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FORMULATION AND EVALUATION OF PARACETAMOL 500 mg TABLETS PRODUCED BY A NEW DIRECT GRANULATION METHOD

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Currently there are three general methods available for producing tablets. These methods are (a) direct compression, (b) double compression or slugging, and (c) wet granulation. The simplest method is direct compression, since the drug need only be mixed with a suitable free flowing excipient and compressed directly into tablets. The process has obvious advantages since the use of a binding agent is avoided and no drying at all is required. As a result it can be used to tablet hydrolysable and thermolabile drugs. Even though it does have many advantages, it also has limitations concerning capacity, colouration and segregation[1]. Perhaps the most serious disadvantage is the segregation of components during handling. Double compression, however, enables the drug and excipients to be fixed in relation to each other and no segregation results. As with direct compression, this method is also useful for hydrolysable and thermolabile drugs. A high capital investment is however necessary to purchase heavy duty tabletting or roller compaction machines and the process is lengthy and outputs slow. The most

commonly used method is wet granulation, because it can be applied to a wide range of materials. The method often aids compression, produces granules usually of good flowability, and prevents segregation of the components making up the formulation. Although in common use, wet granulation suffers from a number of shortcomings since the method is time consuming, labour intensive, and complicated. At least six stages are involved in the process: (1) dry mixing, (2) wet massing, (3) wet screening, (4) drying, (5) dry screening, and (6) dry blending, and in addition the method is not suitable for hydrolysable drugs, such as many antibiotics.

This study aims at evaluating a novel direct granulation method which combines the benefits of direct compression, namely high throughputs and ease of processing, with the advantages of no segregation and improved compression obtained with wet granulation. The principle of the direct granulation method 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 resultant granules fed directly to the tablet compressor. 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. An initial study was conducted[2] using polyethylene glycol as the binding agent. The *in vitro* properties of phenylbutazone 100 mg tablets produced using the method, indicated that the granules were comparable with granules produced by conventional wet granulation. The tablets exhibited short disintegration times and fast dissolution rates. Subsequently Shah et al[3] satisfactorily made tablets from six different drug formulations using a modified method in which polyethylene glycol 6000 was melted by means of hot air. This work evaluates stearic acid as a dry binder for the production of paracetamol 500 mg tablets.

MATERIALS

Paracetamol (Evans Medical Ltd., Liverpool). Stearic acid, starch, sodium lauryl sulphate and calcium hydrogen phosphate anhydrate (British Drug Houses, Poole). Fumed silica (Cab-O-Sil, Cabot Corporation, U.S.A.). Sodium starch glycollate (Explotab, K & K Greeff Fine Chemicals Ltd., Croydon). Microcrystalline cellulose (Avicel PH102, Honeywell & Stein Ltd., Surrey).

METHODS

Granules of paracetamol were prepared containing paracetamol, stearic acid as binding agent, starch or sodium starch glycollate as disintegrant, sodium lauryl sulphate as a wetting agent, calcium hydrogen phosphate or microcrystalline cellulose as diluents and fumed silica as a glidant.

Apparatus

A Kenwood electronic blender 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 60°C and the stearic acid melted. The motor was left rotating for a further 10 minutes, enabling the stearic acid 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. To improve flowability, fumed silica was added to the granules, but

no further lubricant was added since the granules were effectively self-lubricating. Compression of the granules was effected on a Manesty F3 instrumented machine between ½" punches at 47, 102 and 215 MNm^{-2}.

Weight Variation

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

Crushing Strength

A Schleuniger hardness tester was used to determine the average hardness from 10 tablets from each batch.

Friability

Tablet friability was determined using a Roche Friabilator. About 10g of tablets were accurately weighed, placed in the friabulator and rotated 100 times. The percentage weight lost was determined.

Disintegration Test

Disintegration time was measured by the B.P. method. The mean of 10 determinations was recorded.

Dissolution Rate

The U.S.P. apparatus was utilised; the basket rotating at 100 r.p.m. The content of paracetamol in solution was measured at 242 nm and the time taken for 50% ($t_{50\%}$) and 90% ($t_{90\%}$) of paracetamol to achieve solution calculated.

Storage

Tablets were stored at varying temperatures and humidities for 15 months. Small quantities of tablets were kept in air tight bottles and stored at temperatures of 25°C, 35°C and 45°C in incubators. Tablets were also stored in containers maintained at 25°C and 43%, 25°C and 80%, 35°C and 43%, and 35°C and 80%

relative humidity. A saturated solution of ammonium sulphate was used to produce 80% relative humidity and a saturated solution of potassium carbonate to produce 43% relative humidity.

RESULTS AND DISCUSSION

The in vitro properties of tablets prepared with varying amounts of sodium lauryl sulphate are shown in Table 1. The sodium lauryl sulphate was distributed (a) intragranularly, (b) half intra and half extragranularly, (c) extragranularly. Increasing the amount of sodium lauryl sulphate reduced the disintegration time of the tablets and correspondingly increased tablet dissolution rates. It can be seen from Table 1 that the optimum concentration of sodium lauryl sulphate was found to be 0.1% distributed extragranularly.

Further batches of tablets were produced, but with varying amounts of maize starch distributed intragranularly, half intragranularly and half-extragranularly, and extragranularly. In all these batches, sodium lauryl sulphate was incorporated extragranularly at a concentration of 0.1%. Table 2 depicts the results obtained.

As starch concentration increased, tablet hardness slightly decreased. This is in agreement with the work of Sakr et al[4] Disintegration time greatly decreased and dissolution rate increased as the starch content increased over the range 5-10%. The best formulation was found to contain 10% starch distributed extragranularly which had a $t_{90\%}$ of 5 minutes.

By preliminary experimentation it was found that granules produced by the direct granulation method required the inclusion of a glidant to improve granule flow. Fumed silica was therefore incorporated extragranularly in varying proportions and, for each batch, tablet coefficient of weight variation was evaluated.

From Table 3 it can be seen that the minimum quantity of fumed silica required was 0.5%; below this concentration, tablet weight variation increased.

TABLE 1

The Effect of Sodium Lauryl Sulphate on the Properties of Paracetamol Tablets

Sodium lauryl sulphate %	Tablet Weight mg (mean ± S.D.)	C.V. %	Hardness s.c.u.	Disintegration time (min)	Dissolution Rate (min)	
					$T_{50\%}$	$T_{90\%}$
0	640.69 ± 2.38	0.372	11.4	> 30	Nothing released after 1 hr	
0.05[a]	654.73 ± 4.95	0.756	15.3	4.58	120	> 3 hr
0.1[a]	636.20 ± 6.53	1.027	11.1	0.65	8.83	120
0.1[b]	664.81 ± 3.59	0.540	11.5	1.02	5.00	13.50
0.1[c]	663.58 ± 2.69	0.391	11.3	0.48	1.50	5.00
0.2[c]	665.13 ± 2.95	0.444	12.7	0.58	1.50	5.00

a = intragranulation., b = half intra and half extragranulation., c = extragranulation., s.c.u. = strong cobb units., S.D. = standard deviation., C.V. = coefficient variation

TABLE 2

The Effect of Maize Starch on the Properties of Paracetamol Tablets

Starch %	Tablet Weight mg (mean ± S.D.)	C.V. %	Hardness s.c.u.	Disintegration time (min)	Dissolution Rate (min)	
					$T_{50\%}$	$T_{90\%}$
5	647.95 ± 3.58	0.553	14.9	5.20	9.23	32.00
7.5	654.27 ± 3.47	0.531	14.0	1.62	4.00	20.00
10[a]	663.78 ± 2.69	0.391	11.3	0.48	2.00	15.00
10[b]	663.78 ± 3.05	0.461	.11.0	0.43	2.00	8.50
10[c]	668.29 ± 2.91	0.435	11.1	0.38	0.75	5.00

a = intragranulation., b = half intra and half extragranulation., c = extragranulation., s.c.u. = strong cobb units., S.D. = standard deviation., C.V. = coefficient variation

TABLE 3

The Effect of Cab-O-Sil on the Weight Variation of Paracetamol Tablets

Cab-O-Sil %	Tablet Weight mg (mean ± S.D.)	C.V. %
0.4	663.75 ± 2.93	0.442
0.5	663.68 ± 2.69	0.391
0.6	661.32 ± 2.74	0.413
0.8	660.18 ± 2.79	0.424
1.0	644.61 ± 2.94	0.450

S.D. = standard deviation., C.V. = coefficient variation

Although at this stage calcium hydrogen phosphate had been used as the sole diluent, the effect of incorporating an alternative diluent, namely microcrystalline cellulose, was investigated Granules and tablets were produced containing either 30 mg/tablet calcium hydrogen phosphate or 30 mg/tablet microcrystalline cellulose. The results (Table 4) showed that the formulation containing microcrystalline cellulose produced tablets with improved uniformity of weight variation. Dissolution rates and disintegration time, however, were comparable. In order to assess the effect of sodium starch glycollate, which was considered a superior disintegrant to starch, granules and tablets of paracetamol made by the direct granulation method and containing either starch 67 mg/tablet or sodium starch glycollate 67 mg/tablet were compared. It was found initially that formulations containing sodium

TABLE 4

The Properties of Paracetamol Tablets Containing Microcrystalline Cellulose and Calcium Monohydrogen Phosphate

Formula	Tablet Weight mg (mean ± S.D.)	C.V. %	Hardness s.c.u.	Disintegration time (min)	Dissolution Rate (min)	
					$T_{50\%}$	$T_{90\%}$
Avicel and Explotab	605.69 ± 5.95	0.983	10.3	0.57	0.75	1.92
Calcium phosphate and Explotab	667.58 ± 6.66	0.998	12.0	0.78	1.50	4.42
Calcium phosphate and 10% starch ext.	668.29 ± 2.91	0.435	11.0	0.38	0.75	5.00
Avicel and 10% starch ext.	669.56 ± 2.37	0.354	13.2	0.38	0.75	4.00

s.c.u. = strong cobb units., S.D. = standard deviation., C.V. = coefficient variation

starch glycollate did not require the inclusion of sodium lauryl sulphate as a wetting agent, unlike the starch formulations. This was considered to be due to the large water sorption properties of sodium starch glycollate. It was found that, in all cases, tablets containing microcrystalline cellulose with either starch or sodium starch glycollate, produced tablets with similar superior properties to tablets produced using calcium hydrogen phosphate as the diluent. Therefore a study was conducted with tablets containing either (a) starch or (b) sodium starch glycollate as disintegrant and microcrystalline cellulose as diluent.

The results from both formulations are shown in Table 5 together with results obtained with a proprietary paracetamol tablet. An increase in compaction pressure for both formulations resulted in a reduction in tablet weight variation, probably due to increased vibration of the tabletting machine at higher compaction pressures. It can also be seen that an increase in compaction pressure also resulted in marked increases in tablet hardnesses and decreased friabilities. Similar findings for wet granulated tablets have been found by Higuchi et al, 1953. Unusually, however, paracetamol tablets produced by the direct granulation method exhibited no change in disintegration time as compression pressure increased. Disintegration times for both formulations remained good at under 1 minute. Similarly, dissolution rate changes at all pressures were insignificant. The $t_{90\%}$ of sodium starch glycollate-paracetamol tablets and starch-paracetamol tablets were all less than or about 8 minutes, which compared very favourably with commercial paracetamol tablets made by wet granulation of about 13.5 minutes.

The effect of storage at different temperatures and humidities on the properties of tablets produced by the new direct granulation method and a proprietary product P are shown in Table 6.

After 15 months storage at 25°C and 35°C the sodium starch glycollate-paracetamol tablets, the starch-paracetamol tablets, and the proprietary tablets showed little change in hardness,

TABLE 5

The Properties of Paracetamol Tablets Produced by New Direct Granulation Method

Formula	Compression Pressure MNm^{-}	Tablet Weight mg (mean ± S.D.)	C.V. %	Hardness s.c.u.	Friability %	Disintegration time (min)	Dissolution Rate (min) $T_{50\%}$	Dissolution Rate (min) $T_{90\%}$
Paracetamol Tablets containing Explotab	47	625.95 ± 2.71	0.432	6.5	5.07	0.40	0.75	2.35
	102	626.38 ± 2.59	0.414	12.4	2.29	0.40	0.90	3.20
	215	636.99 ± 1.84	0.290	23.0	1.48	0.88	1.05	4.15
Proprietary P	-	593.32 ± 6.49	1.121	12.5	0.79	1.48	2.30	13.80
Paracetamol Tablets containing Starch and Sodium Lauryl Sulphate	47	662.70 ± 3.56	0.538	8.4	4.66	0.47	0.80	7.68
	102	661.75 ± 3.23	0.488	14.0	2.71	0.43	1.05	8.30
	215	636.99 ± 1.84	0.290	20.2	1.80	0.42	1.17	7.85

s.c.u = strong cobb units., S.D. = standard deviation., C.V. = coefficient variation

TABLE 6a

The Effect of Temperature and Relative Humidity on the Hardness (s.c.u.) of Explotab-Paracetamol Tablets

Compression Pressure MNm^{-2}	Ageing Time (days)	25°C RH 43%	25°C RH 80%	35°C RH 43%	35°C RH 80%	25°C	35°C	45°C
	15	6.8	6.6	7.7	7.5	7.6	7.9	10.9
	30	6.6	6.3	7.9	7.2	7.2	8.2	9.4
47 a	60	6.9	6.8	8.2	9.2	6.6	8.1	9.3
	210	7.8	7.4	8.7	10.0	7.4	8.5	9.8
	450	8.3	8.8	9.9	12.6	7.3	9.9	9.9
	15	13.6	12.9	14.7	14.3	14.1	15.2	18.4
	30	13.5	12.1	15.5	14.1	13.9	14.7	16.2
102 b	60	12.9	12.4	14.2	15.9	13.3	15.8	16.4
	210	13.1	13.1	15.9	16.7	13.5	15.3	15.8
	450	15.2	16.2	16.8	18.9	14.0	17.0	16.3
	15	23.2	23.1	24.2	24.2	23.6	24.6	24.9
	30	22.5	21.3	23.6	23.1	23.6	23.1	23.7
215 c	60	21.6	21.6	23.4	23.6	22.6	24.1	23.5
	210	21.3	21.8	22.7	22.6	22.9	23.5	23.1
	450	22.6	22.4	24.9	26.7	25.8	25.1	25.7

a = 6.5 s.c.u., b = 12.4 s.c.u. and c = 23.0 s.c.u. at the time of preparation.
s.c.u. = strong cobb units.

TABLE 6b

The Effect of Temperature and Relative Humidity on the Hardness (s.c.u.) of Starch-Paracetamol Tablets and the Proprietary P

Compression Pressure MNm^{-2}	Ageing Time (days)	25°C		35°C		25°C	35°C	45°C
		RH 43%	RH 80%	RH 43%	RH 80%			
	15	8.8	7.6	9.8	10.7	8.9	9.9	14.4
	30	7.9	7.0	10.0	10.0	9.1	10.2	12.8
47 a	60	8.1	7.0	11.0	9.9	8.4	10.2	14.3
	210	8.7	8.4	11.4	10.9	8.4	10.3	14.4
	450	9.8	10.0	12.2	11.8	9.2	11.7	14.9
	15	14.6	13.1	15.9	16.3	14.7	15.8	20.7
	30	14.5	11.7	16.6	14.5	14.8	16.0	19.5
102 b	60	13.9	13.2	16.5	15.8	14.2	16.6	20.8
	210	15.0	13.3	17.5	17.1	14.3	16.3	18.9
	450	16.4	15.9	18.3	16.9	15.9	18.8	20.4
	15	20.7	19.1	21.7	20.9	22.1	22.4	24.5
	30	20.0	19.7	22.1	21.5	21.1	21.4	23.6
215 c	60	19.7	18.4	21.3	20.5	20.9	21.5	24.8
	210	20.6	18.6	21.6	20.8	20.3	22.2	23.5
	450	21.4	20.6	23.4	22.1	21.3	23.4	24.2
	15	12.9	11.7	12.2	12.6	12.2	12.4	12.6
	30	12.5	11.5	11.9	12.1	12.2	11.5	11.5
Proprietary P	60	12.2	11.5	12.1	12.2	12.2	12.6	12.1
d	210	12.4	12.0	12.8	12.8	11.9	10.1	11.6
	450	14.0	13.8	13.3	12.6	12.5	13.2	12.6

a = 8.4 s.c.u., b = 14.0 s.c.u., c = 20.2 s.c.u. at the time of preparation, d = 12.5 at the time of purchase

TABLE 6c

The Effect of Temperature and Relative Humidity on the Disintegration Time (min) of the Explotab-Paracetamol Tablets

Compression Pressure MNm^{-2}		Ageing Time (days)	25°C		35°C		25°C	35°C	45°C
			RH 43%	RH 80%	RH 43%	RH 80%			
47	a	15	0.42	0.43	0.42	0.43	0.42	0.47	1.13
		30	0.37	0.35	0.45	0.45	0.38	0.55	0.83
		60	0.45	0.40	0.57	0.65	0.38	0.48	1.15
		210	0.42	0.45	0.60	0.83	0.40	0.57	1.13
		450	0.48	0.63	0.52	0.72	0.47	0.73	3.00
102	b	15	0.47	0.45	1.22	1.02	0.52	1.15	3.58
		30	0.48	0.52	1.30	1.27	0.55	1.45	4.48
		60	0.65	0.68	0.65	0.72	0.60	1.45	4.50
		210	0.82	0.92	1.88	1.67	0.62	1.48	3.05
		450	1.10	1.75	2.05	4.07	0.93	2.05	7.40
215	c	15	1.13	1.28	5.82	12.02	1.67	6.13	17.78
		30	2.10	1.98	7.33	10.02	2.27	8.25	20.23
		60	3.27	2.25	9.58	13.95	2.45	9.97	21.62
		210	4.15	4.05	12.75	19.80	3.68	10.45	33.00
		450	7.18	9.75	16.92	30.73	5.47	15.65	42.88

a = 0.40 min., b = 0.40 min., c = 0.88 min at the time of preparation

TABLE 6d

The Effect of Temperature and Relative Humidity on the Disintegration Time (min) of Starch-Paracetamol Tablets and Proprietary P

Compression Pressure MNm^{-2}	Ageing Time (days)	25°C RH 43%	25°C RH 80%	35°C RH 43%	35°C RH 80%	25°C	35°C	45°C
	15	0.50	0.48	0.53	0.62	0.43	0.47	1.37
	30	0.47	0.50	0.75	1.07	0.52	0.47	1.75
47 a	60	0.50	0.52	0.67	0.75	0.43	0.53	1.30
	210	0.47	0.63	0.78	0.97	0.48	0.50	2.67
	450	0.42	0.70	1.32	1.53	0.43	0.50	1.32
	15	0.43	0.52	0.78	1.22	0.45	0.65	2.63
	30	0.45	0.48	0.63	1.77	0.48	0.60	3.05
102 b	60	0.48	0.62	0.90	1.72	0.32	0.57	3.72
	210	0.46	0.63	0.78	0.97	0.48	0.83	2.67
	450	0.28	1.17	3.55	2.57	0.38	0.75	6.22
	15	0.47	0.60	0.77	2.22	0.45	0.72	2.50
	30	0.48	0.67	0.72	2.82	0.50	0.60	0.68
215 c	60	0.62	0.88	0.85	0.55	0.45	0.68	2.93
	210	0.50	3.07	2.68	3.38	0.55	0.90	5.60
	450	0.63	1.50	8.75	13.48	0.57	1.30	40.39
	15	2.57	1.00	1.52	2.68	1.78	1.22	2.33
	30	1.52	4.12	3.27	1.53	4.93	1.58	2.62
Proprietary P	60	2.42	7.52	4.73	1.25	1.18	1.67	2.50
	210	2.22	7.00	4.57	1.18	4.03	7.35	3.28
	450	3.22	2.12	3.10	3.08	1.98	6.57	5.83

a = 0.47 min., b = 0.43 min., c = 0.88 min at the time of preparation, P = 1.47 min at the time of purchase

TABLE 6e

The Effect of Temperature and Relative Humidity on the Dissolution Rate, $T_{50\%}$ (min) of the Explotab-Paracetamol Tablets

Compression Pressure MNm^{-2}		Ageing Time (days)	25°C RH 43%	25°C RH 80%	35°C RH 43%	35°C RH 80%	25°C	35°C	45°C
47	a	15	0.62	0.97	0.83	0.83	0.67	0.97	0.90
		30	0.75	1.00	0.97	0.97	0.83	1.13	0.97
		60	0.77	0.75	0.83	0.83	0.83	0.82	0.78
		210	0.77	0.77	0.75	0.72	0.75	0.75	0.97
102	b	15	0.67	0.83	0.83	0.83	0.78	1.00	1.93
		30	1.17	0.85	1.08	1.05	0.80	1.13	2.07
		60	0.98	0.98	0.77	0.83	0.83	0.90	1.70
		210	0.83	0.75	0.75	1.00	0.78	0.93	2.05
		450	0.98	0.85	1.97	1.98	0.80	1.00	2.63
215	c	15	0.80	1.08	2.17	2.63	0.75	2.83	1.93
		30	1.83	1.42	3.80	5.97	1.25	3.87	2.07
		60	1.40	2.05	3.80	8.85	1.95	5.50	11.90
		210	1.05	3.20	4.20	8.12	2.00	5.00	13.00

a = 0.75 min., b = 0.90 min., c = 1.05 min at the time of preparation

TABLE 6f

The Effect of Temperature and Relative Humidity on the Dissolution Rate, $T_{90\%}$ (m-n) of the Explotab-Paracetamol Tablets

Compression Pressure MNm^{-}		Ageing Time (days)	25°C		35°C		25°C	35°C	45°C
			RH 43%	RH 80%	RH 43%	RH 80%			
47	a	15	2.40	2.95	2.75	2.55	2.25	3.05	3.00
		30	2.75	3.40	4.75	3.00	2.40	5.90	3.15
		60	3.10	2.20	2.90	2.80	2.70	3.05	2.50
		210	2.90	2.50	2.85	2.55	2.40	2.65	5.75
102	b	15	2.70	2.85	2.85	2.70	2.50	3.55	5.25
		30	5.25	3.10	3.80	2.65	3.10	4.65	7.35
		60	2.85	4.25	2.60	3.00	3.35	3.15	5.50
		210	3.25	2.85	2.85	3.90	2.75	3.55	6.25
		450	4.62	3.25	6.33	6.00	2.75	4.67	6.00
215	c	15	3.10	3.50	7.65	5.10	2.85	10.45	17.50
		30	4.80	3.90	12.50	10.15	3.60	11.00	19.75
		60	4.00	5.20	9.55	19.05	4.00	12.00	26.75
		210	3.30	5.10	12.20	18.65	4.75	12.00	30.50

a = 2.35 min., b = 3.20 min., c = 4.15 min at the time of preparation

TABLE 6g

The Effect of Temperature and Relative Humidity on the Dissolution Rate, $t_{50\%}$ (min) of the Starch-Paracetamol Tablets and the Proprietary P

Compression Pressure MNm^{-2}	Ageing Time (days)	25°C RH 43%	25°C RH 80%	35°C RH 43%	35°C RH 80%	25°C	35°C	45°C
47 a	15	0.82	0.77	3.80	1.95	0.95	1.70	8.92
	30	0.70	0.72	3.72	4.00	0.80	1.75	5.83
	60	1.30	0.77	3.40	3.50	1.20	3.40	10.15
	210	1.00	0.77	4.65	3.00	1.00	2.85	9.70
102 b	15	1.17	0.83	2.43	3.38	0.83	1.77	9.17
	30	0.87	1.87	1.98	6.72	1.33	1.73	9.70
	60	0.75	0.80	2.67	10.75	0.80	7.15	10.50
	210	0.95	0.30	9.75	6.25	0.95	2.25	14.00
	450	2.58	3.75	4.17	30.00	1.67	8.67	30.00
215 c	15	1.33	1.47	1.50	10.17	1.13	1.33	8.17
	30	0.70	1.50	1.33	11.00	1.27	1.17	8.83
	60	1.20	1.35	2.50	12.85	1.00	2.50	6.50
	210	1.33	2.50	14.00	17.05	1.20	1.85	14.05
Proprietary P d	15	2.50	2.40	4.45	1.63	3.30	2.22	2.50
	30	2.13	2.27	2.13	1.63	2.60	2.47	3.35
	60	3.60	3.05	3.10	2.40	4.65	4.15	6.00
	210	4.75	1.70	6.45	2.00	3.08	6.60	10.40
	450	7.58	2.03	16.83	4.25	17.33	8.95	12.33

a = 0.80 min., b = 1.05 min., c = 1.17 min at the time of preparation, d = 2.30 at the time of purchase

TABLE 6h

The Effect of Temperature and Relative Humidity on the Dissolution Rate, $t_{90\%}$ (min) of the Starch-Paracetamol Tablets and the Proprietary P

Compression Pressure MNm^{-2}	Ageing Time (days)	25°C RH 43%	25°C RH 80%	35°C RH 43%	35°C RH 80%	25°C	35°C	45°C
47 a	15	3.20	4.00	23.00	11.00	14.00	8.90	55.50
	30	4.85	3.25	19.50	12.00	6.75	17.50	27.50
	60	4.45	5.00	59.00	20.50	5.00	27.80	52.75
	210	9.15	5.00	42.50	20.00	6.75	20.00	63.00
102 b	15	9.35	3.95	9.10	11.93	8.75	10.18	79.50
	30	4.65	8.75	12.90	41.75	4.20	11.47	35.50
	60	3.25	4.75	14.25	47.00	4.15	54.00	85.00
	210	9.35	11.25	88.75	55.00	5.85	17.00	> 120
	450	22.00	17.00	> 120	> 120	56.00	48.00	> 120
215 c	15	11.00	7.90	13.75	88.00	7.35	8.50	49.00
	30	2.85	10.75	8.60	43.25	4.75	9.25	33.00
	60	7.00	7.50	20.25	59.00	8.00	11.50	100.00
	210	13.75	120.00	> 120	> 120	6.30	21.25	42.30
Proprietary P d	15	12.75	10.13	14.45	9.55	14.75	7.85	15.50
	30	10.50	12.30	12.00	8.40	14.75	10.35	13.10
	60	21.85	12.45	18.85	10.35	19.50	13.75	21.30
	210	24.50	15.50	70.00	13.15	17.65	58.50	61.00
	450	50.25	14.50	40.75	18.75	77.00	55.00	68.00

a = 7.68 min., b = 8.30 min., c = 7.85 min at the time of preparation, d = 13.80 at the time of purchase

disintegration time and dissolution rate, indicating good long term stability under these conditions. Marginally the tablets containing sodium starch glycollate were somewhat better as far as dissolution was concerned at the highest compaction pressure. At 35°C, 80% relative humidity, all the formulations exhibited poorer dissolution rates and larger disintegration times at high compaction pressures. However, dissolution and disintegration was insignificantly effected at low and medium pressures. At 45°C, a decrease in dissolution rate, an increase in hardness and longer disintegration times were found. However, tablets made containing sodium starch glycollate had a $t_{50\%}$ and $t_{90\%}$ at 47 MNm^{-2} and 102 MNm^{-2} of 0.97, 5.75 and 2.63, 6.00 mins respectively. These rates compared very favourably with the proprietary tablets which exhibited a $t_{50\%}$ and $t_{90\%}$ of 12.33 and 68.00 mins respectively.

Plates 1 and 2 show scanning electron photomicrographs of a granule of paracetamol containing sodium starch glycollate before dissolution (Plate 1) and after dissolution (Plate 2). It can be seen that the stearic acid effectively binds the powder ingredients together by adhesion at points on the powder surface, so producing a porous honeycomb structure. Dissolution then takes place efficiently from this system to ultimately yield an infrastructure composed of non-soluble powder particles (calcium monohydrogen phosphate, sodium starch glycollate, etc.) held together by stearic acid. It would seem that if the concentration of stearic acid is increased, then stearic acid will totally coat the particle surfaces, reducing the dissolution mechanism to a slow leaching process through the film of stearic acid and producing very much slower overall dissolution rates, as is found in sustained release formulations.

CONCLUSIONS

Paracetamol tablets 500 mg have been prepared by a new direct granulation method using stearic acid. The method consisted of

PLATE 1

Electron Photomicrograph of a Paracetamol Granule Before Dissolution ×500

mixing the formulation ingredients in a modified water-jacketed blender. Hot water was passed through the jacket during the mixing stage to melt the stearic acid and coat the powder particles. After a further time interval, cold water was passed through the jacket to produce granules directly in the blender. To improve the flowability of the resultant granules, fumed silica was incorporated extragranularly. Tablets were prepared from these granules and the effect of formulation on the physical and in vitro properties investigated. Long term storage at various

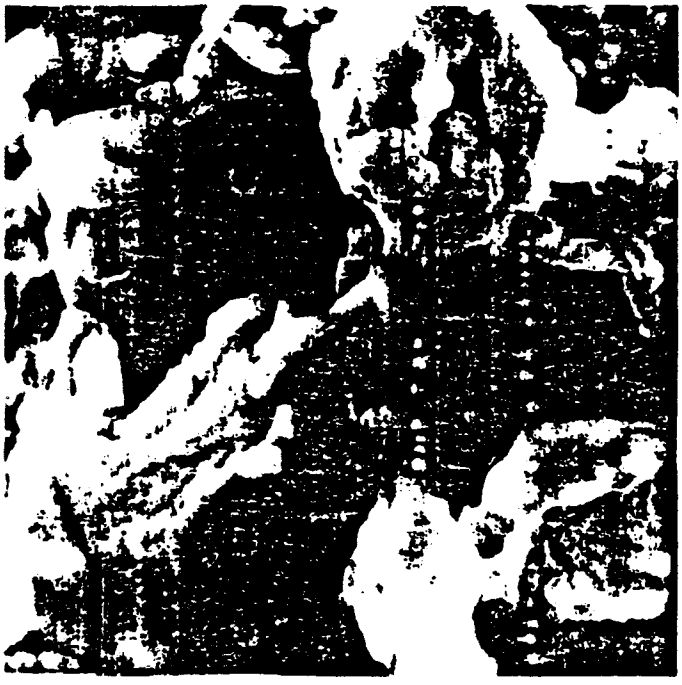

PLATE 2

Electron Photomicrograph of a Paracetamol Granule After Dissolution ×500

temperatures and humidities was also carried out. By optimising the formulation it was found that satisfactory tablets could be produced which contained either maize starch or sodium starch glycollate as disintegrant and microcrystalline cellulose as diluent. The optimal amounts of sodium lauryl sulphate (as a wetting agent) and fumed silica were found by experimentation.

Tablets produced by this method exhibited short disintegration times and rapid dissolution rates. Paracetamol tablets containing sodium starch glycollate had disintegration times of 24, 24 and 54 seconds, with hardnesses of 8.4, 14.0 and 20.2, strong

cobb units at 47, 102 and 215 MNm^{-2} respectively. The corresponding dissolution rates ($t_{50\%}$) were all less than 1 minute, with $t_{90\%}$ of about 3 minutes. Humidity had no effect on the properties of tablets containing sodium starch glycollate compressed at 47 and 102 MNm^{-2} stored for 15 months. At 215 MNm^{-2} the tablet dissolution rates decreased in a humid environment. Humidity, however, adversely affected the maize starch formulations at all compaction pressures. Storage at 45°C considerably decreased the dissolution rates of all the formulations.

In conclusion it has been found that this new direct granulation method using stearic acid produces granules and tablets of paracetamol with acceptable properties which do not diminish upon extended storage up to 35°C. The method provides a means of producing granules which combine the benefits of direct compression, namely high throughputs and ease of processing, with the advantages of improved compression and absence of segregation obtained with wet granulation.

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