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Excipient ability of chitosan for direct tableting

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Summary

This paper describes an investigation of the usefulness of krill chitosan in the production of tablets that meet the standard requirements following long-term storage; 49% (A) and 66% (B) deacetylated chitosans were used. Examination of the granulometric and flow properties of multi-component mixtures containing B and testing of the direct compressibility of chitosan B and B mixtures showed that chitosan fulfills the general requirements for auxiliary substances in the process of direct tableting. When used as a filler or binder, chitosan did not affect mass flow; however, on addition in the proportion of 50% of tablet mass, rapid tablet disintegration resulted. Following long-term storage, tablets produced with the addition of B may be less resistant mechanically (tablet hardness decreases), nevertheless, the tablet disintegration time either remains unaffected or even decreases.

Introduction

The suitability of chitosans, which are partially deacetylated chitin derivatives, for the formulation of dosage forms has been described in several previous papers. For example, chitosans display a number of properties that are characteristic of starch (Bruscato and Danti, 1978), microcrystalline cellulose (Sawayanagi et al., 1982a,d) and water-soluble polycationic forms (Sawayanagi et al., 1982b; Takahashi et al., 1990). Their solubility in acidic solutions depends on the degree of deacetylation.

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The above-mentioned features are of considerable value and the use of chitosans in the process of formulation offers many advantages, as exemplified in the following: powder preparation (Sawayanagi et al., 1982e, 1983b; Koh et al., 1986; Nozawa et al., 1986), dried gel (Miyazaki et al., 1981), granules (Hou et al., 1985; Miyazaki et al., 1988b), tablets via wet granulation (Kawashima et al., 1985c; Brine, 1989) and tablets via direct compression (Sawayanagi et al., 1982c, 1983a; Inouye et al., 1987; Rui et al., 1988; Acartürk, 1989a,b; Brine, 1989). Their application in various granulation and coating technologies led to the successful preparation of specific drug delivery forms as granules (Kawashima et al., 1985a,b), pellets (Bodmeier and Paeratakul, 1989), particles (Bodmeier et al., 1989) and spheres (Nishioka et al., 1989, 1990), to magnetic spheres (Gallo

and Hassan, 1988), implants (Machida et al., 1987), and floating granules and tablets (Inouye et al., 1988, 1989; Miyazaki et al., 1988a).

Despite the considerable body of published data, the question as to whether any drug formulation which fulfills the standard requirements may be produced using chitosan remains to be resolved. In particular, the studies referred to above do not consider the possible effect of storage on the properties of the resulting dosage forms. Since chitosan is a polymer, it can readily interact with remedies, moreover, its properties may evolve due to the external conditions. *

The present investigation represents the continuation of a study of the powder properties of chitosan and of the usefulness of Polish krill chitosan, produced for practical purposes to be employed in the process of direct tableting (Knapczyk and Krówczyński, 1988). The possible influence of storage on the pharmaceutical properties of tablets was also examined.

Materials and Methods

Chitosan A (degree of deacetylation, 49%) and chitosan B (degree of deacetylation, 66%; medium viscosity type) derived from a krill chitin were supplied by the Sea Fisheries Institute (Gdynia, Poland). The other properties of both polymers were in conformity with the commonly accepted requirements (Knapczyk et al., 1989).

Samples with various moisture contents were prepared either by drying at 100°C and storage in a low humidity atmosphere or by storage for 1 week in a desiccator at 100% relative humidity (RH). The moisture content was determined as the weight loss during drying at 105°C. The chitosan sample, drugs [sodium benzoate (POCh, Gliwice), salicylamide and phenformin hydrochloride (both from Polfa, Starogard), paracetamol (Galena, Wroclaw)] and excipients [(potato starch; PZZ, Trzemieszno), lactose monohydrate (special for tableting; lot no. 8195, Merck, Darmstadt), dibasic calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$; POCh, Gliwice), and microcrystalline cellulose (marketed as Somicel F; Chemitex, Sochaczew)] were skin dried at 40°C, reduced to powder and sifted through a 0.3 mm mesh. Different powder mixtures were blended in a KB cube mixer (Erweka, Heusenstamm) at 90 rpm for 30 min. The flow (denoted as tan α) and powder parameters were evaluated according to the method of Sucker et al. (1978) using a glass funnel, a WE 5 electromagnetic flow volumeter (CLAO, Poznań) and a tamped volumeter (OBRMPF Polfa, Kraków).

Samples prepared by spreading drug on the surface of chitosan were obtained by dabbing the surface of B tablets in a rotating DK/KG pan (Erweka, Heusenstamm) with an ethanolic solution of phenformin hydrochloride followed by drying the product at 40°C. The drug content of a single powdered tablet was determined spectrophotometrically by examining an aqueous solution of the sample using an SP-500 spectrophotometer (Unicam, Cambridge) operating at a wavelength of 234 nm.

Flat-faced chitosan tablets were prepared by direct compression using a single-punch EKO Korsch press running at a speed of 30 rpm. An appropriate compression control ensured uniformity of tablet hardness in each series to within 0.5 kg. The entire handling procedure was performed at room temperature and constant humidity. The tablets were stored in closed containers.

Tablet strength was determined after a 30 min relaxation time using a Stokes manual hardness tester and a Roche friability tester (both from OBRMPF Polfa, Kraków).

The disintegration time of a single tablet in water at 37°C was evaluated according to the USP XXI (1985) procedure using a ZT 3 disintegration test apparatus (Erweka, Heusenstamm) equipped with a disc. All other quantitative data were determined as the means of 10 individual measurements.

Results and Discussion

In order to establish the properties of chitosan A and B powders, the characteristics of the fol-

* Part of the above problems has been considered in the previous paper (Knapczyk, 1992).

lowing were determined: (i) samples dried at 100°C and stored under a low-humidity atmosphere (A^1 and B^1); (ii) samples obtained from commercial sources (A^2 and B^2); (iii) samples stored at 100% RH (A^3 and B^3) (Table 1).

Both commercially supplied samples of 49 and 66% deacetylated chitosan differed from each other with respect to moisture content: whereas their moisture contents were comparable immediately after drying (< 1%) the latter form had an appreciably greater content of moisture subsequent to storage under conditions of high humidity. While the humidity of samples did not affect their granularity, the Hausner factor calculated indicated that the less humid and more extensively deacetylated samples should exhibit a tendency to greater flow and regular filling of the matrix during tableting.

The chitosan content of a ternary powder mixture has no influence on the flow of the mixture (Table 2), a result which is consistent with previously reported observations on binary mixtures (Sawayanagi et al., 1982a,d).

The difference in flow behaviour between all of the mixtures of various compositions never exceeded 10° (in tan α) in every case examined; consequently, this factor has no effect on the tableting process.

The effectiveness of chitosan in direct tableting was assessed by examination of the uniformity of tablet weight and phenformin content of a series of continuously pressed tablets (Table 3).

TABLE 2

Flow characteristics of ternary powder mixtures with chitosan

Mixture	Composition (%)					
	1	2	3	4	5	6
Chitosan B	30	60	30	60	30	60
Potato starch	40	10	–	–	–	–
Lactose	–	–	40	10	–	–
$CaHPO_4 \cdot 2H_2O$	–	–	–	–	40	10
+30% SB						
Sliding, tan α °	46	40	33	37	30	36
+30% SA						
Sliding, tan α °	41	41	40	44	40	42
+30% PA						
Sliding, tan α °	42	45	44	50	46	43

SB, sodium benzoate; SA, salicylamide; PA, paracetamol.

The formulation prepared by spreading of the drug on the surface of the excipient generally led to greater uniformity in tablet composition. Tablets produced from a physical mixture of both components also conformed with the standard requirements.

Variation in the hygroscopicity of chitosans A and B governs the effectiveness of both forms in the process of direct tableting via an effect on the granulometric behaviour (Table 4). Whilst tablets of sufficient hardness could not be produced using samples A and B of high moisture content, the tablet disintegration time was only weakly dependent upon powder humidity.

TABLE 1

Chitosan sample powder characteristics

Sample	Moisture content (%)	Sliding tan α (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Bulk volume/ tapped volume
A^1	0.7	41	0.15	0.19	1.24
A^2	4.0–6.4	39–42	0.11–0.12	0.17–0.18	1.50–1.63
A^3	14.4	43	0.12	0.19	1.58
B^1	0.4	40	0.39	0.44	1.14
B^2	12.5–13.3	38–39	0.29–0.30	0.38–0.42	1.30–1.44
B^3	19.2	40	0.29	0.41	1.43

1, samples stored under a low-huminity atmosphere; 2, samples as supplied by the commercial source; 3, samples stored in an atmosphere of 100% RH.

TABLE 3

Tablet weight (X) and phenformin hydrochloride content (Y) uniformity determined for 10 tablets prepared by direct compression of chitosan B with addition of 7% of drug

	Composition			
	Powder mixture		Drug spread on the surface	
	X	*Y*	*X*	*Y*
From (−) to (+) (%):	1.87–2.90	4.87–4.72	1.77–0.79	3.60–1.95
X (mg)	299.8	20.93	305.7	21.78
±SE	4.2	0.6	2.4	0.4
RSD	1.4	2.9	0.8	1.7

The effect of differences in the primary properties of the chitosan samples is more readily observed after storage rather than following compression (Table 4). Tablets derived from chitosan A (less extensively deacetylated and acid-insoluble) exhibit a slight decrease in hardness but no change in disintegration rate. In contrast, tablets prepared using chitosan B (greater degree of deacetylation and acid-soluble) showed an increase in hardness and considerably prolonged disintegration time.

The addition of 50 or 75% potato starch, lactose or microcrystalline cellulose to chitosan B prevents the decrease in disintegration time of tablets during storage (Table 5). However, comparison of the disintegration times indicates that, for rapidly disintegrating tablets, the amount of lactose added should be limited. After storage for 1 year, the mechanical properties of tablets compressed from the above mixtures do not change significantly. A greater (> 10%) decrease in hardness of microcrystalline cellulose-containing tablets may be compensated by using a higher pressure during compression (Sawayanagi et al., 1982a).

Assessment of the properties of tablets that had been stored for 3 years, compressed from ternary physical mixtures of the powders confirmed the effectiveness of chitosan B as a filler and binder (Table 6). In addition, it was demonstrated that when added to a tablet mass in the proportion of between 30 and 60%, chitosan B acted as a disintegrant. Nevertheless, it cannot be considered as a universal excipient. The mechanical characteristics of six series of tablets containing sodium benzoate underwent considerable change during the course of storage and none fulfilled the standard requirements. An attempt

TABLE 4

Moisture-content-dependent properties of 150 mg chitosan tablets (a) directly after compression and (b) after 50 week storage

Sample	Moisture content (%)	Hardness (kg)		Disintegration time (s)	
		a	b (%)	a	b
A^1	0.7	10.0	–	9	–
A^2	4.0	10.0	−7.9	15	15
A^3	14.4	2.1 [a]	–	10	–
B^1	0.4	10.0	–	43	–
B^2	13.0	10.0	+11.5	64	> 3600
B^3	19.2	6.2 [a]	–	44	–

1, samples stored under a low-humidity atmosphere; 2, samples from commercial suppliers; 3, samples stored in an atmosphere of 100% RH.

[a] Tablets obtained by extremely high compression force.

TABLE 5

Properties of 150 mg tablets pressed from binary powder mixtures (a) directly after compression, and (b) after 50 weeks storage

Mixture		Composition (%)					
		1	2	3	4	5	6
Chitosan B		25	50	25	50	25	50
Potato starch		75	50	–	–	–	–
Lactose		–	–	75	50	–	–
Somicel F		–	–	–	–	75	50
Hardness (kg)	a	9.8	9.9	8.0 *	10.0	9.9	10.0
	b (%)	−8.2	−5.7	−6.2	−9.0	−20.0	−16.0
Friability (%)	a	0.8	0.3	0.2	0.1	0.1	0.1
	b (%)	−25.0	+25.0	0.0	0.0	0.0	0.0
Desintegration time (s)	a	122	177	29	73	52	49
	b	148	258	67	726	31	37

[a] Tablets obtained by extremely high compression force.

to resolve the well-known problem due to the interaction between potato starch and sodium benzoate by the partial substitution of chitosan for starch (compositions 1SB and 2SB) was therefore unsuccessful.

Tablets prepared via the compression of mix-

TABLE 6

Properties of 1000 mg tablets pressed from ternary powder mixtures (powder compositions listed in Table 2) (a) directly after compression and (b) after 150 weeks storage

		Composition					
		1SB	2SB	3SB	4SB	5SB	6SB
Hardness (kg)	a	9.9	10.0	10.0	10.0	10.0	10.0
	b (%)	−39.4	−50.2	−49.7	−45.3	−64.8	−40.0
Friability (%)	a	2.2	2.7	1.0	2.1	1.9	1.7
	b (%)	+72.9	+129.5	+367.0	+252.4	+371.2	+199.4
Disintegration time (s)	a	> 3600	26	41	30	30	16
	b	1800	20	21	27	21	20
		Composition					
		1SA	2SA	3SA	4SA	5SA	6SA
Hardness (kg)	a	9.9	10.1	10.1	10.0	10.0	10.2
	b (%)	+6.1	−10.9	−10.9	+4.5	−35.0	−15.4
Friability (%)	a	3.0	2.3	0.9	1.0	2.4	1.4
	b (%)	−32.3	−14.2	−1.2	+23.1	+129.9	+11.4
Disintegration time (s)	a	20	11	15	18	8	8
	b	23	21	23	16	9	9
		Composition					
		1PA	2PA	3PA	4PA	5PA	6PA
Hardness (kg)	a	10.0	10.0	10.0	10.0	10.2	10.0
	b (%)	−20.0	−0.5	+30.0	+4.8	−31.4	0.0
Friability (%)	a	1.5	1.4	0.5	1.2	1.3	1.2
	b (%)	+34.4	−4.2	−44.7	−60.5	+41.2	−25.0
Disintegration time (s)	a	31	18	13	11	8	8
	b	20	23	17	16	10	10

tures containing 30% of a readily tableting remedy (salicylamide or paracetamol) exhibited no difference in properties even after long-term storage.

The decrease in hardness of tablets compressed with the addition of dibasic calcium phosphate dihydrate (compositions 5SA and 5PA) may well be reduced either by increasing the content of chitosan or via the application of greater pressure during the process of tableting.

Conclusion

Chitosan, obtained from krill chitin, meets the standard requirements for auxiliary substances used in direct tableting. As a filler, chitosan has no influence on the flow of the tablet mass. When present at 50% of the amount of tablet mass, it behaves as a disintegrant.

The degree of deacetylation determines the extent of moisture absorption of chitosan being stored at high RH. An excessively high moisture content renders the production of tablets with satisfactory mechanical properties impossible.

Tablets prepared with the addition of chitosan may, following long-term storage, show a decrease in hardness. However, their disintegration time either remains constant or is reduced.

Appendix

The above conclusions led to the development of a tablet formulation with a high content of active ingredients and chitosan. The effectiveness of the formulation as well verification of the tablet quality will be presented in a subsequent paper.

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