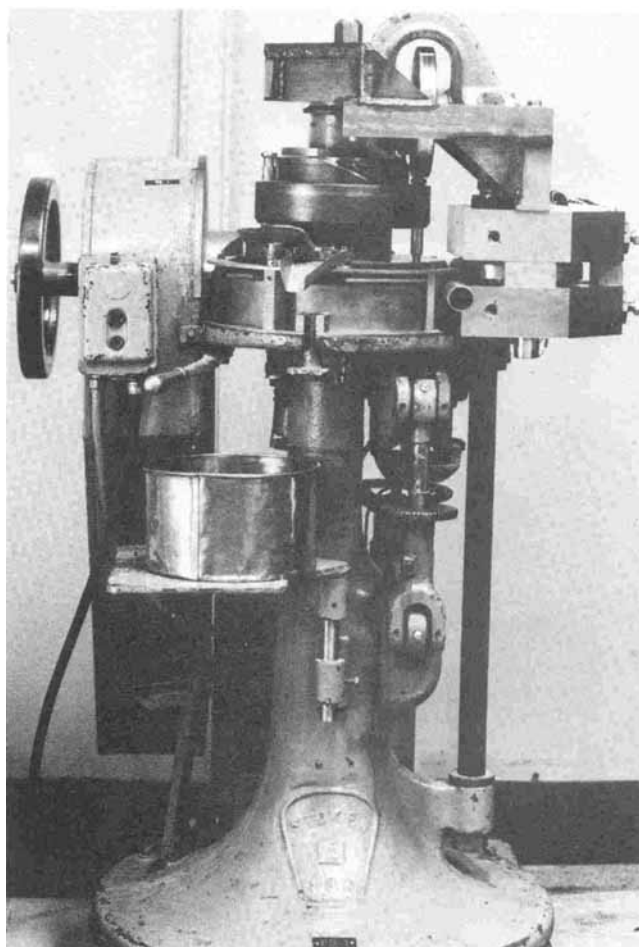


Figure 3—Modified rotary tablet press with triaxial decompression capability.

similar and were prepared in the following manner. All ingredients except magnesium stearate were passed through a 20-mesh screen and blended in a V-blender for 10 min. Subsequently, a portion of this blend was passed through a 20-mesh screen with the magnesium stearate, and all powder was mixed for an additional 2 min. The acetaminophen formulation was prepared by blending, in a V-blender, a portion of a 75% acetaminophen–25% spray-dried lactose mixture with an appropriate amount of a blend of the remaining ingredients to obtain the desired percentage of acetaminophen.

These formulations were prepared to study differences in capping tendencies between conventionally compressed (uniaxially compressed) tablets and tablets compressed in the special triaxial compression die. Other properties such as disintegration and dissolution were not evaluated.

The primary means of assessing capping tendency was visual inspection of each tablet after the hardness test. Breaking strengths were obtained on at least five tablets using an electronic hardness tester¹³. Tablets classified as "capped" normally had the entire intact dome separated from the body of the tablet. Tablets that did not cap in the hardness tester were inspected and broken by hand to check for laminations. Tablets classified as "not capped" had no visible laminations. Friability¹⁴ was determined occasionally but often did not adequately distinguish between capped and noncapped tablets when only small fracture lines were present.

The direct-compression formulations were compressed at various punch and side compression roll forces. Normal operation speed was 24.5 rpm, although one formulation was done at 31.5 rpm. Before operation of the tablet machine, sufficient material was added to fill the feed frame (50–100 g). Normal operation time was 30–60 sec at each die wall and punch pressure setting. This procedure produced ~25–50 tablets; half

² Pfizer, New York, N.Y.

³ Monsanto Co., St. Louis, Mo.

⁴ Eastman Chemical Products, Kingsport, Tenn.

⁵ Avicel PH-101, FMC Corp., Marcus Hook, Pa.

⁶ Cabot Corp., Cab-O-Sil Division, Boston, Mass.

⁷ Morrison and Watkins, West Bloomfield, Mich.

⁸ DiPac, Amstar Corp., New York, N.Y.

⁹ Colorcon, West Point, Pa.

¹⁰ Foremost Foods Co., San Francisco, Calif.

¹¹ International Flavors and Fragrances, New York, N.Y.

¹² Mallinckrodt, Lodi, N.J.

¹³ Heberlein and Co., AG, Zurich, Switzerland.

¹⁴ Chemical and Pharmaceutical Industry Co., New York, N.Y.

Table II—Comparison of Tablets from Uniaxial Die and Triaxial Die^a Ascorbic Acid Formulation

Punch Force, kN	Side Compression Roll Force, kN	Uniaxial Die			Triaxial Die		
		Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost	Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost
25.0	14.4	4.2	100	—	6.0	80	—
24.4	16.3	4.2	100	—	4.3	100	—
25.5	21.9	—	—	—	6.0	50	3.4
25.1	23.8	3.3	100	—	5.3	20	0.79

^a Machine speed at 31.5 rpm.

Table III—Comparison of Tablets from Uniaxial Die and Triaxial Die^a Phenacetin Formulation

Punch Force, kN	Side Compression Roll Force, kN	Uniaxial Die			Triaxial Die		
		Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost	Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost
13.0	16.1	4.8	100	—	4.5	0	2.8
13.2	19.4	3.3	100	—	5.0	0	2.1
12.4	22.7	3.8	100	—	5.3	0	3.8
12.0	26.1	3.6	100	—	4.8	0	1.7
18.2	26.3	6.2	100	—	6.6	80	—
23.2	16.2	5.5	100	—	5.0	100	—

^a Machine speed at 24.5 rpm.

Table IV—Comparison of Tablets from Uniaxial Die and Triaxial Die^a Acetaminophen Formulation

Punch Force, kN	Side Compression Roll Force, kN	Uniaxial Die			Triaxial Die		
		Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost	Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost
11.0	26.0	2.8	100	—	2.4	20	—
15.8	26.0	4.6	100	—	5.0	0	—
21.2	26.1	5.2	100	—	5.0	100	—

^a Machine speed at 24.5 rpm.

Table V—Comparison of Tablets from Uniaxial Die and Triaxial Die^a Ascorbic Acid Formulation

Punch Force, kN	Side Compression Roll Force, kN	Uniaxial Die			Triaxial Die		
		Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost	Breaking Strength, N × 10 ⁻¹	Percent of Tablets Capped	Friability, % of weight lost
18.9	16.7	1.6	100	—	3.6	0	1.5
19.7	11.3	4.3	20	—	5.7	0	—
21.7	15.6	4.4	100	—	6.4	0	—
23.3	18.8	3.0	100	100 ^b	5.1	0	0.93
23.7	16.5	4.2	100	—	5.5	0	0.92
23.8	14.2	4.3	100	—	6.1	0	—
24.4	18.9	4.2	100	—	6.2	0	—
25.2	14.2	3.5	100	100 ^b	5.5	0	0.98

^a Machine speed at 24.5 rpm. ^b Capped.

were compressed in the standard die, and the other half were compressed in the triaxial die. The triaxially compressed tablets were marked with a felt pen as they came off the press to distinguish them from the uniaxially compressed tablets. Tablet weights, breaking strengths, and capping tendencies were checked immediately after completion of the run. Punch forces were set to ensure breaking strengths between 30 and 70 N, depending on the specific formulation.

RESULTS

The results for three test formulations are shown in Tables II–V. These formulations showed a substantial difference between the uniaxially and triaxially compressed tablets. Several other formulations showed no capping or laminations for either kind of tablet. Two test formulations (containing materials known to induce capping) were tested in which both the triaxially and the uniaxially compressed tablets capped. Even with inadequate die wall pressure relief, the triaxially compressed tablets were at least as good as the uniaxially compressed ones. With some materials, adequate die wall pressure relief made the differences very dramatic: good tablets from the triaxial die and laminated ones from the uniaxial die.

The punch and side compression roll load cell outputs were monitored

throughout each experiment. The punch force was obtained by multiplying the voltage output of the strain gauge by an experimentally determined calibration constant. This punch force was the same for both the uniaxially and triaxially compressed tablets under any given set of conditions. The side compression roll force is the sum of the calculated applied forces of the upper and lower load cells and was adjusted before each run to ensure even pressure on the side compression roll.

The average breaking strength of the tablets and the percentage of tablets that had visible laminations upon breaking were recorded. Friability is reported either as the percentage of the tablets that capped in the friabilator or as the percentage of the original weight lost after 4 min. All tablets were compressed at a speed of 24.5 rpm, except for the ascorbic acid tablets (Table II) which were made at 31.5 rpm.

DISCUSSION

The results in Tables II–V demonstrate the differences in capping tendency between the uniaxially compressed and triaxially compressed tablets. Proper adjustment of the punch and side compression roll force generally resulted in triaxially compressed tablets that were superior to those compressed in the standard die.

The results for the ascorbic acid formulation (Table II) were obtained at a relatively constant punch force (24.4–25.5 kN) while the side compression roll force was varied. The uniaxially compressed tablets capped 100% of the time. With adequate die wall compression, the triaxially compressed tablets showed substantial improvement in quality, both in breaking strength and capping tendency. At lower side compression roll forces, the triaxially compressed tablets approached the poorer quality of the uniaxially compressed ones.

Apparently, as the side compression roll force increased, greater deflection of the triaxial die wall occurred. This deflection allowed greater release of die wall pressure on decompression and better relief of accumulated stresses. At lower side compression roll forces, less die wall deflection tended to produce tablets similar to the uniaxially compressed tablets. An apparent minimum side compression roll force is probably necessary for sufficient die wall deflection and adequate die wall pressure release. This minimum side compression roll force has to overcome the resistance of the die wall sleeve to deformation as well as any frictional resistances within the system. The applied punch pressure and the physical properties of the powders in the formulation (*i.e.*, tensile strength, shear strength, brittle fracture propensity, stress relaxation rate, *etc.*) also influence the minimum side compression roll force necessary to eliminate capping.

Similar success was obtained (*i.e.*, superior tablets) in the triaxial die for the phenacetin formulation (Table III). At moderate punch forces (12.0–13.0 kN), tablets compressed triaxially were obtained that showed no capping and that had tablet breaking strengths of 45–53 N. At this compression force, a range of side compression roll forces (16.1–26.1 kN) produced acceptable tablets. Conversely, the tablets compressed in the standard die showed a severe capping tendency, with some tablets capping upon ejection from the die. All uniaxially compressed tablets showed laminations that would make them unacceptable for production purposes. At higher punch forces, adequate release of residual die wall pressure could not be attained even with the maximum available compression roll force of 26.3 kN (*i.e.*, the design limitation), and the triaxially compressed tablets began to show capping.

The acetaminophen formulation (Table IV) showed the effect of varying the punch force without altering the side compression roll force. Only compressions at three punch forces were done, but differences between the tablets from the two dies were seen. Only at the high punch force was the quality of the triaxially compressed tablets reduced to become comparable to the uniaxially compressed tablets, *i.e.*, they showed excessive capping. Higher side compression roll force may have decreased capping in the triaxial die at the highest pressure, but this machine was incapable of such high forces. However, correct adjustment of the punch and side compression roll forces produced excellent tablets from the triaxial die.

The influence of machine speed on capping tendency can be seen by comparing the results for the ascorbic acid formulation in Tables II and V. A 30% increase in the machine speed changed the properties of both tablets. Uniaxially compressed tablets were of poor quality at both speeds. Although the triaxially compressed tablets were, in general, superior to the uniaxially compressed tablets at both rotation speeds, the triaxially compressed tablets showed evidence of capping at the higher speed. At the lower speed, a wide range of punch and side compression roll forces produced excellent tablets from the triaxial die (Table V). At the higher speed, capping was not eliminated completely with this material even at the maximum available side compression roll force, due perhaps in part to the time-dependent nature of stress relaxation.

The time-dependent nature of stress relaxation is an important mechanism of stress relief at the higher speed even in the triaxial die unless the stress relief rate of the punch and die wall is matched to minimize internal stress. Apparently, the longer time that the tablet spent in the die at the slower rotation speed allowed greater stress relief due to plastic flow within the compact. The large difference in the quality of the uniaxially and triaxially compressed tablets made at the lower speed shows that mechanical release of some die wall pressure by the triaxial die improves the tablet quality. At the higher speed, the mechanical release of the die wall pressure in the triaxial die was not sufficient by itself to eliminate capping. Future machines should have increased capacity and thus be capable of applying larger die wall forces, which would permit greater latitudes in the die wall forces applied. In this way, more die wall pressure could be released when the formulation and compression characteristics warrant it.

SUMMARY

These preliminary investigations show that the mechanical release of die wall pressure, using a specially designed die with a flexible die wall, decreases or eliminates capping in three direct-compression formulations when compared to the same formulation compressed in a standard die. Correct adjustment of the applied side compression roll force and punch pressure allows sufficient release of residual die wall pressure on decompression to prevent or diminish capping due to the excessive stress concentrations within the compact during decompression or ejection. The force required for the side compression roll and for success in eliminating capping during decompression or ejection is dependent on the physical properties of the formulation, the applied punch pressure, the viscoelastic properties of the formulation materials, and the efficiency with which the applied force from the side compression roll is transmitted to the die wall.

This preliminary report (an outgrowth of the principles developed from basic research on the physical properties of materials) demonstrates the feasibility of designing and constructing equipment for the successful manufacture of otherwise troublesome formulations. This design offers the advantages of simultaneous and more uniform release of residual die wall pressure, as well as the capability of adjusting the pressure applied to the die wall. Further engineering efforts can result in practical production equipment design and utilization.

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ACKNOWLEDGMENTS

The authors thank Chester Sperry, Robert Melson, Donald McLain, and Harry Dankert of the Mechanical Engineering Department, The Upjohn Co., for the design and construction of the machine and special die.