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COMPARATIVE EVALUATION OF SOY POLYSACCHARIDE AS DIRECT COMPRESSION EXCIPIENT

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ABSTRACT

Commercial soy polysaccharide (Emcosoy^{R}) has been evaluated as direct compression excipient in comparison with two frequently used materials, microcrystalline cellulose (Avicel pH 101) and pregelatinized maize starch (Sta-RX 1500).

Moisture sorption and desorption data analysed according to the Young and Nelson and the GAB equations and mechanical properties such as tensile strength, brittle fracture probensity, interparticle bonding isotropy and yield pressure of compacted excipients after storage at various environmental relative humidities are reported. Tableting characteristics such as punch force ratio, weight variation, tensile strength, friability, capping tendency, disintegration and dissolution of mixtures of the excipients and paracetamol are compared.

Emcosoy has been found to behave like Avicel as direct compression binder but like Sta-RX as disintegrant.

INTRODUCTION

Many materials have been evaluated for their use as direct compression excipients in pharmaceutical tablets. These evaluations

are generally based either on the flow and compression properties of the excipients or on the characteristics of tableted formulations including the excipients.

Soy polysaccharide is a group of high molecular weight polysaccharides obtained by processing defatted soy beans. It contains mainly the remnant of the cell wall, and has been evaluated as a disintegrant in tablets made by direct compression[1] and wet granulation[2,3]. It has been found to perform well as disintegrant, giving tablets with stable dissolution profiles after storage under ambient conditions for six months. Besides, it reduced the friability and did not soften the tablets, even when employed at high use level, thus indicating that it has some dry bonding properties. Soy protein has been evaluated as tablet excipient (filler and binder) as well. It gave strong tablets with quick drug release affected from the environmental relative humidity[4].

The present paper attempts to evaluate commercial soy polysaccharide (Emcosoy^{R}) as a direct compression excipient in comparison with Avicel pH 101 and Sta-RX 1500 which possess good binding and disintegrating properties. For this purpose the moisture sorption and desorption, at 25°C, and the physico-mechanical properties of compacted Emcosoy are evaluated and compared to those of Avicel pH 101 and Sta-RX 1500 already reported in a previous paper[5]. Furthermore, mixtures of paracetamol with increasing Emcosoy, Avicel and Sta-RX content are compressed at various pressures and their tableting performance is evaluated.

EXPERIMENTAL

Materials:

The materials used in this study were: Soy polysaccharide (Emcosoy^{R}, E. Mendel-Forum house, Redhill, Surrey, England), with specifications given in Table 1, pregelatinized maize starch (Sta-RX 1500, Colorcon Ltd, Indianapolis, USA), microcrystalline cellulose (Avicel pH 101, Vanderbilt, RT Co., Norwalk, Connecticut, USA), and paracetamol BP powder (Cambrian Chemicals, U.K.).

Table 1

Specifications of Emcosoy^R used[6].

High molecular weight polysaccharides (moisture-free basis)	*80% (typical)*
Protein (moisture-free basis)	*17.5% maximum*
Loss on drying	*10.0% maximum*
Residual soy lipids	*2.0% maximum*
Ash	*6.0% maximum*
Fiber	*16.0% maximum*
Heavy metals (as lead)	*20 ppm maximum*
pH (5% slurry in water)	*6.5 - 7.5*
Bulk Density	*0.45 g/ml maximum*
Particle size	*90% passes through 100 mesh (U.S. Standard) screen*

Moisture sorption and compression properties of the excipients:

Moisture sorption and desorption at 25°C were determined and analysed according to the Young and Nelson[7] and the GAB[8] equations.

Intact and perforated cylindrical compacts were prepared after storage of the excipients at various environmental relative humidities; their diametral breaking strength was determined and the brittle fracture index (B.F.I.)[9] calculated. Yield pressure was also determined from Heckel plots[10]. Rectangular compacts were formed and their interparticle bonding isotropy was measured[11]. Details about the procedures used for all the above mentioned determinations have been previously given[5].

Preparation and testing of Paracetamol tablets:

Paracetamol, Emcosoy, Avicel and Sta-RX powders were dried for 12 h at 60°C in an oven and were stored in airtight glass jars at 20°C and 52% relative humidity. The appropriate amounts of powders to give 300 g of mixtures with excipient mass fractions 0.25, 0.30, 0.35 and 0.40 were placed in a 1 lit bottle and mixed together by rotating them for 30 min using a turbula mixer (WAB, type T2C, Switzerland). 6 g of silicon dioxide (Aerosil R 972) and

3 g of magnesium stearate were added to each batch before mixing, as glidant and lubricant respectively.

The resulting mixtures were compressed at up to five different forces (20-30 kN), on an instrumented single-punch tableting machine (Manesty Type F3, Liverpool, England) using a 10.5 mm diameter punch and die set. Two piezoelectric transducers (PCB Piezotronics Inc) placed directly between each punch and punch holder, an amplifier and an oscilloscope (Nicolet) were employed for monitoring the upper and lower punch compression force. The resulting tablets were collected in well-sealed glass jars and stored for one week and their weight variation, tensile strength, capping tendency, friability, disintegration time and dissolution rate were measured.

The target tablet weight was 250 mg and weight variation was determined for 20 tablets from each lot. Tablet thickness (t) and diameter (D) were measured to the nearest 0.01 mm and the maximum force tansmitted before they broke in tension (P) was determined for 10 tablets by using a CT 40 tester (Engineering System, Nottingham England). The tensile strength (T) was obtained by applying the relationship[12]: $T=2P/3.14\ D\ t$.

Capping tendency was determined by placing 20 tablets in a Roche friabilator and rotating 300 times at a speed of 30 rpm. Every 30 revolutions the capped tablets were noted and replaced by new, intact ones. The number of capped tablets was plotted vs the number of revolutions, and the slope obtained from regression analysis representing an arbitrary value between 0 and 100 was taken as a measure of capping tendency[13]. The results presented are mean values of three slope determinations. For tablets with no capping tendency, the percent weight loss after the 300 revolutions was noted as friability.

Disintegration times of 6 tablets were determined in simulated gastric fluid by using the USP method. Three tablets from each lot were subjected to drug dissolution test. A standard USP (Method II padle) dissolution apparatus connected to a UV-spectrophotometer and compact desk computer was employed. The dissolution medium was 1000 ml of simulated gastric fluid. It was stirred at 100 rpm

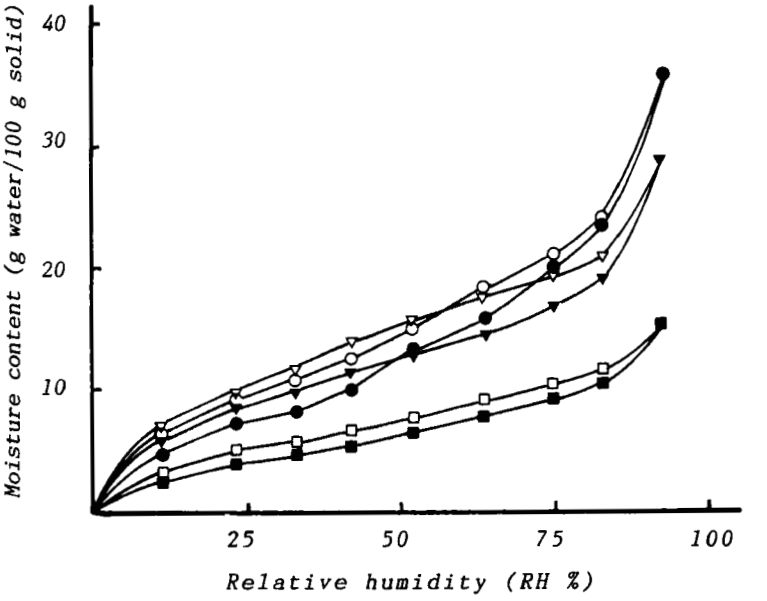

FIGURE 1
Moisture sorption and desorption isotherms (25°C) of: ● -Emcomsoy, ■- Avicel and ▼-Sta-RX (open symbols for desorption conditions).

and absorbance measurements were taken up to 1 hour. The spectrophotometric determination was made at 243 nm.

RESULTS AND DISCUSSION

The experimentally measured moisture sorption and desorption isotherms are illustrated in Fig. 1. For Emcomsoy the isotherms are close to that of Sta-RX and exhibit hysteresis which was analysed for three locations of moisture: monolayer adsorbed moisture, externally condensed moisture and internally absorbed moisture, (according to the hypothesis of Young and Nelson), by using a combination of iteration and multiple regression technique[5,7]. The computed values of the parameters in the Young and Nelson equations and the amount of moisture present as a monolayer ($A.\theta$), the amount of the externally adsorbed moisture ($A(\theta+\beta)$) and the amounts of the internally absorbed moisture during the sorpion cycle ($B.\psi$) and

TABLE 2
Computed values of parameters in the Young and Nelson, the G.A.B equations, derived moisture distribution and enthalpy terms

Parameters and terms	Excipient Emcosoy	Avicel	Sta-RX
Young & Nelson Eqns			
E	0.217	0.075	0.054
A	0.078	0.036	0.065
B	0.025	0.014	0.036
(r)	0.994	0.998	0.994
A.θ at 52% RH	6.47	3.38	6.23
A(θ+β) "	11.51	5.93	10.91
B.ψ "	1.07	0.70	1.77
B.θ RHmax "	1.91	1.25	3.17
A.θ at 93% RH	7.64	3.58	6.52
GAB Equation			
Wm.100	7.5	4.2	7.8
C_G	14.44	18.07	34.31
K	0.846	0.763	0.756
(r)	0.973	0.988	0.970
Enthalpy terms			
$(q_1 - q_L)$ kcal/mole	0.91	1.53	1.73
$(H_1 - H_L)$ "	1.68	1.87	2.26

during the desorption cycle (B.θ. RHmax) for the mean environmental (52%) and the maximum experimental (93%) relative humidity are given in Table 2 together with the highest correlation coefficient of the iteration and multiple regression for the three excipients under investigation.

By applying polynomial regression analysis the moisture sorption data were also analysed according to the G.A.B. equation which takes into account three states of sorbed water: tightly bound; less tightly bound; and bulk water[5,8]. The calculated values of the weight of tightly bound water in the form of a monolayer (Wm) and the parameters C_G akd K which are related to the heat of sorption are

listed in Table 2 together with the correlation coefficients of the polynomial regression analysis. For all the excipients the values of Wm are close to that of A.θ at 93% RH and for Emcosoy both Wm and A.θ values are close to those of Sta-RX as expected from the similarity in the sorption and desorption isotherms in Fig. 1.

In Table 2 the values of the enthalpy terms ($q_1 - q_L$) and ($H_1 - H_L$) are also given. They were derived from the parameters E, C_G and K and express the difference between the heat of sorption of water in the first sorbed or tightly bound monolayer (q_1 or H_1) and the normal heat of condensation (q_L or H_L). The enthalpy terms calculated on the basis of both the moisture sorption models used (Young & Nelson and G.A.B) seem to be comparable.

The tensile strength (T) measured by diametral breaking of cylindrical compacts has been expressed for a fixed packing fraction (p_f) by using the equation Log $T = A_1 p_f + B_1$. A_1 and B_1 were numerical terms which depended on the excipient, the relative humidity and the storage conditions. The tensile strength results at p_f 0.9 for storage under sorption and desorption conditions are plotted against the moisture content in Fig. 2. It is seen that for Emcosoy the moisture uptake produces significant changes in tensile strength only when the moisture content is lower than 10% and higher than 25% w/w, corresponding to environmental relative humidity of 40 and 85% respectively. For Avicel the tensile strength exhibits a small initial plateau before it starts to decrease; as far as Sta-RX is concerned it increases initially, reaches a maximum and then decreases with the moisture content. For Emcosoy the change of the tensile strength due to moisture content seems to be more complex, showing some similarity to those of Avicel and Sta-RX. For Emcosoy the moisture uptake initially produces a decrease in tensile strength; this is followed by a slight increase to a maximum and then another decrease. This complex tensile strength change of Emcosoy may be attributed to its composition, including (see Table 1) fiber, protein, high molecular weight polysaccharides and lipids (2%), and can be explained as a result of combined effects of moisture distribution on: a) maximizing the tensile strength reduction due to the lipid

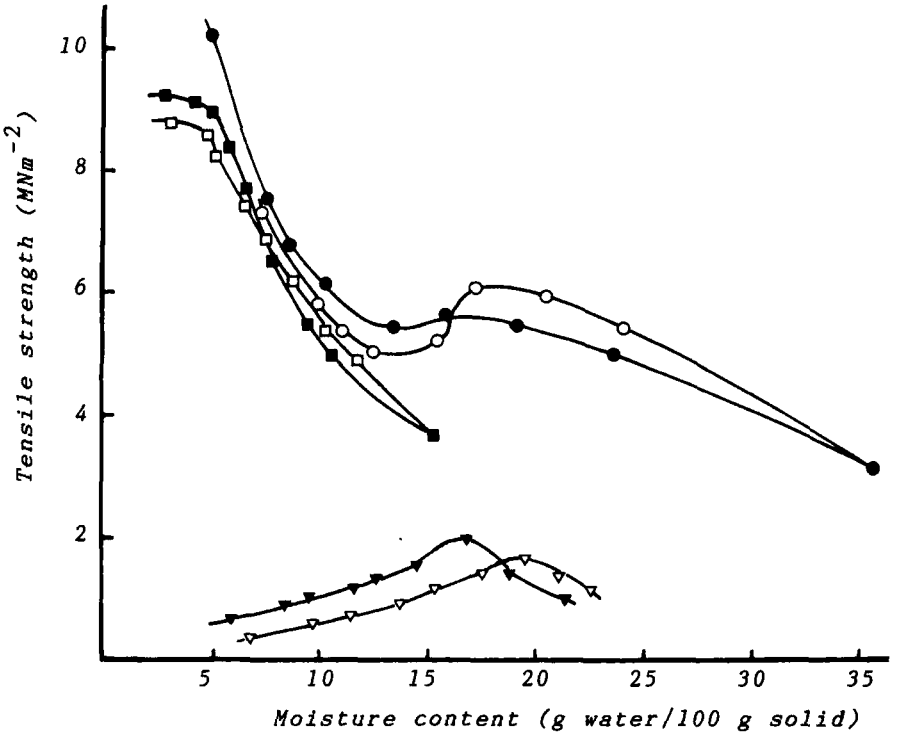

FIGURE 2
Tensile strength from diametral breaking of cylindrical compacts (pf 0.9) of excipients stored under sorption and desorption conditions (symbols as in Fig. 1).

content, b) increasing the interparticle attractive forces and c) plasticizing of the excipient particles.

The monomolecular (or tightly bound or adsorbed to the solid-air interphase) water may increase the action of the Emcosoy lipids as lubricant, or as physical barrier masking the van der Waals forces and reducing the tensile strength[14], while it may simultaneously increase the interparticle attractive forces by smoothing out the surface microirregularities or reducing the interparticle separation[15]. Finally when the water vapor is internally absorbed or is dissolved into the solid it may decrease the tensile strength because of the softening of the interparticle solid contacts by reducing the hydrogen bonding between adjoining molecules of the solid particles[16,17].

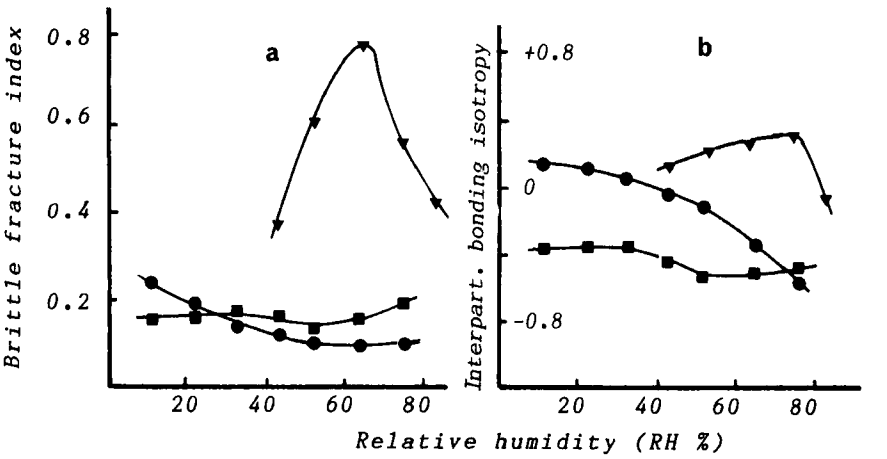

FIGURE 3(a, b)
Effect of relative humidity during storage under sorption conditions on: a, brittle fracture index. b, interparticle bonding isotropy (symbols as in Fig. 1).

In Fig. 2 one can also see that for Emcosoy the tensile strength under sorption conditions is higher than that of desorption but only for the initial range of relative humidities (adsorption phase). At the higher relative humidities (absorption phase) the tensile strength for sorption conditions is lower than that of desorption. Cross-over of the sorption and desorption tensile strength curves and maxima before the strength finally starts to decrease, occur at 16% w/w moisture content, that is almost double the mean of the corresponding Wm and A.θ at 93% RH values given in Table 2. Similar observations have been reported previously for Avicel and Sta-RX[5] and may constitute evidence that the internally absorbed moisture is responsible for the final tensile strength decrease, Fig. 2.

In Fig. 3a and 3b the brittle fracture index (B.F.I.) and the interparticle bonding isotopy results are plotted against the relative humidity. The B.F.I. for both Emcosoy and Avicel is lower than 0.25 for all the relative humidities employed and the tensile strength isotropy of Emcosoy is between those of Sta-RX and Avicel. The curves in Fig. 3a and 3b are similar in shape and in relative position

TABLE 3
Yield pressure for the excipients after storage at different relative humidities

Excipient	Yield pressure (MNm^{-2}) for RH %								
	11	23	33	43	52	64	75	83	93
Emcosoy	202	195	174	170	148	106	91	88	81
Avicel	117	113	111	110	102	100	94	92	71
Sta-RX	204	200	167	160	139	103	66	53	32

as expected[5] and for the different excipients the relative positions of the curves in Fig. 2 and 3 (a and b) are effectively reversed. These similarities and reversed positions may be attributed to the plasto-elasticity of the excipients under investigation. The plasto-elasticity quantified as yield pressure derived from Heckel plots (reciprocal of slope, Py) is given in Table 3. It shows continuous decrease with moisture content for all the excipients studied. For Emcosoy the yield pressure is close to that of Sta-RX when the relative humidity is lower than 64% (moisture content = 16%) but at higher humidity it is close to that of Avicel.

The physical properties of paracetamol mixtures tableted at two different compression forces are given in Table 4. The punch force ratio values which depend, among other factors, on the lubricant used and may be affected by the excipient under investigation do not show significant differences. Also, the weight uniformity of the tablets expressed as the coefficient of variation (C.V.%) is small for all the formulations and no significant difference could be demonstrated.

The tensile strength of the tablets increases with excipient content and compression force. At fixed compression force and excipient mass fraction the tensile strength is higher for tablets containing Avicel and lower for Sta-RX. For tablets containing Emcosoy the tensile strength is close to that for Avicel.

TABLE 4

Physical properties of tableted paracetamol mixtures

Excipient mass fraction		Mean compression force (kN)	Punch force ratio	Weight variation C.V%	Tensile strength (MNm^{-2})	Friability & capping* tendency (%)	Disintegration time (min)	50% Dissolution time (min)
Emcosoy	0.25	20	0.89	0.88	0.75	12*	0.4	2
"	"	30	0.92	1.14	1.02	22*	0.5	2
"	0.30	20	0.93	0.84	0.80	7.3	0.7	2
"	"	30	0.95	1.18	1.29	5.1	0.8	2
"	0.35	20	0.93	1.06	1.15	4.3	0.9	2
"	"	30	0.98	1.39	1.72	3.8	1.0	2
"	0.40	20	0.94	1.65	1.29	3.6	0.7	2
"	"	30	0.99	1.31	2.09	2.5	1.0	2
Avicel	0.25	20	0.98	1.92	0.79	68*	14	5
"	"	30	0.98	2.24	0.77	82*	18	6
"	0.30	20	0.93	2.31	1.32	6*	26	7
"	"	30	0.98	1.92	1.59	12*	31	8
"	0.35	20	0.95	1.55	1.79	7.1	26	10
"	"	30	0.98	2.06	2.08	3.1	38	10
"	0.40	20	0.94	1.71	1.92	3.3	30	12
"	"	30	0.99	1.46	2.42	2.4	52	16
Sta-RX	0.25	20	0.94	0.57	0.60	16*	0.2	2
"	"	30	0.98	2.04	1.00	34*	0.2	2
"	0.30	20	0.97	1.92	0.69	10.3	0.3	2
"	"	30	0.99	2.10	1.05	6.6	0.3	2
"	0.35	20	0.98	2.07	0.85	8.2	0.4	2
"	"	30	0.99	1.52	1.11	6.0	0.4	2
"	0.40	20	0.96	1.19	0.86	7.8	0.4	2
"	"	30	0.98	0.85	1.17	6.0	0.5	2

Tablets with Emcosoy or Sta-RX mass fraction 0.25 and Avicel mass fractions 0.25 and 0.30 showed capping which was increasing with the compression force applied. The friability results decreased with compression force and were consistent with those of tensile strength (inversely related).

The tablets containing Sta-RX and Emcosoy gave extremely low disintegration times which were not affected by the compression force applied. On the contrary, tablets containing Avicel gave disinte-

gration times in the range of 14-52 min which were affected either by the compression force or the excipient content and were proportionally related to the tensile strength. The dissolution results were consistent with those of disintegration.

This study shows that the interparticle bonding of Emcosoy is not affected significantly in a wide range of environmental relative humidity between 40 and 85%. The behaviour of Emcosoy as direct compression binder is similar to that of Avicel and this similarity may be related to their plasto-elastic properties. Furthermore, Emcosoy behaves similarly to Sta-RX as disintegrant and the water sorption and distribution properties may reflect on this last similarity.

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