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EVALUATION OF STEARIC ACID AND POLYETHYLENE GLYCOL AS BINDERS FOR TABLETING POTASSIUM PHENETHICILLIN

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INTRODUCTION

A method referred to as "the direct granulation method" has been proposed by Rubinstein[1]. The principle of direct granulation (DG) is the utilization of a binding agent which melts or softens at relatively low temperatures. The molten binding agent then coats the powder particles in the formulation and, upon cooling, granules are formed directly. It has been found that the whole process can be conducted in a jacketed high speed mixer-granulator, and the granules fed directly to the tableting machine. Apart from reducing most of the stages in the granulation process, the method also eliminates the expensive and time consuming drying stage of wet granulation, thereby significantly increasing the efficiency of tablet production. A similar process involving the use of waxy materials such as stearic acid and polyethylene glycol (PEG) has previously been used for the preparation of sustained release solid dosage forms[2,3]. A patent assigned to Hoffman la Roche specifically refers to the use of stearic acid, carbowax and glyceryl monostearate[3]. In an example quoted in the patent to obtain sustained release tablets of vitamin B complex and ferrous

sulphate, stearic acid was used as the binder and delayed release agent. Rubinstein[1,4] however, modified the process by including a surface active agent and a tablet disintegrant together with PEG[1] as the binding agent. The *in vitro* properties of phenylbutazone 100mg tablets produced using this method, showed that the granules were comparable to those produced by conventional wet granulation. The tablets exhibited short disintegration times and fast dissolution rates. Subsequently Shah *et al*[5] satisfactorily made tablets from six different drug formulations using a modified method in which PEG 6000 was melted by means of hot air. In a recent study Rubinstein and Musikabhumma[6] showed that good quality paracetamol tablets were obtained using stearic acid as a binder. These tablets exhibited disintegration and dissolution times ($t_{50\%}$) of less than one minute and showed good stability on long term storage.

Since the DG method does not involve the use of water to moisten the binders, it was decided to examine the application of this technique for tableting a moisture sensitive drug. Potassium phenethicillin was chosen as representative of a moisture sensitive drug and this work reports the tableting properties of phenethicillin granules prepared using stearic acid and PEG as binding agents.

MATERIALS

The following materials were used:
Potassium phenethicillin (Broxil*, batch no. 4340, Beecham Pharmaceuticals, Worthing, U.K.), polyethylene glycol (PEG 6000), stearic acid, sodium lauryl sulphate and magnesium stearate (British Drug Houses Ltd., Poole, U.K.), microcrystalline cellulose (Avicel PH102, Honeywell and Stein Ltd., Surrey, U.K.), colloidal silica (Aerosil 200, Bush, Beach and

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Segner Bayley Ltd., London), sodium starch glycolate (Explotab, K. & K. Greef Fine Chemicals Ltd., Surrey, U.K.).

Formulation and Methods for Incorporating the Binders

Formulation A - stearic acid as binder

(Ai) Direct Granulation

The following formulations were used to determine the effect of stearic acid concentration (2.5, 5.0 and 7.5% w/w) on the tablet properties:

	% w/w
Stearic acid	2.5, 5.0, 7.5
Potassium phenethicillin	to 100

Method

An electronic blender (Kenwood Model A525A) was modified to produce a small scale high speed mixer-granulator. The sharp blades of the blender were replaced with paddle blades which could be progressively rotated at speeds up to 4200 r.p.m. Copper tubing was wound around the bowl of the blender in order to allow hot or cold water to warm up or cool down the bowl contents. Hot water at 70°C was circulated through the copper tubing from a constant temperature water bath. The ingredients of the various formulations were weighed and placed in the blender bowl. The paddle was rotated at an appropriate speed to ensure adequate mixing for about 10 minutes. During this time the blender contents reached a temperature of about 60°C. Blending was continued for a further 10 minutes to enable the binder to homogenously spread itself over the surface of the powder particles. Cold water was then circulated around the blender bowl, reducing the contents to room temperature to produce dry granules. The granules were removed from the mixer and passed through a 16 mesh sieve.

Tableting was carried out on an instrumented Manesty F3 tableting machine using 5/16" flat faced punches[7].

Aii) To further improve the tableting properties, intragranular microcrystalline cellulose was added at a concentration of 10 and 20% w/w. 5% w/w sodium starch glycolate was included as a disintegrant.

The following base formulations were used:

	% w/w
Microcrystalline cellulose (MCC)	0, 10 and 20
Stearic acid	5, 7·5 and 10
Sodium starch glycolate	5
Potassium phenethicillin to	100

0·5% Colloidal silica was added to the granules to improve granule flow.

Aiii) Direct Compression

A direct compression formulation identical to Aii but without stearic acid was used for comparison. Magnesium stearate at 1·0, 1·5 and 2% w/w was included in the formulations to compare its effect on the compressibility of potassium phenethicillin with that of stearic acid.

Formulation:

	% w/w
Potassium phenethicillin	71·5 - 72·5
Microcrystalline cellulose	20
Sodium starch glycolate	5
Magnesium stearate	1 - 2
Colloidal silica	0·5

Formulation B - PEG 6000 as binder

Bi) Direct granulation

The following base formulation was used:

	% w/w
PEG	7·5
Sodium starch glycolate	5
Potassium phenethicillin to	100

The granulation was prepared using the method described under Ai. 1% magnesium stearate was added outside the granules to prevent binding during compression.

Bii) Pre-Compression

The drug, sodium starch glycolate, PEG and 1% magnesium stearate were pre-compressed and milled using an Apex comminuting mill (Apex Construction Ltd., North Fleet, Kent) through a No. 0·077" aperture screen at low speed using hammers forward.

Biii) Moist granulation using water as the granulating agent

The drug, PEG and sodium starch glycolate were placed in a planetary mixer and the granulating fluid was added to mass the blend. The wet mass was forced through a No.12 mesh screen and dried at 60°C for 1½ hours in laboratory fluid bed dryer (PRL Engineering Ltd., Mostyn, Flintshire, U.K.). The dried granules were passed through a No.16 sieve. 1% extragranular magnesium stearate was added before compression.

Biv) Moist granulation using methylene chloride as the granulating agent

The process described for Biii was used except that the wet mass was dried for 45 minutes.

Bv) Direct Compression

The formulation described under Bi was directly compressed.

Granule Properties

Bulk and tapped densities of the granules were measured. In some selected cases, true density was also determined using a Pycnometer (Beckman Model 930, Beckman Instruments, London). The friability of the granules was determined by a technique described previously[8].

Tablet Properties

20 tablets from each batch were individually weighed and the mean, the standard deviation, and the coefficient of variation

TABLE 1

The Effect of Granulating Agent Concentration and Compression Pressure on the Properties of Potassium Phenethicillin Tablets Prepared from Direct Granulating Using Stearic Acid and PEG 6000 as Granulating Agents.

Formulation		Compression Pressure (MNm^{-2})	Tablet Weight mg (mean ± S.D.)	C.V. %	Crushing Strength (Kp)	Relative Density g cm^{-3}	Porosity %
Stearic Acid	2.5%	82	138 ± 2.3	1.67	4.4	0.7554	24.46
		163	143 ± 1.4	0.98	4.7	0.8752	12.46
		245	144 ± 0.3	0.27	5.6	0.9271	7.29
		327	142 ± 1.3	0.92	7.3	0.9437	5.63
	5.0%	82	145 ± 2.4	1.67	4.3	0.7215	27.85
		163	143 ± 4.5	3.20	4.3	0.7713	22.87
		327	145 ± 3.1	2.13	7.9	0.8292	17.08
		490	146 ± 0.5	0.40	7.9	0.8330	16.70
	7.5%	82	158 ± 2.6	1.64	5.7	0.7187	28.13
		163	161 ± 0.7	0.49	7.2	0.7819	21.81
		327	159 ± 1.8	1.16	8.5	0.8116	18.84
		490	160 ± 0.6	0.41	8.9	0.8209	17.91
PEG 6000	2.5%	82	151 ± 1.0	0.71	5.5	0.8441	15.59
		163	152 ± 1.5	0.99	5.8	0.9135	8.64
		245	151 ± 2.6	1.78	6.7	0.9431	5.69
		327	148 ± 1.9	1.29	6.8	0.9412	5.88
	5.0%	82	157 ± 1.1	0.72	6.6	0.8532	14.86
		163	158 ± 0.8	0.55	5.1	0.9251	7.49
		245	159 ± 0.8	0.52	4.5	0.9501	4.99
		327	154 ± 1.7	1.11	3.8	0.9486	5.14
	7.5%	82	163 ± 2.2	1.39	5.0	0.8622	13.78
		163	165 ± 0.4	0.27	6.4	0.8965	10.35
		245	161 ± 1.1	0.71	6.0	0.9065	9.35
		327	162 ± 0.6	0.38	6.4	0.9129	8.71

evaluated. The dimensions of the tablets were measured using a micrometer and the apparent tablet density calculated. From a knowledge of the true density of the compression mix, the porosity of the compacts was obtained. The crushing strengths were determined using a Schleuniger hardness tester; a mean of at least ten tablets being obtained. Friability was measured using a Beecham Friabilator. This consisted of six screw capped metal cylinders 3.8 cm in diameter and 8.7 cm long. The cylinders containing the tablets were rotated at 1 cycle per second and the apparatus was run for 1000 revolutions. The percentage loss in weight was determined. Disintegration times were measured using the B.P. method except that 2 tablets were used in each tube and a mean of three determinations was recorded. Dissolution rates were measured by a similar method to that described in the USP[7]. The concentration of phenethicillin in the dissolution medium was measured at 268 nm. Tablets were stored at 20°C, 30°C and 37°C for six months, and their disintegration times, crushing strengths and dissolution rates measured.

RESULTS AND DISCUSSION

The effect of stearic acid concentration on the tableting properties of potassium phenethicillin prepared by the direct granulation process is shown in Table 1. The results show that an increase in stearic acid concentration tends to increase tablet porosity particularly for compacts made at higher pressures. For tablets containing 2.5% stearic acid, bonding is mainly by drug to drug contact and thus compaction will be influenced principally by the behaviour of the drug. An increase in compaction pressure will increase consolidation which will result in a progressive decrease in tablet porosity. However for tablets containing 5 and 7.5% stearic acid, the reduction in porosity with an increase in compaction pressure is significantly smaller. This is probably due to the stearic acid absorbing a large proportion of the energy of compaction to deform plastic-

TABLE 2

The Effect of Stearic Acid Concentration on Bulk and Tapped Densities and Friability of Granules Prepared from Formulations Aii

Stearic Acid %	Bulk Density (gm cm^{-3})	Tapped Density (gm cm^{-3})	Friability %
5.0	0.464	0.561	17.74
7.5	0.496	0.526	7.89
10.0	0.513	0.594	1.71

ally and form stronger compacts by asperity melting. Only a small proportion of the compression energy is utilised in particle rearrangement and consolidation and thus porosity is reduced only slightly.

Table 2 shows the results of the effect of stearic acid on the bulk and tapped densities and friabilities for formulations Aii. An increase in stearic acid concentration increases bulk and tapped densities and reduces friability of granules, indicating that at a higher stearic acid level more robust granules are produced.

Table 3 shows the effect of MCC on the tableting properties of tablets containing 5, 7.5 and 10% stearic acid and Figs.1 and 2 the properties of tablets containing 5, 7.5 and 10% stearic acid with the inclusion of 10 and 20% of MCC. As expected the tablet crushing strength increased with the addition of MCC. At the same time the tablet ejection force slightly decreased because of the self lubricating properties of MCC. The slight increase in the disintegration time of the tablets containing 20% MCC is caused by the better compressibility of the formulation as shown by their higher crushing strengths. As seen in Table 1, an

TABLE 3

The Effect of the Addition of MCC on the Properties of Potassium Phenethicillin Tablets Containing Stearic Acid (Formulation Aii)

Stearic Acid % w/w	MCC % w/w	Compression Pressure (MNm^{-2})	Tablet Weight mg (mean ± S.D.)	C.V. %	Apparent Density ($gm\ cm^{-3}$)	Crushing Strength (Kp)	Ejection Force (Newton)	Disintegration Time (Min)
5	0	82	170 ± 2.1	1.21	1.129	5.7	524	3.43
		163	154 ± 0.8	0.50	1.204	8.0	628	3.18
		327	155 ± 0.6	0.38	1.291	11.1	628	3.48
		490	156 ± 2.6	1.66	1.319	9.6	628	3.83
	10	82	184 ± 0.7	0.38	1.116	4.2	366	3.88
		163	182 ± 1.9	1.06	1.228	8.8	393	4.33
		327	182 ± 1.7	0.92	1.275	12.1	628	3.48
		490	181 ± 1.5	0.81	1.341	12.5	733	3.65
	20	82	200 ± 2.5	1.24	1.112	6.6	340	4.85
		163	198 ± 2.4	1.20	1.230	11.0	419	4.72
		327	200 ± 0.7	0.35	1.210	14.7	445	5.57
		490	203 ± 2.1	1.05	1.329	14.8	524	5.62
7.5	0	82	156 ± 2.3	0.14	1.104	5.7	262	3.78
		163	165 ± 1.7	0.99	1.231	8.8	288	4.18
		327	160 ± 1.9	1.20	1.284	9.3	288	4.73
		490	159 ± 2.6	1.61	1.292	9.6	445	4.67
	10	82	182 ± 0.9	0.47	1.173	7.9	209	4.67
		163	183 ± 1.1	0.57	1.252	10.6	235	4.60
		327	183 ± 5.1	2.76	1.310	10.9	235	4.90
		490	183 ± 2.8	1.54	1.313	11.1	340	5.45
	20	82	203 ± 2.1	1.00	1.135	7.3	235	6.60
		163	214 ± 2.2	1.03	1.260	12.7	235	7.12
		327	203 ± 1.9	0.95	1.302	14.5	262	7.53
		490	204 ± 1.4	0.66	1.322	15.0	314	7.18
10	20	82	215 ± 2.4	1.11	1.140	7.0	183	8.95
		163	215 ± 1.1	0.51	1.249	11.5	235	9.38
		327	214 ± 1.0	0.47	1.312	14.1	235	11.45
		490	217 ± 2.0	0.95	1.314	15.1	262	11.10

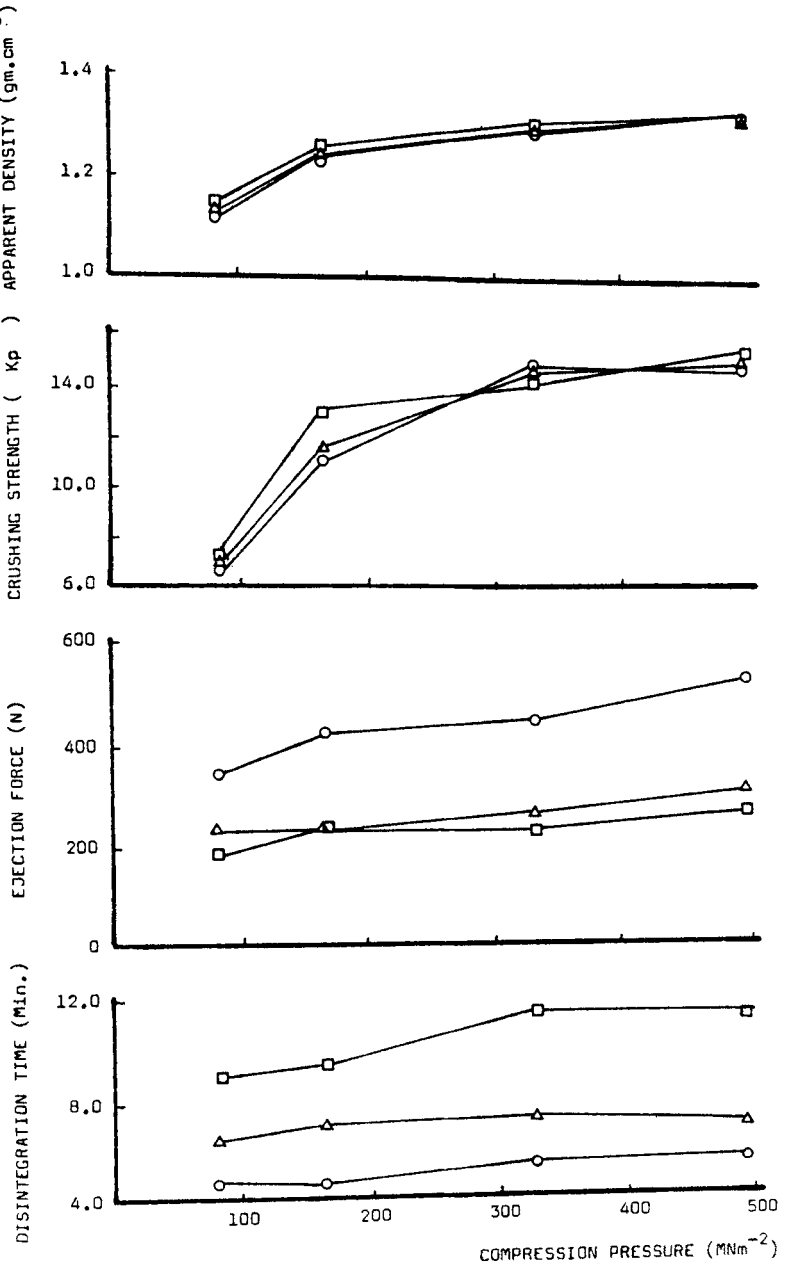

Figure 1: Effect of Stearic Acid on the Properties of Potassium Phenethicillin Tablets (o, Δ, □, 7.5 and 10% Stearic Acid)

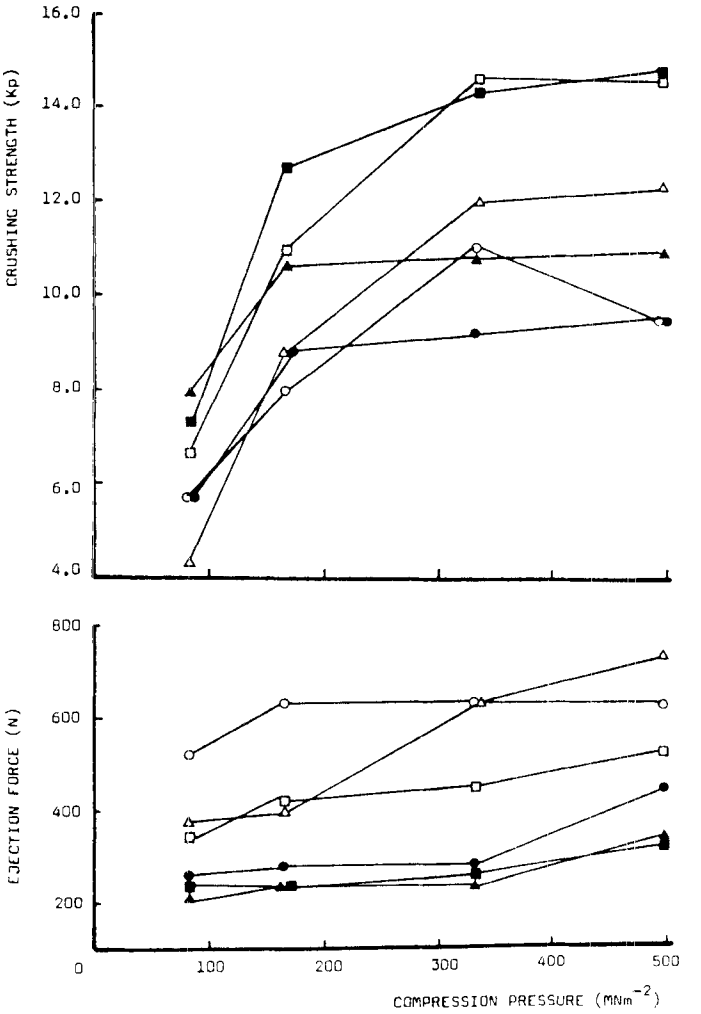

Figure 2: Efect of the Additional Microcrystalline Cellulose on the Properties of Potassium Phenethicillin Tablets (o,Δ, ◻ , 0, 10%, 20% of MCC; opened and closed Symbols are 5% and 7.5% Stearic Acid)

TABLE 4

The Effect of the Addition of MCC on the Friability of Potassium Phenethicillin Tablets Containing 5, 7.5 and 10% Stearic Acid (Formulation Aii) Compressed at 162 MNm

Stearic Acid %	MCC %	Friability %
	0	10.97
5.0	10	3.05
	20	1.64
	0	3.17
7.5	10	2.26
	20	1.54
10.0	20	1.47

increase in stearic acid concentration from 5 to 7.5% does not further improve crushing strength even in the presence of MCC. However, as expected, the tablets containing 7.5% stearic acid showed lower ejection forces than those containing 5% stearic acid and the former also produced slightly longer disintegration times.

The effect of the addition of MCC on the friability of tablets containing 5, 7.5 and 10% stearic acid is shown in Table 4. These results show that tablets containing only stearic acid as a binder are relatively friable and at 5% stearic acid concentration a friability of nearly 11% was recorded. Thus, it appears that a stearic acid concentration of at least 5% is required and that the addition of MCC is necessary to reduce the friability of tablets to acceptable levels. The results of tableting the direct compression formulation without stearic acid (which was replaced with magnesium stearate at 1, 1.5 and 2.0%) are presented in Table 5. The results show that the

TABLE 5

The Compressional Properties of the Direct Compression Formulation of Potassium Phenethicillin (Aiii) Containing 1, 1.5 and 2.0% Magnesium Stearate

Magnesium Stearate % w/w	Compression Pressure (MNm^{-2})	Tablet Weight mg (mean ± S.D.)	C.V. %	Apparent Density (gm cm^{-3})	Crushing Strength (Kp)	Ejection Force (Newton)	Disintegration Time (Min)
1.0	82	185 ± 2.7	1.46	1.112	10.6	786	3.15
	163	187 ± 4.6	2.46	1.154	12.8	786	3.40
	327	186 ± 2.9	1.59	1.286	14.6	890	3.82
	490	187 ± 2.2	1.19	1.320	16.4	890	4.10
1.5	82	194 ± 0.9	0.47	1.099	10.5	759	3.75
	163	195 ± 1.4	0.73	1.214	13.8	786	4.58
	327	192 ± 1.1	0.56	1.300	14.6	786	4.25
	490	192 ± 0.9	0.50	1.334	14.0	838	4.37
2.0	82	192 ± 2.3	1.20	1.071	8.8	681	3.95
	163	196 ± 2.6	1.29	1.192	13.4	786	4.15
	327	196 ± 1.8	0.89	1.301	16.1	786	4.47
	490	192 ± 2.2	1.13	1.329	14.4	786	4.50

TABLE 6

The Ageing Effect (6 months) on the Crushing Strength, Disintegration and Dissolution Time of Potassium Phenethicillin Tablets Prepared from Direct Granulation Using Stearic Acid as a Granulating Agent (Formulation containing 20% MCC, compressed at 164 MNm^{-2})

Stearic Acid %	Initial	20°C	30°C	37°C
	Crushing Strength (Kp)			
5.0	11.0	10.9	11.7	11.2
7.5	12.7	12.3	9.8	12.6
10.0	11.5	11.2	11.4	12.4
	Disintegration Time (Min)			
5.0	4.42	3.68	3.38	3.56
7.5	4.39	3.17	3.24	3.12
10.0	9.22	8.14	8.59	9.53
	Dissolution Time, $t_{90\%}$ (Min)			
7.5	10.23	10.15	10.98	9.90

crushing strength of tablets prepared by the DG process containing 5 and 7.5% stearic acid and 20% MCC are similar to that of the direct compression formulation without stearic acid but containing 20% MCC and magnesium stearate at 1, 1.5 and 2.0% levels (Tables 3 and 5). The disintegration time of the direct compression formulation is only marginally shorter but the ejection forces are higher. The crushing strength of the direct compression formulation was only slightly reduced at higher magnesium stearate concentrations (Table 5). The results presented in Tables 3 and 5 therefore show that although stearic acid assists the formation of granules which flow better, it does not increase the compressibility of the formulation containing 20% MCC. However, as with paracetamol[4], rapidly disintegrating and dissolving tablets containing stearic acid

were produced and their properties were unaffected by storage at elevated temperatures for 6 months (Table 6).

Table 1 shows the results of the tableting properties of potassium phenethicillin tablets containing 2.5, 5.0 and 7.5% PEG 6000. The crushing strength, at higher pressures, of the tablets containing PEG 6000 is slightly lower than that of tablets containing stearic acid, although stearic acid containing tablets are more porous.

The results of bulk and tapped densities of the granules prepared by incorporating PEG by the various processes indicated that all the formulations had similar bulk densities of about 0.4 g cm^{-3} and tapped densities of about 0.5 g cm^{-3}, except the direct compression mix with corresponding values of 0.28 and 0.40 g cm^{-3}.

Table 7 and Fig.3 show the results of the properties of tablets containing PEG 6000 incorporated using the various processes. The crushing strengths, porosities and disintegration times are similar and appear to be unaffected by the method of addition or activation of the granulating agent used. However, wet granulation using methylene chloride does produce the hardest tablets even at low compaction pressures. An examination of the properties of the control formulation C reveals that the presence of 7.5% PEG 6000 has little or no effect on tablet strength.

In fact these results, when compared with those of tablets containing stearic acid, show that the granulating agent is relatively ineffective in improving the tableting properties of potassium phenethicillin. The dissolution data on tablets containing PEG 6000 incorporated by the various methods show that the dissolution time ($t_{90\%}$) of tablets prepared by the direct granulation method was the slowest of all the tablets and dissolution of the control tablets was the fastest. The reduction in dissolution is probably caused by high local concentrations of PEG around the phenethicillin particles inhibiting phenethicillin dissolution into water, by the formation of viscous layers. As

TABLE 7

The Properties of Potassium Phenethicillin Tablets Prepared by Various Methods Using PEG 6000 as a Granulating Agent. Bi) Direct Granulation, Bii) Single Slugging (slugging pressure at 98 MNm^{-2}), Bv) Direct Compression, Biii) Wet Granulation (using water), Biv) Wet Granulation (using methylene chloride). C) Granulated with Water without PEG 6000

Formulation	Compression Pressure (MNM^{-2})	Tablet Weight mg (mean S.D.)	C.V. %	Crushing Strength (Kp)	Relative Density	Porosity %	Disinteg-ration Time (Min)	Dissolution Time (Min) $t_{50\%}$	Dissolution Time (Min) $t_{90\%}$
Bi	82	159 ± 1.0	0.63	8.8	0.8320	16.8	4.46	9.34	22.34
	163	159 ± 1.2	0.80	12.7	0.9050	9.7	4.85	10.22	25.78
	327	159 ± 1.4	0.91	11.1	0.9391	6.09	4.77	11.00	30.23
	490	157 ± 1.4	0.89	8.9	0.9376	6.24	5.43	10.14	26.22
Bii	82	154 ± 3.1	2.06	3.0	0.8016	19.84	3.24	4.69	10.53
	163	162 ± 1.7	1.08	8.5	0.8838	11.62	3.24	5.69	12.89
	327	162 ± 2.3	1.41	11.0	0.9235	7.65	3.71	5.79	14.01
	490	162 ± 2.5	1.59	11.5	0.9468	5.32	3.37	5.19	12.18
Bv	82	152 ± 1.3	0.91	5.5	0.7640	23.60	3.13	3.89	8.45
	163	152 ± 1.2	0.80	11.2	0.8675	13.25	3.18	4.04	8.71
	327	154 ± 2.2	1.47	9.1	0.9150	8.50	2.76	3.74	8.03
	490	156 ± 1.6	1.08	8.8	0.9412	5.88	3.03	4.40	9.83
Biii	82	158 ± 1.8	1.18	7.5	0.8505	14.95	3.48	6.60	10.95
	163	155 ± 1.9	1.25	10.9	0.9164	8.36	3.42	6.43	15.08
	327	154 ± 3.3	2.17	11.2	0.9391	6.09	3.43	5.96	14.59
	490	154 ± 3.5	2.27	10.8	0.9497	5.03	3.45	6.23	14.46
Biv	82	161 ± 5.2	3.25	11.2	0.8441	15.59	3.24	4.53	9.90
	163	162 ± 3.8	2.39	14.8	0.9107	8.93	3.35	4.60	10.19
	327	162 ± 2.8	1.74	12.4	0.9461	5.39	3.18	4.71	10.13
	490	154 ± 1.9	1.28	13.8	0.9412	5.88	2.92	4.40	10.10
C	82	152 ± 1.7	1.11	5.6	0.8228	17.72	2.71	3.66	7.65
	163	153 ± 3.0	1.97	9.3	0.8824	11.76	2.75	3.83	8.63
	327	150 ± 2.4	1.16	12.5	0.9305	6.95	2.37	4.09	8.66
	490	153 ± 2.0	1.33	11.2	0.9490	5.10	2.59	3.95	8.24

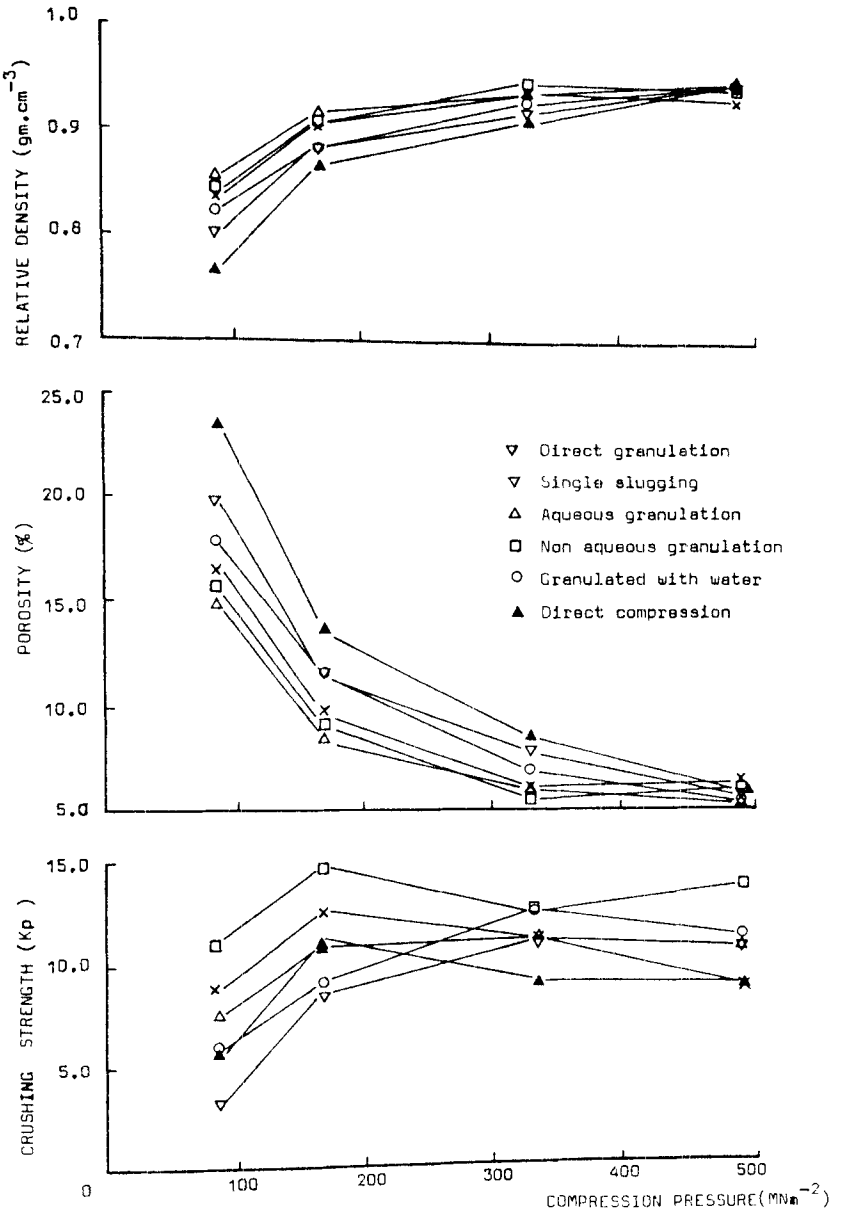

Figure 3: Effect of Compression Pressure on the Properties Potassium Phenethicillin Tablets Prepared by Various Methods

has been found previously[4], a porous honeycomb structure is required for dissolution to proceed speedily. The formation of viscous layers around the dry particles effectively seals the pores within the dissolving tablet and so dissolution can only proceed by a slow leaching process through these static layers of PEG of high viscosity. Table 7 shows that direct compression tablets had the fastest dissolution of all the formulations containing PEG 6000. Direct compression produces tablets of the highest porosity (Table 7) and thus dissolution can proceed at a fast rate by virtue of the high internal surface area of the tablets and the absence of the drug particles being completely surrounded by PEG solution. The dissolution time of tablets prepared by using PEG 6000 dissolved in methylene chloride (Biv) as the granulating agent was shorter than those tablets prepared using PEG dissolved in water (Biii). The faster dissolution of the former was mainly due to the relative insolubility of the drug in methylene chloride which produced a more porous granule as shown by the lower tapped density of these granules (Table 7) as compared to those prepared using water.

CONCLUSIONS

Potassium phenethicillin tablets have been prepared by direct granulation (DG) using stearic acid and polyethylene glycol 6000 (PEG 6000) as binders. Increasing the stearic acid concentration from 2.5 to 7.5% w/w increased tablet porosity, bulk and tapped densities and reduced granule friability. Inclusion of microcrystalline cellulose improved the crushing strength of the tablets and at the same time tablet ejection force was slightly reduced. Disintegration times of the tablets were, however, somewhat longer. Tablets prepared by direct granulation were compared with similar tablets produced by direct compression containing 20% w/w microcrystalline cellulose and up to 2% w/w magnesium stearate. Shorter disintegration times for the direct compression tablets were found (around 4 minutes) in comparison with about 7 minutes for the DG tablets.

Good tablet crushing strengths (between 7 and 15 Kp) could be achieved for both methods of tablet preparation. Ejection forces for the direct compression tablets were about 3 times greater than for the stearic acid containing tablets.

Tablets produced by direct granulation were stored for 6 months at 20, 30 and 37°C. Ageing did not affect the tablets and good dissolution rates could still be achieved of a $t_{90\%}$ of under 10 minutes after 6 months storage. Thus direct granulation, although producing tablets with slightly longer disintegration times than tablets produced by direct compression, still produces tablets with rapid disintegration times and good dissolution rates.

Tablets produced by direct granulation using PEG 6000 had crushing strengths lower than similar tablets prepared containing stearic acid. Tablets containing PEG 6000 were also prepared by (a) wet granulation using water as the granulating agent, (b) wet granulation using methylene chloride as granulating agent, (c) slugging, and (d) direct compression.

The results indicated that with the exception of direct compression, bulk and tapped densities of the granules and crushing strengths, porosities and disintegration times of the tablets were all similar and appeared to be unaffected by the method of addition or activation of the granulating agent. However dissolution rates of the tablets were significantly different. Direct compression produced the fastest dissolution of all the formulations ($t_{90\%}$ of 8-9 minutes), whilst direct granulation exhibited the slowest ($t_{90\%}$ of 22-30 minutes). The dissolution rates ($t_{90\%}$ of 9.9 - 10.2 minutes) of tablets prepared by using methylene chloride as granulating agent were faster than those tablets prepared using water ($t_{90\%}$ of 10.9 - 15.1 minutes).

In conclusion the study has shown that tablets of potassium phenethicillin can be produced with acceptable physical characteristics by direct granulation with stearic acid. Disintegration, although rapid, was not as good as has been found

previously with tablets produced similarly containing paracetamol. Microcrystalline cellulose was found to be necessary in the formulation so as to improve tablet hardness and reduce tablet friability. Polyethylene glycol 6000 was shown not to be a satisfactory dry binder for use in the direct granulation method for tableting potassium phenethicillin.

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