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Investigations into the use of pregelatinised starch to develop powder-filled hard capsules

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Abstract

The use of pregelatinised starch in tamp filling of hard capsules with powder formulations containing a low-solubility drug (theophylline anhydrous) with very poor powder flow and stickiness to metal surfaces was investigated. Twenty-one mixtures containing the drug, pregelatinised starch, lactose monohydrate and magnesium stearate were produced, with their quantitative composition based on a central composite design. These mixtures were filled into hard capsules using an instrumented tamp-filling machine. Seven different compression settings ranging from "no" to "firm" compression were employed, and the tamping force was recorded on stations 3 and 4. It was found that the use of pregelatinised starch as an excipient in the manufacture of powder-filled hard capsules could be beneficial in terms of reducing the coefficient of fill weight variability. To improve drug dissolution of poorly soluble drugs, larger amounts of this excipient were required, and the maximum capsule fill weight that could be achieved was slightly reduced at the same time.
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Keywords: Pregelatinised starch; Powder-filled hard capsules; Theophylline anhydrous; Tamp filling

1. Introduction

The development of novel excipients for solid oral dosage forms predominantly targets direct compression of powders for tabletting. None of the excipients on the market was specifically developed for capsule filling. However, formulations used in filling of powders into hard capsules are very different from those used in tabletting, as the requirements for such formulations are unique:

(a) The flow properties should be rather average to moderately good. Very good powder flow results in underfilled capsules due to "flooding" when using the tamp-filling mechanism (Podczeck and

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Newton, 1999), or due to insufficient powder plug formation when using dosator nozzle filling machines (Jolliffe and Newton, 1982).

(b) Except for high-dose drug formulations, where a maximum of powder is forced into the capsule shells, there is no need for high compressibility and compactability of the formulations. It is advisable to densify the powder to the tapped density only to ensure good drug dissolution (Newton, 1987).

(c) Modern "super-disintegrants" usually do not work in capsule formulations. The powder plug produced is highly porous, and the super-disintegrants, which act by swelling, can expand into the pore space. Hence, there is not enough force to disrupt the powder plug. For this reason, the majority of capsule formulations currently on the market does not include a disintegrant at all (Lai et al., 1995), or the formulations include materials such as starch, which, due to capillary activity ("wicking"), draw larger amounts of water into the powder plug. The major drawback of starches, however, is that the capillary activity and the elasticity of the deformed starch particles depend on the powder being dried prior to use.

Pregelatinised starch as an excipient is more consistent in its average moisture content than unprocessed starch. It normally does not require drying to function as a disintegrant or flow agent. Despite being partially pregelatinised, the material has retained its capillary activity, plus it swells to some degree when in contact with moisture (Bolhuis and Chowhan, 1995). Pregelatinised starch also shows self-lubricating properties, which allow for a reduction in lubricant concentration in the powder mixtures. This in return will improve drug dissolution from capsule formulations. The powder is also considerably less adhesive than, for example, lactose monohydrate (Podczeck, 1999), and hence could reduce stickiness of powder mixtures to the metal parts of manufacturing machinery. However, the material is not cheap compared to ordinary maize starch, and larger quantities might be required in capsule formulation. The aim of this work was to study the potential application of pregelatinised starch in tamp filling of hard capsules with powder formulations containing a drug with fairly low-solubility (theophylline anhydrous; saturation solubility at 37 °C 10.8 ± 0.5 g/l) with very poor powder flow properties and stickiness to establish the minimum levels required for this excipient in order to function as disintegrant and flow agent. Poor powder flow and stickiness are the major factors in capsule filling, preventing direct-filling formulations from being used. Granulation, however, adds another manufacturing step, and hence to the costs of the product. Theophylline anhydrous comprising poor flow properties and stickiness is therefore an ideal choice to test pregelatinised starch as an excipient for general use in such cases.

2. Materials and methods

2.1. Materials

Pregelatinised starch (Starch 1500®, Colorcon Ltd., West Point, USA, batch 8090201, cold water solubility 19.6%), lactose monohydrate (Borculo Whey Products Ltd., Saltney, UK, batch 749035), magnesium stearate dihydrate (Colorcon Ltd., West Point, USA, batch 972065) and theophylline anhydrous (Knoll, Harlow, UK, batch 95658) were used as received.

2.2. Experimental design

A central composite design with five main and two interaction levels per factor was employed as shown in Table 1. This design would allow linear and non-linear modelling of relationships between formulation and capsule filling performance, if these exist.

2.3. Physical properties of the powders

For all powders, the particle size distribution, average particle shape, moisture content and apparent particle density were determined using standard techniques. Air jet sieving (Alpine, Augsburg, Germany) was used to determine the particle size distributions. Sieves of 32, 45 and 63 μm were used (Haver and Boecker, Westfalen, Germany) with 30 g of material for 15 min, starting with the smallest sieve. The remaining material larger than 63 μm was sieved for 10 min using a vibratory shaker (Endecotts, London, UK), fitted with sieves following a root 2 progression up to 710 μm. The results are the mean and standard deviation of three replicates. Scanning electron

Table 1
Central composite design used to study the influence of pregelatinised starch on the powder and capsule filling properties of mixtures with theophylline anhydrous

Formulation	Factor 1	Factor 2	Factor 3
	Pregelatinised starch (%) in excipient	Theophylline (%) in mixture	Magnesium stearate (%) in mixture
1 = CG	60	45.0	0.750
2	60	45.0	0.250
3	60	45.0	0.500
4	60	45.0	1.000
5	60	45.0	1.250
6	60	15.0	0.750
7	60	30.0	0.750
8	60	60.0	0.750
9	60	75.0	0.750
10	20	45.0	0.750
11	40	45.0	0.750
12	80	45.0	0.750
13	100	45.0	0.750
14 = I	30	22.5	0.375
15 = I	30	67.5	0.375
16 = I	30	22.5	1.125
17 = I	30	67.5	1.125
18 = I	90	22.5	0.375
19 = I	90	67.5	0.375
20 = I	90	22.5	1.125
21 = I	90	67.5	1.125

"Excipient": mixture of lactose and pregelatinised starch, used to bulk up the mixture; CG: centre point of the design; I: interaction terms.

microscopy (Philips SEM XL 20, Eindhoven, Netherlands and Emitech K550 gold sputter system, Ashford, UK) was used to get an overall view of particle shape and morphology. Thermogravimetric analysis (TGA 2850 Thermogravimetric Analyser, TA Instruments, Surrey, UK) was undertaken with 10–15 mg of powder (three replicate runs), depending on the density of the material. The samples were heated in an open aluminium pan at a rate of 5 °C/min from 23 °C (ambient room temperature) to 200 °C. The nitrogen flow connected to the balance-purge inlet was 40 ml/min, and 60 ml/min to the purge inlet. Air comparison pycnometry (Model 930, Beckman Scientific Instruments, Marca, Canada) was used to determine the apparent

Table 2
Physical properties of the powders

	Pregelatinised starch	Lactose monohydrate	Theophylline anhydrous	Magnesium stearate
Median particle size (μm)	51.0 ± 2.1	47.0 ± 2.0	114.0 ± 6.5	N/A
Interquartile range (μm)	80	60	235	N/A
Mode (μm)	<32	32–45	32–45	N/A
Particle shape descriptor	Angular	Angular	Needle-shaped	Flaky
Moisture content (%)	9.48 ± 0.04	5.02 ± 0.10	0.12 ± 0.00	5.22 ± 0.18
Apparent particle density (g/cm^3)	1.492 ± 0.001	1.550 ± 0.006	1.475 ± 0.005	1.143 ± 0.009

N/A: due to a size of less than 20 μm, detailed particle size analysis was not attempted. The results are the mean and standard deviation of three replicates.

Table 3
Packing and flow properties of the powder mixtures

Mixture	ρ_b (g/cm^3)	ρ_t (g/cm^3)	CI (%)	ϕ (°)	T
1	0.628 ± 0.001	0.848 ± 0.005	26.0 ± 0.5	18.2 ± 0.4	15.8 ± 0.9
2	0.584 ± 0.009	0.827 ± 0.007	29.4 ± 1.0	19.8 ± 0.5	20.2 ± 2.1
3	0.620 ± 0.010	0.842 ± 0.006	26.3 ± 1.1	18.7 ± 0.5	16.4 ± 1.6
4	0.643 ± 0.004	0.863 ± 0.004	25.5 ± 0.9	17.1 ± 0.3	15.3 ± 1.2
5	0.652 ± 0.008	0.865 ± 0.002	24.6 ± 0.8	17.0 ± 0.2	13.1 ± 1.3
6	0.657 ± 0.003	0.879 ± 0.002	25.2 ± 0.2	16.5 ± 0.1	14.3 ± 0.9
7	0.642 ± 0.003	0.864 ± 0.001	25.7 ± 0.4	17.3 ± 0.1	14.4 ± 0.7
8	0.618 ± 0.006	0.838 ± 0.006	26.3 ± 0.8	18.7 ± 0.4	14.6 ± 0.3
9	0.607 ± 0.003	0.834 ± 0.004	27.3 ± 0.5	18.7 ± 0.3	14.8 ± 2.3
10	0.624 ± 0.004	0.874 ± 0.006	28.6 ± 0.7	16.9 ± 0.4	16.3 ± 0.8
11	0.628 ± 0.008	0.860 ± 0.002	27.0 ± 1.0	17.6 ± 0.1	15.3 ± 0.9
12	0.633 ± 0.005	0.845 ± 0.003	25.0 ± 0.7	18.2 ± 0.2	14.8 ± 2.7
13	0.625 ± 0.005	0.835 ± 0.001	25.2 ± 0.6	18.7 ± 0.1	15.3 ± 0.5
14	0.638 ± 0.012	0.882 ± 0.002	27.7 ± 1.5	16.8 ± 0.1	20.7 ± 2.3
15	0.634 ± 0.009	0.851 ± 0.006	25.5 ± 1.3	17.9 ± 0.4	17.0 ± 2.0
16	0.667 ± 0.010	0.908 ± 0.004	26.5 ± 0.9	15.0 ± 0.2	15.5 ± 0.4
17	0.660 ± 0.014	0.854 ± 0.003	22.6 ± 1.5	17.6 ± 0.2	15.0 ± 0.9
18	0.636 ± 0.004	0.853 ± 0.002	25.5 ± 0.4	17.7 ± 0.2	15.1 ± 1.7
19	0.584 ± 0.004	0.812 ± 0.002	28.0 ± 0.5	20.4 ± 0.2	16.3 ± 0.3
20	0.672 ± 0.002	0.876 ± 0.005	23.2 ± 0.5	16.1 ± 0.3	12.4 ± 0.8
21	0.645 ± 0.020	0.844 ± 0.004	23.6 ± 2.2	17.8 ± 0.2	13.3 ± 0.9

ρ_b: Minimum bulk density; ρ_t: maximum ("tapped") bulk density; CI: Carr's compressibility index; ϕ: angle of internal flow; T: compaction constant.

particle density of the powders. The results are summarised in Table 2.

2.4. Powder mixing

Powder mixing was undertaken in a Y-cone blender (Erweka Apparatebau GmbH, Heusenstamm, Germany) at 43 rev/min. To determine the optimum mixing time, five samples were taken using a sampling thief (Model I, Globe Pharma, New Brunswick, NJ, USA) from various positions in the mixer after 5, 8 and subsequently every 2 min up to 40 min. The theophylline content of the samples was determined by UV spectroscopy at a wavelength of 272 nm (Model 554, Perkin Elmer, Beaconsfield, UK). The lactose content was quantified by polarimetry (B–S model, Bellingham and Stanley Ltd., London, UK; see Schweiger et al., 1997, for methodological details), and the pregelatinised starch content was assumed to form the remainder of each sample. Magnesium stearate was added only after the optimum mixing time, i.e. the smallest sample standard deviation had been reached, and the mixture was blended at 28 rev/min for a further 5 min.

Table 4
Relationships between the mixture composition and the packing and flow properties of the mixtures (linear regression; the values provided are the *normalised regression coefficients*, as these can be directly compared; the regression equations as such are of little value)

Statistical parameter	ρ_b	ρ_t	CI	ϕ	T
R^2	0.872	0.926	0.839	0.896	0.744
Overall F-test	89.61	165.38	87.15	113.37	30.46
P	0.000	0.000	0.000	0.000	0.000
RMS (%)	2.15	1.08	4.65	3.84	10.32
b_0	0.493	0.756	33.443	15.780	24.670
PGS	0.930	0.443	−0.964	0.507	−0.773
Lactose	0.708	1.029	n.s.	n.s.	−0.191
THEO	n.s.	n.s.	n.s.	0.997	n.s.
MgSt	n.s.	n.s.	n.s.	n.s.	n.s.
PGS × Lactose	n.s.	n.s.	n.s.	n.s.	−0.343
PGS × THEO	n.s.	n.s.	0.177	0.120	−0.365
PGS × MgSt	0.184	0.337	n.s.	−0.296	n.s.
Lactose × THEO	0.310	0.208	−0.249	n.s.	n.s.
Lactose × MgSt	n.s.	n.s.	n.s.	n.s.	n.s.
THEO × MgSt	0.612	0.312	−0.655	−0.388	−0.728

R^2: linear determinant; P: error probability; RMS: root mean square deviation (residual analysis); b_0: intercept; PGS: pregelatinised starch; THEO: theophylline; MgSt: magnesium stearate; n.s.: P above 0.05 (not included into equation).

Table 5
Capsule fill weight, coefficient of fill weight variability (CFV) and maximum plug density achieved at different cumulative tamping distances (CTD)

Mixture	CTD	Fill weight (mg)	CFV (%)	Plug density* (g/cm^3)
1	0	428 ± 6	1.43	0.730
	3	428 ± 6	1.29	0.735
	6	434 ± 7	1.54	0.744
	10	445 ± 5	1.12	0.761
	14	456 ± 6	1.21	0.776
	18	466 ± 5	1.09	0.790
	22	471 ± 4	0.88	0.796
2	0	418 ± 5	1.20	0.714
	3	421 ± 6	1.31	0.719
	6	426 ± 5	1.17	0.728
	10	441 ± 7	1.51	0.748
	14	457 ± 5	1.09	0.772
	18	464 ± 4	0.76	0.777
	22	468 ± 3	0.64	0.778
3	0	422 ± 5	1.07	0.723
	3	425 ± 5	1.06	0.728
	6	430 ± 5	1.05	0.735
	10	444 ± 6	1.35	0.756
	14	458 ± 6	1.33	0.776
	18	466 ± 5	1.09	0.784
	22	471 ± 4	0.88	0.789
4	0	429 ± 5	1.06	0.735
	3	429 ± 5	1.17	0.736
	6	435 ± 5	1.04	0.745
	10	452 ± 6	1.35	0.768
	14	464 ± 5	1.11	0.788
	18	471 ± 4	0.85	0.797
	22	476 ± 4	0.87	0.805
5	0	429 ± 5	1.17	0.736
	3	429 ± 5	1.06	0.737
	6	439 ± 5	1.03	0.750
	10	452 ± 6	1.22	0.771
	14	464 ± 5	1.10	0.789
	18	473 ± 4	0.75	0.799
	22	477 ± 4	0.74	0.804
6	0	431 ± 5	1.05	0.739
	3	431 ± 4	0.93	0.738
	6	438 ± 5	1.04	0.748
	10	450 ± 5	1.01	0.766
	14	457 ± 4	0.77	0.777
	18	462 ± 3	0.65	0.785
	22	464 ± 4	0.76	0.785
7	0	427 ± 5	1.06	0.731
	3	427 ± 5	1.06	0.732
	6	435 ± 5	1.17	0.743
	10	451 ± 5	1.00	0.767
	14	460 ± 4	0.77	0.779
	18	467 ± 3	0.64	0.788
	22	469 ± 4	0.75	0.791

Table 5 (*Continued*)

Mixture	CTD	Fill weight (mg)	CFV (%)	Plug density* (g/cm^3)
8	0	423 ± 6	1.31	0.723
	3	427 ± 6	1.30	0.730
	6	433 ± 6	1.39	0.739
	10	448 ± 6	1.34	0.762
	14	464 ± 7	1.44	0.782
	18	471 ± 6	1.17	0.790
	22	481 ± 6	1.27	0.800
9	0	435 ± 7	1.63	0.744
	3	434 ± 7	1.63	0.741
	6	440 ± 7	1.59	0.753
	10	454 ± 9	1.88	0.770
	14	467 ± 8	1.71	0.787
	18	483 ± 7	1.45	0.801
	22	485 ± 8	1.70	0.806
10	0	448 ± 7	1.46	0.770
	3	451 ± 7	1.57	0.774
	6	455 ± 7	1.54	0.780
	10	468 ± 8	1.72	0.797
	14	480 ± 7	1.39	0.812
	18	494 ± 8	1.52	0.828
	22	498 ± 5	1.00	0.837
11	0	434 ± 5	1.18	0.744
	3	436 ± 5	1.15	0.748
	6	441 ± 6	1.25	0.755
	10	456 ± 7	1.43	0.779
	14	468 ± 7	1.51	0.796
	18	479 ± 5	1.04	0.808
	22	485 ± 5	1.05	0.813
12	0	422 ± 5	1.07	0.725
	3	423 ± 4	0.95	0.727
	6	430 ± 4	0.93	0.738
	10	444 ± 5	1.15	0.749
	14	457 ± 5	1.10	0.777
	18	462 ± 5	0.98	0.781
	22	467 ± 5	1.02	0.789
13	0	416 ± 4	0.96	0.713
	3	419 ± 5	1.08	0.719
	6	424 ± 5	1.07	0.729
	10	441 ± 5	1.13	0.755
	14	452 ± 4	0.89	0.767
	18	457 ± 3	0.66	0.775
	22	463 ± 4	0.76	0.784
14	0	442 ± 6	1.38	0.753
	3	443 ± 5	1.15	0.754
	6	447 ± 6	1.24	0.761
	10	460 ± 6	1.20	0.780
	14	471 ± 6	1.29	0.794
	18	478 ± 5	1.05	0.804
	22	484 ± 5	0.94	0.811

Table 5 (*Continued*)

Mixture	CTD	Fill weight (mg)	CFV (%)	Plug density* (g/cm^3)
15	0	439 ± 7	1.60	0.755
	3	442 ± 7	1.48	0.752
	6	444 ± 8	1.69	0.757
	10	461 ± 9	2.00	0.777
	14	474 ± 11	2.32	0.792
	18	488 ± 6	1.30	0.806
	22	491 ± 6	1.23	0.811
16	0	449 ± 6	1.34	0.767
	3	451 ± 6	1.22	0.772
	6	455 ± 6	1.21	0.777
	10	472 ± 6	1.29	0.805
	14	478 ± 5	1.07	0.815
	18	488 ± 4	0.82	0.827
	22	490 ± 5	0.92	0.830
17	0	435 ± 7	1.61	0.749
	3	432 ± 6	1.41	0.743
	6	442 ± 8	1.73	0.759
	10	455 ± 8	1.65	0.778
	14	465 ± 8	1.78	0.789
	18	486 ± 8	1.66	0.816
	22	492 ± 6	1.22	0.820
18	0	413 ± 4	0.97	0.710
	3	415 ± 4	0.94	0.713
	6	426 ± 4	0.94	0.729
	10	435 ± 4	0.81	0.744
	14	441 ± 4	0.80	0.749
	18	444 ± 4	0.80	0.754
	22	448 ± 3	0.67	0.762
19	0	417 ± 6	1.46	0.714
	3	420 ± 7	1.68	0.721
	6	426 ± 8	1.76	0.729
	10	439 ± 8	1.82	0.746
	14	452 ± 8	1.82	0.764
	18	464 ± 7	1.41	0.776
	22	469 ± 5	1.09	0.782
20	0	424 ± 4	0.94	0.729
	3	423 ± 5	1.07	0.728
	6	430 ± 4	0.93	0.740
	10	446 ± 3	0.67	0.765
	14	452 ± 3	0.56	0.776
	18	457 ± 3	0.66	0.781
	22	462 ± 3	0.65	0.787
21	0	422 ± 6	1.44	0.725
	3	426 ± 6	1.41	0.731
	6	431 ± 7	1.51	0.740
	10	447 ± 7	1.57	0.763
	14	460 ± 6	1.20	0.781
	18	469 ± 5	0.96	0.793
	22	475 ± 4	0.74	0.797

The values are the mean and standard deviation of 60 measurements.

*Mean of 12 measurements.

2.5. Bulk properties of the mixtures

The flow and packing properties were determined using an automatic tap volumeter (Jencons Scientific, Radon Ind. Electronics Co. Ltd., Worthing, UK). A 250 ml graduated glass cylinder was used. The tapping frequency was 30 ± 1 taps/min and the lift height 25.4 mm. Approximately 200 ml of powder was carefully filled into the tared measuring cylinder ensuring a flat top surface. The maximum bulk volume was read. The volumeter was tapped once and the volume read again. This procedure was repeated increasing the number of taps between readings when appropriate. The minimum bulk volume was determined, after 3 times 200 taps did not reduce the volume occupied any further. The measuring cylinder was then weighed to obtain the powder weight. Three replicates were run using a fresh sample each time. Carr's compressibility index (Carr, 1965), the angle of internal flow (Varthalis and Pilpel, 1976) and the compaction constant *T* (Mohammadi and Harnby, 1997) were calculated from the readings obtained.

2.6. Capsule filling

The powder mixtures were filled into hard gelatin capsules size 1 (Shionogi Qualicaps, Alcobendas, Madrid, Spain) on an instrumented tamp-filling machine (GKF 400S, Robert Bosch GmbH, Waiblingen, Germany). The instrumentation is described in detail by Podczeck (2000). A 19.6 mm dosing disk and a 20 units powder bed height were used. Seven compression settings ranging from "no compression" (cumulative tamping distance (CTD) = 0 mm) to "firm compression" (CDT = 22 mm) (see Podczeck, 2000 for determination of CTD) were employed to test the influence of powder flow and compressibility on the filling performance of the powder mixtures.

The capsule fill weight and the coefficient of fill weight variability (CFV) were obtained from 60 cap-

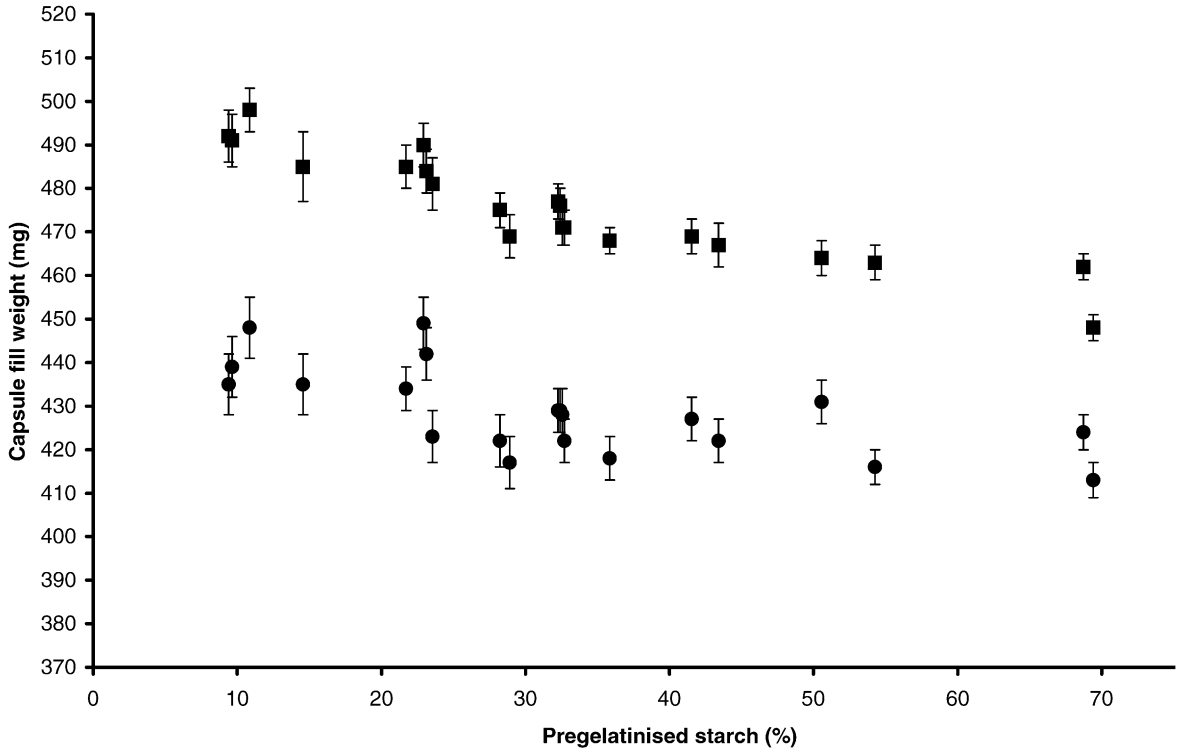

Fig. 1. The influence of the pregelatinised starch concentration on the capsule fill weight observed with "no compression" (CTD = 0 mm ●) and "firm compression" (CTD = 22 mm ■).

sules taken during the run, for which also the tamping force was recorded on tamping stations 3 and 4. A capsule weight verification system (KKE-2000, Robert Bosch GmbH, Waiblingen, Germany) was utilised. The accuracy of the weight determination was ±2 mg. All weights were corrected for the weight of the empty capsule shells.

The capsule dosing lengths of twelve capsules per run were determined with an image analyser (Seescan Sonata, Cambridge, UK) fitted with a black/white CCD-camera (Rengo Co., Toyohashi, Japan) and a zoom lens (18–108/2.5, Olympus Europe, Hamburg, Germany). Using the inner capsule dimensions and the fill weight, the density of the plugs could be determined. Due to the height of the dosing disk, the capsule shells were filled completely in all cases, and hence this procedure allows the plug density to be estimated.

2.7. Disintegration and dissolution

The disintegration test was carried out on six randomly taken capsules using the BP disintegration tester (Copley Scientific Instruments Ltd., Nottingham, UK). The disintegration time was determined for each capsule individually using 800 ml deionised water at 37 °C. The dissolution tests were undertaken following the BP paddle method using a Pharmatest dissolution tester (TPWS 2L Pharmatest, Hamburg, Germany). A volume of 900 ml deionised water at 37 ± 1 °C was used and stirred at 50 rev/min. The aqueous solution was filtered and continuously pumped to a flow cell of a UV spectrophotometer (Cecil CE 2020, Cecil Instruments, Cambridge, UK), and the absorbance was recorded at 272 nm. Six capsules were tested per batch.

2.8. Statistical analysis

All statistical calculations were carried out using SPSS 10.0 (SPSS UK Ltd., Woking, UK).

3. Results and discussion

The flow and packing properties of the powder mixtures are listed in Table 3. Statistical analysis was car-

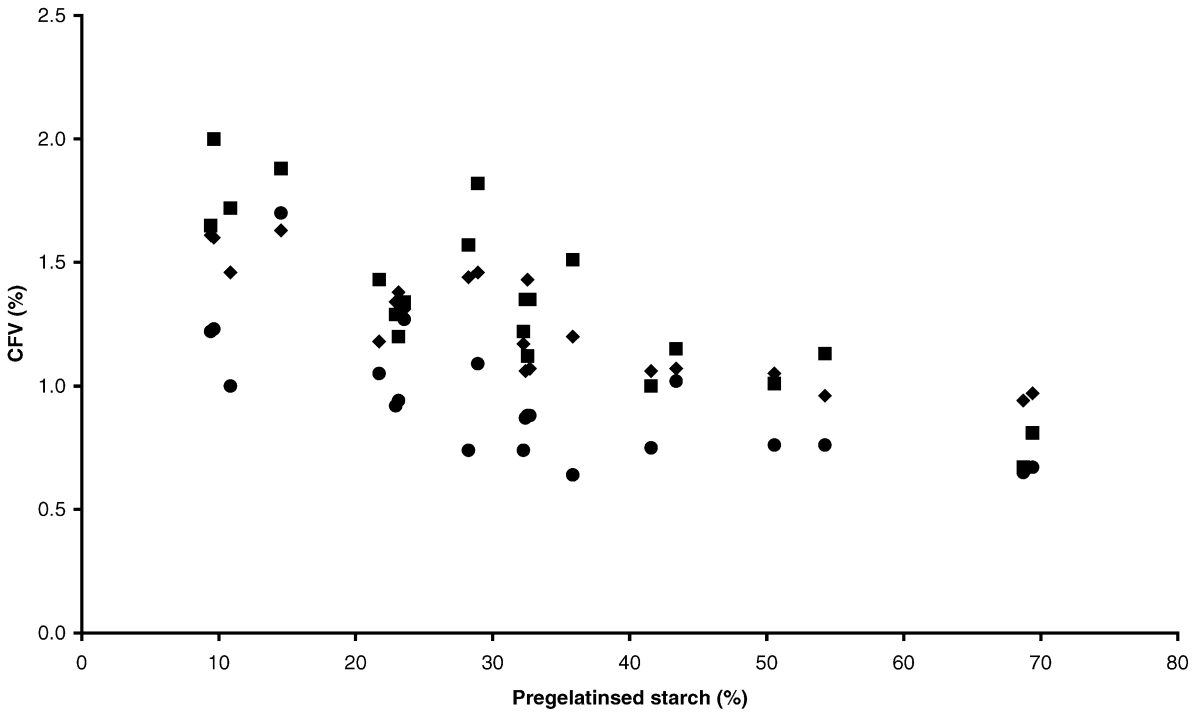

Fig. 2. The influence of the pregelatinised starch concentration on the coefficient of fill weight variability observed with “no compression” (CTD = 0 mm ♦), “moderate compression” (CTD = 10 mm ■) and “firm compression” (CTD = 22 mm ●).

ried out to identify correlations between these parameters. A strong relationship was identified between the minimum bulk density and the angle of internal flow (linear determinant $R^2 = 0.873$, root mean square deviation/residual analysis RMS = 1.00%). However, while the minimum bulk density was mainly dominated by the concentration of pregelatinised starch in the mixture, the angle of internal flow was found to be related mainly to the theophylline content (Table 4). No other close relationships were identified between the flow properties, and the relationships between these and the concentration of the individual components of the mixtures were rather complex and are not very informative (see Table 4).

Table 5 provides the weights and coefficients of fill weight variability for the different mixtures filled at seven different cumulative tamping distances (CTD), plus the maximum plug density achieved.

In Fig. 1, the influence of the concentration of pregelatinised starch on the capsule fill weight is compared

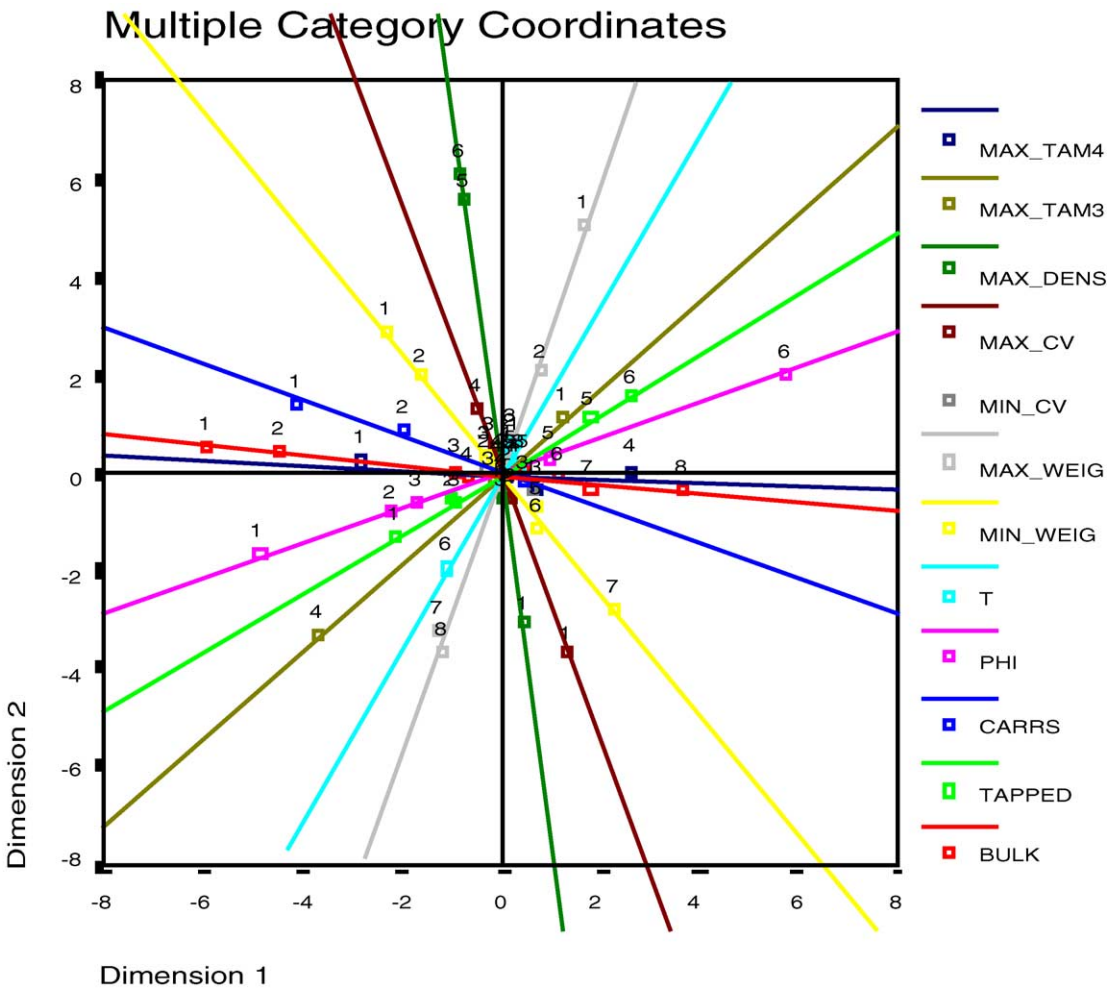

Fig. 3. Perceptual map to investigate the relationships between powder packing and flow properties and the capsule filling performance. Dimensions 1 and 2 describe the multiple category coordinates derived. MAX_TAM3, MAX_TAM4 = maximum tamping force measured on stations 3 and 4; MAX_DENS = maximum plug density; MIN_CV, MAX_CV = minimum and maximum coefficient of fill weight variability; MIN_WEIG, MAX_WEIG = minimum and maximum fill weight; T = compaction constant; PHI = angle of internal flow; CARRS = Carr's compressibility index; TAPPED = maximum bulk density; BULK = minimum bulk density.

for “no compression” (CTD = 0 mm) and “firm compression” (CTD = 22 mm). For a CTD of 0 mm, i.e. the filling process being dominated by the flow properties of the powder mixtures, there is a trend for the fill weight to decrease with an increase in pregelatinised starch concentration, yet the individual data points are fairly scattered. However, when the compression (“tamping”) process dominates the filling (CTD = 22 mm), the same trend is obtained with much less scatter. As the increase in pregelatinised starch concentration was accompanied by an increase in the angle of internal flow, it can be concluded that in the mixtures studied here, increased amounts of pregelatinised starch hindered the densification process to some extent. One reason for this could be the increased surface roughness of those starch particles that had been disrupted in the pregelatinisation process.

In Fig. 2, the influence of the pregelatinised starch concentration on the coefficient of fill weight variability is shown for three different compression settings, i.e. no (CTD = 0 mm), moderate (CTD = 10 mm) and firm compression (CTD = 22 mm). Although the fill weight of the capsules as such decreased with an increase in pregelatinised starch content (see above), the coefficient of fill weight variability decreased significantly at the same time. Hence, overall the filling performance of the powder mixtures into hard capsules improved, if larger amounts of pregelatinised starch were present. The required amount of pregelatinised starch appears to lie above 40% because most coefficients of fill weight variability were close to or even below 1% above this concentration.

To investigate the influence of flow and packing properties of the powder mixtures on the capsule filling performance, a perceptual mapping technique was used (Tenenhaus and Young, 1985). The perceptual map was constructed using the data presented in Table 3 plus the minimum and maximum capsule weight achieved, the minimum and maximum coefficient of fill weight variability observed, the maximum plug density (all extracted from Table 5) and the maximum tamping forces observed on tamping stations 3 and 4. The resulting perceptual map is shown in Fig. 3. The technique is purely explorative and relies on the interpretation of

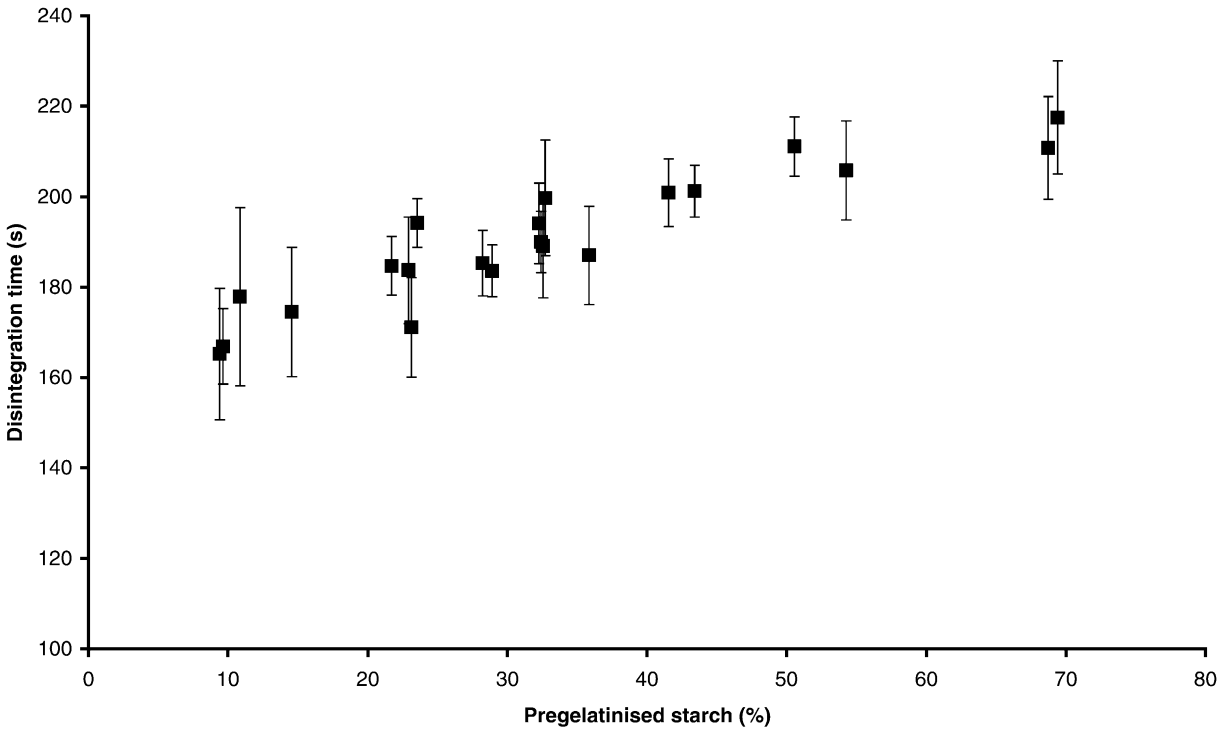

Fig. 4. The influence of the pregelatinised starch concentration on the disintegration time of capsules.

the perceptual map. The data undergoes an optimal scaling procedure, and both linear and non-linear relationships can be investigated. In the graph of the multiple category coordinates (Fig. 3), similarly to Principal Component Analysis, two dimensions encompassing the majority of the variance of the individual variables (here, however, grouped according to Tables 3 and 5) have been used to illustrate the relationships between the individual observations. For each variable, a line can be fitted showing the trend of the observations to increase or decrease within the two dimensional coordinate system. These lines have different colours for each variable; for example, Carr's compressibility index follows the blue line, whereas the minimum fill weight achieved in the different experiments follows the yellow line. Properties, which are related, will have similar multiple category coordinates, and the fitted lines will be close to each other, i.e. have similar slopes. It can be seen that the minimum bulk density (red line), the maximum tamping force on station 4 (dark blue line) and to some extent the maximum ("tapped") bulk density (green line) and the maximum tamping force on station 3 (olive green line) are related as their lines are very close to each other. This is not surprising as on station 3 most capsule plugs have reached their final length and density (Podczeck, 2001), whereby on such machines, the tap density is usually achieved but not exceeded. Further tamping does not contribute to the plug length, but losses due to friction between the plug and the tamping ring might cause the plug to move down in the die bores, and loose powder will then fill the die cavities above the plug. All other performance indicators are obviously more related to the ingredients of the powder mixtures as such, and hence, their lines are spaced apart and have clearly different slopes.

The disintegration times of the capsules were also related to the pregelatinised starch concentration, and Fig. 4 illustrates this. As there was no statistically sig-

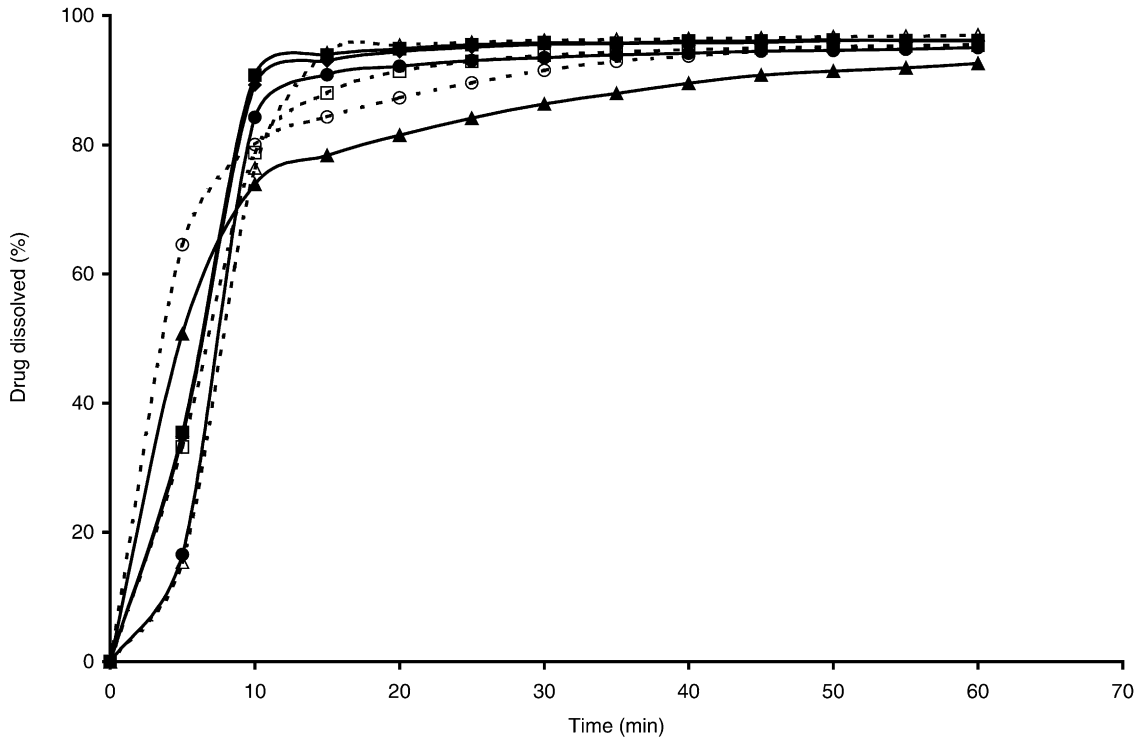

Fig. 5. Drug dissolution profiles for capsules filled at a cumulative tamping distance of 22 mm. For mixture numbers selected refer to Table 1: (♦) mixture 1 (average composition), (■) mixture 5 (high magnesium stearate concentration), (▲) mixture 9 (high theophylline concentration), (●) mixture 13 (no lactose in excipient mixture), (□) mixture 2 (low magnesium stearate concentration), (△) mixture 6 (low theophylline concentration) and (○) mixture 10 (low pregelatinised starch concentration).

nificant difference between the disintegration times from capsules produced with different cumulative tamping distances, the data shown in the figure have been pooled for each mixture. An increase in the pregelatinised starch content resulted in a slight increase in disintegration time. However, all capsules disintegrated in the maximum time span allowed, as specified in the various Pharmacopoeias. The reason for the increase in disintegration time might be the rapid swelling and gelation behaviour of the excipient, which, as a result, could lead to blocking of pores and slight hindrance of water uptake. Again, as with super-disintegrants, the large porosity of the powder plugs produced in capsule filling appears to be the origin of the effects seen because in tabletting, where the porosity of the specimens is almost 10 times less, pregelatinised starch has been found to be an effective disintegrant (Rudnic et al., 1982; Manudhane et al., 1969).

Also the dissolution studies confirmed that an increase in pregelatinised starch concentration could improve dissolution of poorly soluble drugs and prevent adverse effects on drug dissolution caused by larger amounts of hydrophobic lubricants. Fig. 5 shows seven examples of dissolution profiles obtained from capsules produced with the highest compression setting. As can be seen, a minimum amount of excipients is required, of which half should be pregelatinised starch for highest efficacy.

4. Conclusions

The use of pregelatinised starch in tamp filling of powders into hard capsules as an excipient can be beneficial in terms of reducing the coefficient of fill weight variability and the drug dissolution time from capsules. To improve drug dissolution of poorly soluble drugs, larger amounts of this excipient appear to be required, and the maximum capsule fill weight that can be achieved might be slightly reduced.

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