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Antimycotic buccal and vaginal tablets with chitosan

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Summary

On the basis of the biomedical properties of 66% deacetylated krill chitosan, formulations of tablets containing nystatin or clotrimazole were prepared. Tablets obtained by direct compression disintegrate either slowly in water (buccal), or rapidly in a 0 1% lactic acid solution (vaginal). The stability of the tablet properties, as well as the microbiological and chemical stability of the applied drugs, both recorded after storage, considerably extend the applicability of chitosan as an auxiliary substance for use in direct tableting.

Introduction

Chitosan, a partially deacetylated chitin, is an auxiliary substance widely used in pharmaceutical technology (Machida and Nagai, 1989). In another paper (Knapczyk, 1993), it was demonstrated that when used as a filter, chitosan has no effect on the flow of a multicomponent powder mixture and is suitable for use in the process of direct tableting on the basis of its binding properties: addition of chitosan in the proportion of 50% of the tablet mass ensured the rapid disintegration of tablets. In contrast, following long-term storage of chitosan-containing tablets, the mechanical properties of the tablets may deteriorate.

However, the extent to which the properties are modified depends more strongly on the type of drug as compared to any differences between the primary characteristics of chitosan samples.

In comparison with other natural water-insoluble polymers, chitosan exhibits low toxicity, has the ability to depolymerize enzymes, is safe biologically (Knapczyk et al., 1989a; Seo et al., 1990), biocompatible after both i.v. and oral administration (Hirano et al., 1988) and digestible on long-term oral administration (Hirano et al., 1990).

Chitosan lacks irritant or allergic effects and is biocompatible with both healthy and infected human skin (Knapczyk et al., 1989c). Chitosan is not a drug, but rather, a substance that displays dose-dependent bioactivity (Knapczyk, 1991). When added in large amounts to antimycotic

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drug formulations such as tablets (Knapczyk et al., 1989c; Liber et al., 1990) or gel-making powders and gels (unpublished data), chitosan increases the efficacy of the drug. It also inhibits the adhesion of *Candida albicans* cells to human vaginal epithelial cells (similar to buccal cells), acts non-specifically on fungal and epithelial cells and prevents the development of mycosis (Knapczyk et al., 1992). Additionally, use is made of chitosan's protective and dressing properties, its biostimulatory activities in reparative processes and its capability of tissue reconstruction (Knapczyk, 1991). The present work was aimed at the development of new formulations suitable for therapeutic use of (i) buccal tablets (containing 66% deacetylated chitosan, 500 000 nystatin units and 10 mg lidocaine hydrochloride, disintegrating in water within 30–60 min) and (ii) vaginal tablets (containing 66% deacetylated chitosan, 500 000 nystatin units or 400 mg clotrimazole, rapidly disintegrating in a 0.1% solution of lactic acid).

Materials and Methods

Chitosan derived from krill chitin was supplied by the Sea Fisheries Institute, Gdynia, Poland.

TABLE 1

Primary characteristics of chitosan samples

Parameters	Sample		
	A	B	F
Solubility in acidic solutions	no	yes	yes
Degree of deacetylation (%)	49	66	93
Viscosity grades	–	medium	low

The primary characteristics of the samples used are listed in Table 1, the other properties meeting the requirements of the common standards (Knapczyk et al., 1989b).

The drugs, nystatin of potency 4000 units per mg (Polfa, Kraków), micronised clotrimazole (Polfa, Poznań), lidocaine hydrochloride (POCh, Gliwice), and excipients, lactose monohydrate special for tableting, lot no. 8195 (Merck, Darmstadt), potato starch (PPZ, Trzemieszno), carboxymethylcellulose sodium (JEL, London), boric acid, sorbic acid, sodium bicarbonate (all from POCh, Gliwice) were obtained from the indicated sources and were used as powders of particle size lower than 0.3 mm.

Multicomponent powder mixtures and 15 mm flat-faced buccal or 22 mm biconvex oval vaginal

TABLE 2

Properties of buccal tablets containing 500 000 nystatin units (a, directly after compression, b, after 50 weeks storage)

Mixture		Composition of formulation (mg)							
		1	2	3	4	5	6	7	8
Nystatin		125	125	125	125	125	125	125	125
Lactose		125	275	125	225	225	125	125	125
Lidocaine HCl		10	10	10	10	10	10	10	10
Chitosan B		250	250	250	250	–	250	250	250
Chitosan F		–	–	–	–	250	–	–	–
Chitosan A		–	–	–	–	–	–	250	250
Potato starch		–	–	–	–	–	250	–	–
Sorbic acid		40	–	–	–	–	–	–	–
Boric acid		–	100	–	–	–	–	–	–
CMC Na		–	–	100	100	100	100	100	150
pH		6 2	7.1	7.7	7 8	7 4	7 7	8.1	8 1
Hardness (kg)	a	10.0	10.5	10 5	10.0	10 0	10 0	10 5	10.0
	b (%)	−45.0	−40 0	−48.0	−35.0	−16.0	−25.5	−4.8	−5.0
Disintegration time (min)	a	32.6	30 0	60 0	53 0	45.0	59 0	21.0	47 7
	b	0 9	6.1	58.0	39.3	42.0	57.0	18.5	43.7

TABLE 3

Properties of vaginal tablets containing 500 000 nystatin units (a, directly after compression; b, after 50 weeks storage)

Mixture		Composition of formulation (mg)							
		1	2	3	4	5	6	7	8
Nystatin		125	125	125	125	125	125	125	125
Lactose		125	125	125	–	–	125	125	125
Chitosan B		400	–	400	400	400	400	400	400
Chitosan F		–	400	–	–	–	–	–	400
Chitosan A		–	–	–	400	400	400	400	400
Potato starch		–	–	200	–	200	–	200	–
pH		7.5	7.2	7.4	7 6	7 7	7.8	7 8	7 8
Hardness (kg)	a	13 5	13.5	13.5	13 5	13.5	13 5	13.5	13.5
	b	–	–	–	–	13.5	13.5	13.5	13.5
Disintegration time	a	15 0	12.3	13.5	13 3	4.6	5.5	4.3	1.4
(min)	b	–	–	–	–	3.3	4 4	3.2	1 3

tablets were prepared and verified by means of described methods (Knapczyk, 1993).

The pH values of the tableting mixtures were measured potentiometrically in well mixed aqueous suspensions (1 g + 10 ml) of powdered tablets. The disintegration times of buccal tablets in water at $37 \pm 0.5\,^{\circ}C$ were determined using a ZT3 disintegration test apparatus (Erweka, Heusenstamm) without the disc, according to the USP XXI (1985) procedure. In the case of vaginal tablets, the above test was performed in a 250 ml flask by registering complete unit disintegration in a 100 ml volume of 0.1% lactic acid solution allowed to stand at 35–39 °C; the mixture was swirled every 5 min (FP V procedure).

The microbiological determination of nystatin activity and detection of possible clotrimazole decomposition products were performed according to supplementary USP XXI (1985) procedure.

Results and Discussion

Tablets with nystatin should always contain lactose, a substance commonly used for diluting antibiotics. The neutral reaction of an aqueous

TABLE 4

Properties of clotrimazole vaginal tablets (a, directly after compression; b, after 50 weeks storage)

Mixture		Composition of formulation (mg)							
		1	2	3	4	5	6	7	8
Clotrimazole		400	400	400	400	400	400	400	400
Chitosan B		200	200	–	–	600	400	–	–
Chitosan F		–	–	–	–	–	–	600	400
Chitosan A		–	–	600	400	–	–	–	–
$NaHCO_3$		100	100	–	–	–	–	–	–
Potato starch		–	100	–	200	–	200	–	200
pH		8.6	8.5	8 4	8.4	7.5	7.4	7.6	7 6
Hardness (kg)	a	13.5	13.5	13 5	13.5	13.5	13 5	13.5	13.5
	b	13.5	13 5	13.5	13.5	13 5	13.5	13.5	13.5
Disintegration time	a	9 0	7.5	0 8	0.7	1.2	1 0	1 5	1.7
(min)	b	10 0	8 3	0.7	0.7	1 1	1 2	1 7	1.5

suspension of a tablet mass ensures the stability of antibiotics in tablets during storage.

Buccal tablets with nystatin, chitosan B and lidocaine hydrochloride disintegrating in water within 30–60 min (Table 2) may be prepared by the addition of an acid (formulations 1 and 2) or water-soluble polyanion (formulations 3–8). Slow disintegration of tablets in water results from the formation of a chitosan gel in acidic solution. The disintegration time depends upon the type of acid, the ratio of the amount of acid to that of chitosan and the properties of the polymer (unpublished data).

The rate of disintegration of tablets containing CMC-Na varies solely according to the properties and the amount of polyanion that is applied. According to the results of Inouye et al. (1987), this substance abolishes the influence of other tablet mass components on the disintegration time.

Evaluation of tablets stored for 50 weeks indicated that the use of an acid was unfavourable. The disintegration times of tablets prepared by adding various amounts of an acid to their masses were considerably reduced, however, their mechanical resistance was distinctly reduced (unpublished data).

In the case of tablets containing CMC-Na, only the tablet hardness was reduced, the extent of reduction being evidently dependent on the composition of the tableted mixture. Addition of insoluble chitosan A to the mass stabilized the mechanical properties of a tablet. In spite of an increase in tablet mass (Tables 3 and 4), the disintegration time was not reduced. Nystatin tablets of all proposed formulations disintegrated within 15 min in 0.1% lactic acid solution (Table 3), i.e., conditions representing a standard requirement for vaginal tablets. However, in the case of the direct tableting of an antibiotic/lactose mixture with deacetylated chitosan B or F which is soluble in acidic medium (formulations 1 and 2), potato starch (formulation 3) or insoluble chitosan A substituting the lactose (formulation 4), tablets disintegrating within 12–15 min may be prepared.

Considerably accelerated tablet distintegration with nystatin and chitosan B is achieved by the addition of chitosan A mixed with potato starch (formulation 5), lactose (formulation 6), both potato starch and lactose (formulation 7) or lactose and chitosan F (formulation 8). The greater the amount of substances admixed with chitosan A in relation to the proportion between nystatin and chitosan B, the shorter is the disintegration time.

The introduction of chitosan B and a mixture of chitosan A, both in equal amounts, into a tablet with nystatin results in the tablet hardness and disintegration time in water and in acidic medium remaining unchanged during long-term storage.

The formulation of vaginal tablets containing clotrimazole and chitosan that rapidly undergo disintegration in acidic medium is a simple task (Table 4). If fillers such as chitosan B with $NaHCO_3$ (formulation 1) or the latter mixed with potato starch (formulation 2) are added in amounts comparable to that of an effective remedy, a disintegration time shorter than 15 min is achieved. Similarly to the case of tablets with nystatin, an increase in the amounts of chitosan and filler in the directly tableted mass (formulations 3–8) substantially reduces the distintegration time.

In constrast to nystatin, clotrimazole is structurally homogeneous, thus explaining why clotrimazole tablets, analogously to those pressed from

TABLE 5

Microbiological activity of nystatin [a] (a, established for declared nystatin content, b, determined after 100 weeks storage)

Test sample	Mass (mg)	a (%)	b (%)
Nystatin, substance	125	109.3	81 1
Nystatin + lactose (in equal parts)	250	109 3	88 0
Buccal tablet (Table 2, composition 1)	550	109 1	92 6
Vaginal tablet (Table 3, composition 1)	650	106.6	93 6

[a] Based on test organism *Saccharomyces cerevisiae* ATCC 9763.

TABLE 6

Data used for testing chemical stability of clotrimazole by means of thin-layer chromatography

Stored test sample	Substance and vaginal tablets (Table 4, compositions 1 and 2)	
Search product	(*o*-chlorophenyl)diphenylmethanol, triphenyl-1-methylimidazole	imidazole
Stationary phase	silica gel plate (F_{254})	silica gel plate (F_{254})
Mobile phase	isopropyl ether saturated with ammonia	methanol : chloroform (3 2), chloroform methanol : strong ammonia solution (60 : 10 . 1)
Location procedure	short-wavelength UV light, Dragendorff reagent	short-wavelength UV light, saturated iodine vapour, acidified iodine solution, iodoplatinate solution

a mixture of salicylamide or paracetamol with chitosan B (Knapczyk, 1993) retain their properties during long-term storage.

The effectiveness of chitosan in antimycotic tablet formulations was verified by determination of the microbiological activity of nystatin in specimens that had been stored for 100 weeks (Table 5) and evaluation of the chemical stability of clotrimazole in samples that had been in storage for 150 weeks (Table 6).

The smaller extent of decrease in antibiotic activity in tablets than in a substance as well as the lack of additional spots on the plates developed during chromatographic tests indicated the absence of decomposition products of clotrimazole in tablets, thus demonstrating that the objective of the present study had been achieved.

Conclusion

The appropriate choice of the proportions of chitosans of various degrees of deacetylation prevents the deterioration of the mechanical properties of tablets during storage. In the case of tablets containing large amounts of readily tableting drugs (clotrimazole) the addition of 49% deacetylated chitosan to a directly tableted mass is unnecessary and tablet disintegration is accelerated on increase in the content of fillers.

In contrast, if slowly disintegrating (buccal) tablets are produced, the use of a mixture of deacetylated chitosans with the addition of CMC-Na is advisable. Such tablets retain their properties during storage.

Neither the activity of nystatin nor the chemical stability of clotrimazole in stored tablets is affected by the applied acid-soluble deacetylated chitosan.

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