International Journal of Pharmaceutics, 93 (1993) 233–237

IJP 02968

Notes

Chitosan hydrogel as a base for semisolid drug forms

Jan Knapczyk

Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Nicholas Copernicus Medical Academy, Kraków (Poland)

(Received 4 February 1992)
(Modified version received 10 June 1992)
(Accepted 30 June 1992)

Key words: Chitosan; Cationic excipient; Stability; Gel formulation; Interaction

Summary

A transparent and water-soluble/miscible gel ointment base was obtained by dissolving 93% deacetylated chitosan F in a solution of lactic acid. Rheological tests indicated that such a base was stable when clotrimazole, piroxicam, estradiol, progesterone, lidocaine HCl or a sodium salt of heparin were used. On the other hand, liquefaction of the gels took place on dissolving metronidazole or suspending hydrocortisone. Gels prepared on the basis of 66% deacetylated chitosan B were less stable. Changes in their consistency depended on the drug introduced. Due to the formation of an adduct between the acetyloamide of chitosan B lactate and the OH-groups of metronidazole or hydrocortisone, the gel initially hardened but did subsequently liquefy. The lower stability of gels prepared using less extensively deacetylated chitosan and the possible interaction of chitosan of lower degree of deacetylation with drugs do not exclude the use of this biopolycation in the ex temporare preparation and application of semisolid drug forms.

The application of chitosan as an auxiliary substance for disintegrating tablet formulations by direct compression has recently been reported (Knapczyk, 1993). The present investigation describes a simple technique for preparing a water-soluble or miscible drug carrier of stable transparency and ointment consistency at room temperature. Comparative studies may be envisaged, involving examination of drug gels during long-term storage, in order to determine the standard requirements for chitosan and the drugs which may be incorporated into the resulting base at therapeutically applicable concentrations.

Chitosan was supplied by the Sea Fisheries Institute (Gdynia, Poland) and was derived from krill chitin of 66% (B) and 93% (F) degree of deacetylation. All of its parameters fulfilled the standard requirements. Other substances used in this study were USP XXI (1985) or Clarke (Moffatt, 1986) grade.

Gels having the compositions listed in Tables 1 and 2 were prepared either by adding lactic acid to aqueous suspensions of appropriate powders or by mixing suitable powder mixtures with water. The water always contained suitable amounts of methylparaben added as a 10% (w/w) ethanolic solution and disodium edetate. The samples were

Correspondence to: J. Knapczyk, Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Nicholas Copernicus Medical Academy, Krupnicza 16, 31–123 Kraków, Poland.

TABLE 1

Composition of gels prepared with chitosan B (in g)

Ingredients	Gel								
	1	2	3	4	5	6	7	8	9
Chitosan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactic acid (ml)	0.5	0.5	0.5	–	–	–	–	–	–
Boric acid	–	–	–	5.0	5.0	5.0	5.0	5.0	5.0
Heparin Na	–	–	–	–	0.22 [a]	–	–	–	–
Lidocaine HCl	–	–	–	–	–	1.0	–	–	–
Metronidazole	–	1.0	–	–	–	–	1.0	–	–
Hydrocortisone	–	–	–	–	–	–	–	1.0	–
Clotrimazole	–	–	5.0	–	–	–	–	–	5.0
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Na_2EDTA	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water to	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
pH	5.7	5.7	5.7	7.1	7.1	7.1	7.1	7.1	7.1

[a] 0.22 g = 30 800 units.

mixed for 5 min at 5000 rpm in a homogenizer (Mechanika Precyzyjna, Warszawa) and stored in closed glass containers either in a cold place (5 ± 3°C) or at room temperature (25 ± 5°C). After conditioning the specimens for 24 h at 25 ± 0.1°C, their shear stresses were determined for increasing and decreasing shear rates on a Rheotest cylinder viscosimeter (Medingen, Dresden). The pH values of gels were measured potentiometrically in thoroughly mixed aqueous sample solutions (1 g + 10 ml).

For studying interactions, gel samples were freeze-dried using an OE 950 laboratory freeze drier (Labor Instrument Works, Esztergom). The components were examined by IR spectroscopy on a Digilab FTS-15 Fourier transform spectrom-

TABLE 2

Composition of gels prepared with chitosan F (in g)

Ingredients	Gel								
	10	11	12	13	14	15	16	17	18
Chitosan F	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Lactic acid (ml)	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
Heparin Na	–	0.22 [a]	–	–	–	–	–	–	–
Lidocaine HCl	–	–	1.0	–	–	–	–	–	–
Metronidazole	–	–	–	1.0	–	–	–	–	–
Hydrocortisone	–	–	–	–	1.0	–	–	–	–
Clotrimazole	–	–	–	–	–	5.0	–	–	–
Estradiol	–	–	–	–	–	–	0.06	–	–
Progesterone	–	–	–	–	–	–	–	1.0	–
Piroxicam	–	–	–	–	–	–	–	–	1.0
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Na_2EDTA	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water to	100.0	100.0	100.0	100.0	100.0	100.0	100.1	100.0	100.0
pH	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0

[a] 0.22 g = 30 800 units.

eter (Biorad, Düsseldorf), according to a previously described procedure (Zięba and Knapczyk, 1988).

UV absorption spectra of metronidazole were acquired by means of an SP 500 spectrophotometer (Unicam, Cambridge) using samples dissolved in a suitable solvent (USP XXI, 1985; Moffatt, 1986).

The biologically safe lactic acid appeared to be a universal solvent for chitosan. The resulting transparent gels had no unpleasant organoleptic features and behaved analogously to skin and mucous membranes. Gels of greater density could be spread and rubbed readily and were easily removed with water. When excessive amounts were used, they dried rapidly forming an elastic membrane. On storage in hermetic containers (e.g., tubes), they neither dried nor reacted with laminated surfaces of the tubes.

Chitosan B gels obtained using boric acid showed neutral reactions, which may be supposed to slow down the depolymerization of chitosan.

Selection of the appropriate proportions of lactic and boric acids and chitosan B (Table 1) or lactic acid and chitosan F (Table 2 resulted in gels of very similar consistencies (Table 3). Directly after preparation, the flow behavior and viscoelastic properties of particular gels differed slightly between gels and depended on the chitosan applied (B or F), gel reaction and amount of suspended drug (clotrimazole, hydrocortisone, piroxicam, estradiol, progesterone) or dissolved drug (metronidazole, lidocaine HCl or heparin sodium salt).

Examination of the evolution of the rheological properties of gels after a 25 week storage period were directed at the determination of the desired properties of chitosan and the selection of drugs which may be incorporated into the resulting base at appropriate concentrations.

Even if minor changes in consistency ($< 20\%$) are ignored, accompanied by no difference in other pharmaceutical characteristics of the gels, the results obtained demonstrate the degree of

TABLE 3

Rheological properties of gels prepared with chitosan B (1–9) and F (10–18) after (a) preparation, and storage for (b) 10 weeks or (c) 25 weeks in a cold place (CP), or at a room temperature (RT)

Gel	a		b				c			
	T	*V*	*T* (CP)	*T* (RT)	*ΔV* (CP)	*ΔV* (RT)	*T* (CP)	*T* (RT)	*ΔV* (CP)	*ΔV* (RT)
1	2.13	11.92–4.31	–	1.74	–	−12.4	–	1.74	–	−28.8
2	3.87	12.10–3.77	–	17.11	–	+55.7	–	6.38	–	−10.4
3	5.94	15.31–4.74	–	3.33	–	−5.8	–	2.03	–	−12.8
4	0.87	10.96–3.67	4.64	1.96	+0.6	−3.2	3.77	1.30	−16.6	−25.7
5	0.87	10.96–4.06	–	0.29	–	−11.4	–	0.29	–	−29.5
6	2.13	12.24–4.25	–	1.74	–	−17.2	–	1.01	–	−24.9
7	1.77	11.28–3.99	–	U	–	U	–	5.80	–	+102.4
8	1.29	9.89–4.06	–	9.28	–	+92.5	–	13.92	–	+147.2
9	2.61	13.53–5.22	–	1.74	–	+18.2	–	2.90	–	−7.0
10	0.14	8.70–5.32	0.14	0.14	+6.0	−5.2	0.14	0.14	+9.3	−4.7
11	0.14	9.99–5.56	–	0.14	–	−1.2	–	0.29	–	+4.6
12	0.14	9.99–5.56	0.29	0.14	−0.6	−1.7	0.29	0.14	−0.6	−5.4
13	0.14	9.89–5.70	0.14	0.0	−3.0	−58.0	0.14	0.0	−11.7	−80.0
14	0.14	9.99–5.80	0.14	0.14	−5.9	−37.0	0.14	0.0	−14.9	−73.0
15	0.14	14.02–6.96	1.88	1.53	+6.7	+18.0	1.88	1.88	+10.6	+19.6
16	0.29	9.67–5.56	–	0.29	–	−4.6	–	0.14	–	−9.3
17	0.29	10.47–5.90	–	0.30	–	+1.1	–	0.27	–	−0.6
18	0.14	10.63–5.90	–	0.46	–	+7.6	–	1.26	–	+20.7

T, thixotropy (Pa s) by rate of shear $D = 27\ s^{-1}$; *V*, viscosity (Pa s) by rate of shear $D = 24.3–81.0\ s^{-1}$; *ΔV*, difference in viscosity (in %); U, undeterminable.

deacetylation of chitosan to exert an influence and the possibility of an interaction occurring between chitosan and the incorporated drug.

Irrespective of the acid employed (gels 1 and 4) and gel reaction, stable gels were not produced using chitosan B. Introduction of drugs of different solubility (gels 3 and 9 or 5 and 6) did not prevent a gradual decrease in the consistency of gels. The stabilizing effect of suspending greater amounts of clotrimazole should still be verified following storage for longer periods.

Gels containing chitosan B (gels 2 and 7) hardened after the introduction of soluble metronidazole. This effect, which was particularly evident in the case of gels displaying neutral reactions, was too strong for measurement by means of the available equipment. During further storage, the gels gradually liquefied and showed a systematic darkening in color. Similar changes were observed, albeit later, for hydrocortisone suspended in a neutral gel with chitosan B (gel 8).

The above changes in gel consistency probably resulted from an initially predominant process of chitosan-drug adduct formation followed at a later stage by depolymerization of chitosan. Low-temperature storage of gels did not prevent their liquefaction, the process only being retarded. The foregoing interpretation was supported by the evaluation of gels prepared using chitosan F. This biopolymer, exhibiting a higher degree of deacetylation, allowed the preparation of stable gels (gels 10–12 and 15–18). Similarly to gels prepared with chitosan B, the system was stabilized by suspending a substance (gels 15 and 18). In contrast, addition of metronidazole (gel 13) or hydrocortisone (gel 14) led to liquefaction of the gel together with a progressive change in color. Nevertheless, hardening of the gel did not take place. Changes in consistency of metronidazole- and hydrocortisone-containing gels during storage were different and depended on the degree of deacetylation of the chitosan employed. Such changes resulted from adduct formation between the acetyloamide groups of chitosan lactate and OH groups of both drugs. In the case of chitosan B, this process led to the initial hardening of the gel. In addition, the possible participation of chitosan OH groups in the formation of an adduct with metronidazole (Fig. 1) should be capable of being observed by analysis of pure compounds (Zięba and Knapczyk, 1988; Sanzgiri et al., 1990; Takayama et al., 1990). For metronidazole or freshly prepared gel 2, the position of the maximum UV absorption intensity demonstrated shifts

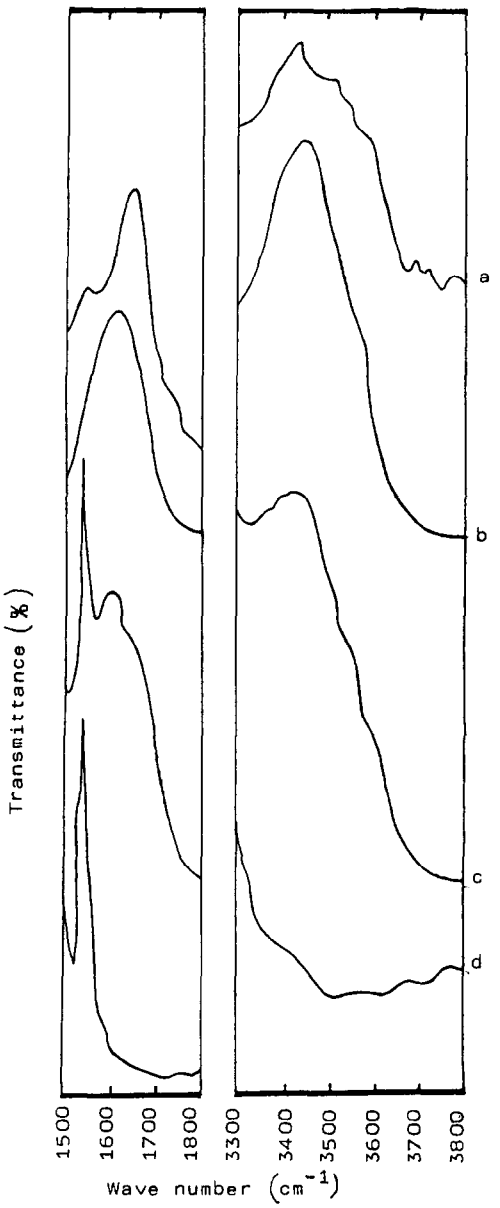

Fig. 1. IR spectra of chitosan B (a); freeze-dried gel 1, stored 10 weeks at room temperature (b); freeze-dried gel 2, stored 10 weeks at room temperature (c); and metronidazole (d).

after 10 weeks storage at room temperature from 277.2 to 276.1 nm (in 0.1 N HCl), from 276.7 to 268.8 nm (in methanolic H_2SO_4) or from 320.5 to 310.8 nm (in 0.1 N NaOH). The observed shifts indicate the occurrence of changes in the drug molecule, confirming the existence of the suggested mechanism of interaction.

The above interpretation was also verified by the behavior of both gels with clotrimazole, a substance which possesses an imidazole group (like metronidazole) but lacking OH groups. The introduction of clotrimazole into gels with chitosan B (gels 3 and 9) was followed by neither hardening nor liquefaction, even after prolonged storage. On the other hand, when incorporated into a gel with chitosan F (gel 15), clotrimazole initially led to its acceptable hardening. The consistency of the gel then remained stable irrespective of the storage temperature.

Acknowledgements

The author wishes to thank Dr J. Zięba for recording and interpreting the IR spectra. Helpful suggestions made by Professors T. Nagai and L. Krówczyński are gratefully acknowledged.

References

Moffatt, A.C., *Clarke's Isolation and Identification of Drug in Pharmaceuticals, Body Fluids, and Postmortem Materials,* Pharmaceutical Press, London, 1986.

Knapczyk, J., Excipient ability of chitosan for direct tableting. *Int. J. Pharm.*, 89 (1993) 1–7.

Sanzgiri, Y.D., Blaton, C.D. and Gallo, J.M., Synthesis, characterization, and in vitro stability of chitosan-methotrexate conjugates. *Pharm. Res.*, 7 (1990) 418–421.

Takayama, K., Hirata, M., Machida, Y., Masada, T., Sannan, T. and Nagai, T., Effect of interpolymer complex formation on bioadhesive property and drug release phenomenon of compressed tablet consisting of chitosan and sodium hyaluronate. *Chem. Pharm. Bull.*, 38 (1990) 1993–1997.

US XXI-NF XVI, US Pharmacopeial Convention, Rockville, MD, 1985.

Zięba, J. and Knapczyk, J., Drug adducts with microcrystalline chitosan and microcrystalline cellulose. *Acta Pharm. Technol.*, 34 (1988) 84–87.