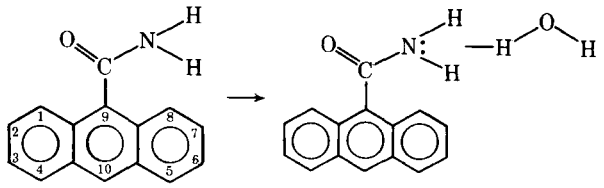

Scheme I

In aprotic solvents, this interaction is strong enough to overcome the steric barrier to it and allows the exocyclic group to attain a coplanar configuration. However, in water and ethanol, the carboxamido group is hydrogen bonded to the solvent (Scheme I), with the result that the group and its solvent cage become more bulky. The resonance interaction even upon excitation is not great enough to overcome the steric interference from the interaction between the *peri*-hydrogen atoms and the solvent cage.

Once 9-anthramide is protonated at the amido nitrogen, the effect of the hydrogen bond donor solvent cage is lost. This loss removes the possibility of hydrogen bonding at the carboxamido group and is observed as a loss of the mirror image relationship between the absorption and fluorescence spectra, with the result that the emission spectrum shifts to much longer wavelengths (Fig. 2).

While the ground-state pKa of 9-anthramide is −2.00, excited-state protonation occurs in this compound, as revealed by variations in the fluorescence spectra with pH or Hammett acidity. 9-Anthramide is more basic in the excited state and exhibits an excited-state pKa* value of 1.50. The decrease in acidity of the protonated amide in the lowest excited singlet state reflects the transfer of electronic charge from the anthracene ring to the exocyclic group upon excitation.

The effect of protonation on the conjugation of the exocyclic group can be observed by following the absorption and fluorescence band shapes and band maxima as they vary with pH or Hammett acidity. In the ground state, in the region below Hammett acidity of −2.0, protonation of the carboxamido group is observed as a slight smearing and red-shift in the absorption spectrum (Fig. 1). In the ground state, protonation apparently causes the resonance interaction to increase enough to allow the exocyclic group to reach a configuration that is nearly coplanar to the ring. The effect of protonation in the excited state is more dramatic, the large red-shift of the emission spectrum, on protonation, suggesting essentially complete conjugation in the excited state.

The solvents used in this study covered a wide range of polarity and hydrogen bond donor capability. It was found that excited-state conjugation in the neutral molecule can occur only in aprotic solvents (regardless of polarity). The hindrance observed in the excited state in hydrogen bond donor solvents is due to the solvent caging effect at the carboxamido group; this effect makes the group too bulky to overcome the steric interference from the *peri*-hydrogen atoms in the 1- and 8-positions of the anthracene ring.

The solvent cage has thus been shown to play an important role in chemical structure. A conclusion that may be drawn from these studies is that the chemical structure (and presumably the reactivity) of a compound may vary substantially from solvent to solvent. As illustrated by the differences in the spectra of 9-anthramide in water and heptane, strongly interacting solvents do affect chemical structure. These findings suggest that studies of structure and reactivity of drugs in nonaqueous solvents and solid matrixes may not always be validly applied to the interpretation of phenomena observed in strongly interacting solvents such as biological fluids because of the solvent caging effect.

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[x] To whom inquiries should be directed.

Effect of Variation in Compaction Force on Properties of Six Direct Compression Tablet Formulations

KARRAR A. KHAN [*] and C. T. RHODES [‡x]

Abstract □ The effect of variation in compaction force on six direct compression tablet matrixes was investigated. An instrumented tablet press allowed direct measurement of applied and ejection forces. Hardness, apparent tablet density, and disintegration times also were determined. The disintegration time of spray-dried lactose tablets was essentially independent of compaction force. However, in the other systems investigated, the properties studied showed varying types of dependence on compaction pressure. A direct compression formula was developed and exhibits a decrease in disintegration time as compaction force is increased.

Keyphrases □ Tablets—six matrixes, effect of various compaction forces on hardness, apparent density, and disintegration time □ Compaction force—effect on tablet hardness, apparent density, and disintegration time, six matrixes □ Hardness, tablet—six matrixes, effect of various compaction forces □ Density, apparent—six tablet matrixes, effect of various compaction forces □ Disintegration time, tablet—six matrixes, effect of various compaction forces □ Dosage forms—tablets, six matrixes, effect of various compaction forces on hardness, apparent density, and disintegration time

The production of pharmaceutical tablets by the direct compression technique has several advantages for many drugs in comparison with wet granulation or other methods. In particular, the relatively small labor content of this technique makes it increasingly attractive to the pharmaceutical industry (1).

Several well-proven materials can be used as tablet matrixes for direct compression, and some investigators

Table I—Properties of Formula I Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
702.7	696.4	5.47	1.30	10.6	69.7	30.3
1241.9	696.8	5.21	1.36	>15	95.4	34.0
2287.0	699.9	5.01	1.42	>15	121.1	34.4
3513.5	701.4	4.91	1.45	>15	146.8	32.3

Table II—Properties of Formula II Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
666.5	429.9	3.92	1.13	0.2	36.7	1.0
1402.5	450.5	3.78	1.24	1.5	36.7	1.4
1575.0	466.1	3.95	1.22	1.7	36.0	3.9
2514.0	455.1	3.66	1.29	3.1	37.0	27.0

Table III—Properties of Formula III Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
242.0	657.3	4.25	1.58	0.28	41.1	7.8
963.0	660.5	3.77	1.80	7.0	37.8	0.6
1950.6	659.5	3.53	1.93	14.5	63.8	0.6
3362.2	658.9	3.43	1.98	>15	91.0	0.6

also proposed blends of various materials for direct compression. Furthermore, a number of direct compression materials are now widely available commercially. However, there is a paucity of comparative quantitative evaluations of direct compression matrixes.

In this study, the effect of variation of compaction force on ejection force, apparent tablet density, hardness, and disintegration time of six direct compression tablet formulations was investigated. Spray-dried lactose, whose properties as a direct compression diluent are well known, was included since it can be regarded, to some extent, as a reference standard.

EXPERIMENTAL

Materials—The six direct compression tablet matrixes had the following percentage (w/w) compositions:

Formula I—spray-dried lactose[1], 99.0; and magnesium stearate[2], 1.0.

Formula II[3]—modified potato starch, 81.0; colloidal silica, 3.0; polyethylene glycol 4000, 3.0; talc, 12.0; and magnesium stearate, 1.0.

Formula III[4]—dicalcium phosphate dihydrate, 89.0; starch, 7.5; microcrystalline cellulose, 2.5; and magnesium stearate, 1.0.

Formula IV—dicalcium phosphate dihydrate[5], 91.5; microcrystalline cellulose[6], 5.0; sodium starch glycolate[7], 2.5; and magnesium stearate, 1.0.

Formula V—microcrystalline cellulose, 24.0; special starch[8], 75.0; and stearic acid,1.0.

Formula VI—dicalcium phosphate dihydrate, 89.3; calcium phosphate–carbonate complex[9], 4.7; cation-exchange resin[10], 5.0; and magnesium stearate, 1.0.

Methods—The components of the various tablet formulations were blended by quartering and shaking vigorously in a plastic bag as described previously (2). A single-punch tablet press[11], used to prepare the tablets [punch size 1.09 cm (0.42 in.), shape flat], was instrumented as described elsewhere (3, 4). Apparent tablet densities were estimated from tablet weight and thickness measurements. Disintegration times were determined using the BP method, without disk.

RESULTS AND DISCUSSION

The data for spray-dried lactose (Table I) demonstrate its good compressibility; hard tablets were produced at low compaction pressures. The disintegration time was not radically modified by an increase in compaction force; indeed, the tablets dissolved rather than disintegrated or broke up into small lumps. The dissolution, which primarily takes place from the external surface, was essentially independent of compaction force. A similar finding was reported in an investigation of sodium chloride tablets (5).

The ejection forces were fairly high and increased with an increase in compaction force, although 1% magnesium stearate was present in the formula. Richman (6), who examined the lubrication of spray-dried lactose, found that lubrication efficiency improved with an increase in lubricant concentration up to 5% instead of reaching an optimum between 1 and 2% as is common for many granulations. Spray-dried lactose tablets were of low friability.

Formula II was a commercially available direct compression tablet matrix. The tablets produced in this study were somewhat disappointing (Table II), being soft and very friable. Disintegration time increased as compaction force was increased. This increase may have been due to some plastic deformation of starch (7), reducing the rate of water penetration into the tablet structure. Ejection forces generated during compaction were low and appeared to be independent of the compaction force. This behavior is similar to that reported for microcrystalline cellulose (8).

Formula III, another well-known commercially available direct compression excipient, was initially marketed as reported in this in-

[1] McKesson and Robbins Ltd., Ramsgate, England.
[2] British Drug Houses, Poole, England.
[3] Nal-Tab, Victor Blagden and Co., London, England.
[4] Emcompress Standard, Kingsley and Keith, Croyden, London, England.
[5] Albright and Wilson Ltd., Oldbury Division, Worcestershire, England.
[6] Honeywell and Stein Ltd., London, England.
[7] Primojel.
[8] Sta-R$_x$ 1500 Starch, Staley Co., London, England.
[9] Calfos 50 mesh, Calfos, London, England.
[10] Amberlite IRP 88, Lennig Chemicals, London, England.
[11] Manesty type F3.

Table IV—Properties of Formula IV Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
227.1	655.0	4.27	1.57	0.4	41.1	2.0
439.3	667.5	3.97	1.72	1.0	44.0	0.7
1774.2	657.1	3.56	1.89	6.4	63.5	0.6
3492.1	663.7	3.44	1.99	>15	91.5	3.3

Table V—Properties of Formula V Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
393.8	382.9	3.49	1.13	3.9	34.1	1.1
1514.4	387.9	3.06	1.32	10.1	36.3	3.9
3210.5	381.3	2.98	1.33	12.6	37.8	4.4
3393.3	383.2	3.04	1.31	11.5	39.6	4.5

Table VI—Properties of Formula VI Tablets Prepared at Different Compaction Pressures

Applied Compression Force, kg	Weight, mg	Thickness, mm	Apparent Tablet Density, g/cm³	Hardness, Erweka Units	Ejection Force, kg	Disintegration Time, min
575.5	686.3	4.25	1.66	2.1	42.2	8.0
1553.8	694.8	3.88	1.85	9.7	60.5	1.2
3634.6	692.8	3.66	1.95	>15	98.3	0.5

vestigation. Recently, the suppliers excluded the other adjuvants and marketed only dicalcium phosphate dihydrate, which was claimed to be in a special physical form. The compression properties of this excipient are shown in Table III. This material had an excellent pressure–hardness profile. The tablets made at the lowest pressure had longer disintegration times than those made at higher pressures. This behavior may have been due to the swelling effect of starch, which is more pronounced in tablets made at higher pressures (low porosity). The effect of pressure on disintegration of tablets containing various disintegrants was described elsewhere (3).

Formulation IV contained an unmilled grade of dicalcium phosphate dihydrate. Its particle-size distribution was reported previously (2). The compression properties of this formulation (Table IV) were similar to those of Formula III (Table III), except that the disintegration time showed a minimum. This minimum may have been caused by the differences in the disintegrant action of corn starch and sodium starch glycolate (3). This study, therefore, appears to indicate that the coarse, unmilled, or graded form of dicalcium phosphate dihydrate is a useful direct compression diluent (9). Also, sodium starch glycolate is an effective disintegrant for insoluble tablet systems (2, 3, 9).

Formulation V was basically similar to that developed by Manudhane (10). Initial experiments with special starch showed that it was not possible to compress this material containing 1% magnesium stearate, which is an indication of a very low compacity of this excipient. The results (Table V) show that the addition of 24% microcrystalline cellulose improved tablet hardness (10); it reached a maximum value of about 12 Erweka units. The disintegration time increased only slightly with increasing compression force, and a further increase in applied force (above 1514 kg) had no effect on tablet disintegration time. It is evident that apparent tablet density, hardness, and disintegration time reached maximum values at the same compression force. The reason that the disintegration time was independent of the compression force may be that no further compaction took place. The results on the ejection force are similar to those obtained with microcrystalline cellulose formulations (8).

Table VI provides useful quantitative data on the formula developed by the present authors, in which the calcium phosphate–carbonate complex was used as a tableting aid instead of microcrystalline cellulose. The selected formula produced hard tablets at moderate and high compaction forces. Ejection forces increased significantly with an increase in compaction force, whereas disintegration time decreased. Formulas III, IV, V, and VI all yielded tablets of low friability.

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ˣ To whom inquiries should be directed.