ELSEVIER

International Journal of Pharmaceutics 112 (1994) 125–131

international journal of pharmaceutics

Physico-chemical characterization and tabletting properties of Scleroglucan

S. Rizk [a], C. Duru [a,*], D. Gaudy [a], M. Jacob [a], F. Ferrari [b], M. Bertoni [b], C. Caramella [b]

[a] *Laboratoire de Pharmacie Galénique, Pharmacotechnie et Biopharmacie Université de Montpellier I, Montpellier, France*
[b] *Dipartimento di Chimica Farmaceutica Universita di Pavia, Pavia, Italy*

Received 4 March 1994; accepted 28 April 1994

Abstract

The aim of this work was to describe those characteristics of scleroglucan that are relevant to its employment as a sustained release agent in hydrophilic swellable matrices. Besides a brief review of the rheological properties of scleroglucan, various measurements have been effected to define the physical and mechanical properties of scleroglucan and to forecast its behavior as a matrix carrier.

Keywords: Scleroglucan; Polysaccharide; Physical properties; Direct compression; Matrix carrier

1. Introduction

In recent years, hydrophilic polymers have found widespread use in pharmaceutical applications. Many systems are prepared by compression of drugs/tracers and polymer mixtures to form porous, swellable matrices.

In order to investigate the suitability of a polymer as a matrix forming agent, it is necessary to gather sufficient information about its physical and mechanical properties, since the properties of the matrix will mainly depend on the characteristics of the polymer.

Scleroglucan is a water soluble non-ionic natural polymer produced by the fungus *Sclerotium rolfsii* (Johnson et al., 1963).

The chemical structure of scleroglucan consists of β-1,3-D-glucan residues with one β-1,6-D-glucan side chain every three main chain residues (Yanaki et al., 1981; Rinaudo and Vincedon, 1982). Its molecular weight is very high: Mol. Wt 540 000 (Salemis and Rinaudo, 1984).

It has various industrial applications, namely, in the oil industry for thickening drilling muds and enhancing recovery. Thanks to its thickening and suspending properties (Brigand, 1988), it is used also in adhesives, water colour, printing inks, in cosmetics, pharmaceutical and food industries.

Two main grades are marketed: native scleroglucan (Actigum CS6) and purified scleroglucan (Actigum CS11).

* Corresponding author.

SSDI 0378-5173(94)00142-R

To assess its suitability as a sustained release agent, in a previous study (Rizk et al., 1993a), we investigated the rheological properties of scleroglucan solutions and their changes under the influence of different physical variables such as temperature, pH, ionic strength, concentration, and storage time.

It was found that temperature, over the range 20–60°C, pH from 1 to 10 and a storage time up to 48 h caused no significant changes in solution viscosity.

Moreover, for the 1–3% scleroglucan concentration interval and for 0–20% sodium chloride added solutions, the viscosifying behaviour remained stable.

On the other hand, no thixotropic character of the solutions was quantifiable.

In conclusion, the high viscosity of scleroglucan solutions at low concentrations (1–3% w/w) together with their stability make this polymer exploitable in pharmaceutical preparations.

The aim of present paper was to investigate the physico-chemical and mechanical characteristics of scleroglucan (both as a powder and after compression) that may be relevant to its behavior as a gelling agent in drug release.

In particular, X-ray diffraction analysis was performed to establish the amorphous and crystalline nature of the material.

It is indeed known that dissolution medium penetrates more easily the amorphous phases, which are characterised by a weaker molecular cohesion than the crystalline networks.

It is also conceivable that under certain experimental conditions, amorphous phases show a transition to glassy state, a thermodynamically unstable state which becomes rubbery whenever thermodynamic and kinetic factors allow.

Therefore, in order to investigate the conditions leading to a glass transition, which may affect the scleroglucan role in drug release, differential scanning calorimetry (DSC) was also performed

Furthermore, the hydrophilicity of scleroglucan was assessed by means of water uptake measurements, which were performed on a powder bed with a modified Enslin apparatus (Van Kamp et al., 1986; Ferrari et al., 1988).

Other physico-chemical characteristics linked to the hydrophilicity of a polymer powder (humidity loss and regain and specific surface area) were investigated.

Water uptake and specific surface area measurements were also performed on two related polysaccharides: a xanthan gum (xanthan CX90) with matrix-forming properties (Ingani and Moes, 1988); and a cross-linked xanthan gum (xanthan SM) with disintegrant properties (Duru et al., 1992).

Finally, in order to examine the behaviour of scleroglucan upon compression, tablets made only of polymer were prepared at three compression force levels and tested for mechanical and physical properties.

2. Materials and methods

2.1. Materials

Scleroglucan (Actigum CS11), xanthan gum (xanthan CX90) and cross-linked xanthan gum (xanthan SM) (all supplied by Sanofi Bio Industries, Isles Sur Sorgues, France) were used.

2.2. Methods

2.2.1. X-ray diffraction analysis

X-ray diffraction was performed at room temperature (22°C) with a Sigma 80 type CGR diffractometer; target, Cu (λ = 1.54 Å); filter, Ni; voltage, 40 kV; current, 20 mA; time constant, 2 s; measured from 2θ 3° to 2θ 100°.

2.2.2. DSC

DSC was performed using a Perkin Elmer DSC 4-DSC/ATD. Samples of 5–7 mg were predried at 85°C for 1 h, then heated at a rate of 2°C/min through a temperature range of 10–90°C, under a dry nitrogen stream of 10 ml/min.

2.2.3. Humidity loss and recovery

Humidity measurements were performed with an infrared scale balance (Sartorius MA 30, Sartorius, Gottingen, Germany; accuracy 0.05%)

coupled with a multifunction printer (Precia Data Print YDP02–0dV1).

Measurements were performed on a 10 g sample equally distributed on a cupel and placed in the drying chamber preheated to a 90°C. At predetermined time intervals, the weight loss of the sample, re-ordered corresponding to the humidity loss, was measured and recorded.

In order to evaluate the time needed to recover humidity, the predried test specimen was placed on the balance and, at predetermined time intervals, the weight increase of the sample was determined.

2.2.4. Specific surface area

The specific surface area (B.E.T. 'single point' method) was determined with a surface area analyser (model 2300 II, Micromeretics, U.S.A.). The absorbing gas was a mixture of Ar/N_2 (70:30); the outgassing temperature was 150°C and the outgassing time, 3 h.

2.2.5. Water uptake measurements

The measurements were effected using a modified Enslin apparatus described by Van Kamp et al. (1986) and modified by Caramella et al. (1988). The apparatus basically consists of a communicating vessel filled with water. One arm of the apparatus ends with a sintered glass plate covered with a filter paper disc on which the tablet is placed. The other arm is immersed in a measuring vessel, containing water, and is fixed independently of it. The water level is adjusted so that the water in the measuring vessel is at the same level as in the upper side of the other arm. The amount of water taken up by the tablet is measured by the weight loss on the balance (Sartorius L4P02P, Sartorius, Göttingen, Germany) connected by a serial interface RS232-C to an IBM AT personal computer (IBM Italia, Milan, Italy).

Water uptake vs time profiles were fitted by the Weibull equation (according to Ferrari et al., 1988).

In particular, two parameters were retained in order to compare the three materials: Q_{max}, denoting the maximum water uptake value of the fitted curve and water penetration rate, which is the derivative of the fitted curve at time $t_{63.2\%}$, the time value which corresponds to the centre of the Weibull distribution function.

2.2.6. Tabletting and tablet properties

Tablets containing 500 mg of scleroglucan were directly compressed on an instrumented (Duru et al., 1987) alternative press (OA Frogerais Vitry/Seine, France).

Three tablet series were prepared at three compression force levels: 15, 25 and 50 kN, in order to obtain three different porosity values. Tablets were checked for porosity with a mercury porosimeter (Porosimeter 9320, Micromeritics France) and for physical structure with the X-ray diffractometer.

3. Results and discussion

3.1. Scleroglucan physical characteristics

3.1.1. X-ray diffraction analysis

The scleroglucan X-ray scan (Fig. 1) shows no diffraction peak, which indicates that the structure is completely amorphous.

3.1.2. DSC thermogram analysis

The DSC scan (Fig. 2) shows no thermal event between 10 and 90°C.

3.1.3. Humidity loss and recovery

Fig. 3 shows that the sample gradually loses humidity for 5 min, after which the test specimen contains no more moisture. Such a rapid loss of humidity can be attributed to the absence of chemical bonds between free water molecules and the polymer.

Fig. 4 shows that the dried sample recovers the entire humidity lost within 1 h. Therefore, the dried product should be protected in a water-tight environment to guarantee its stability upon storage.

3.1.4. Specific surface area

In Table 1 the specific surface area of scleroglucan (Actigum CS11) is compared to that of xanthan CX90 and xanthan SM. Each value is the

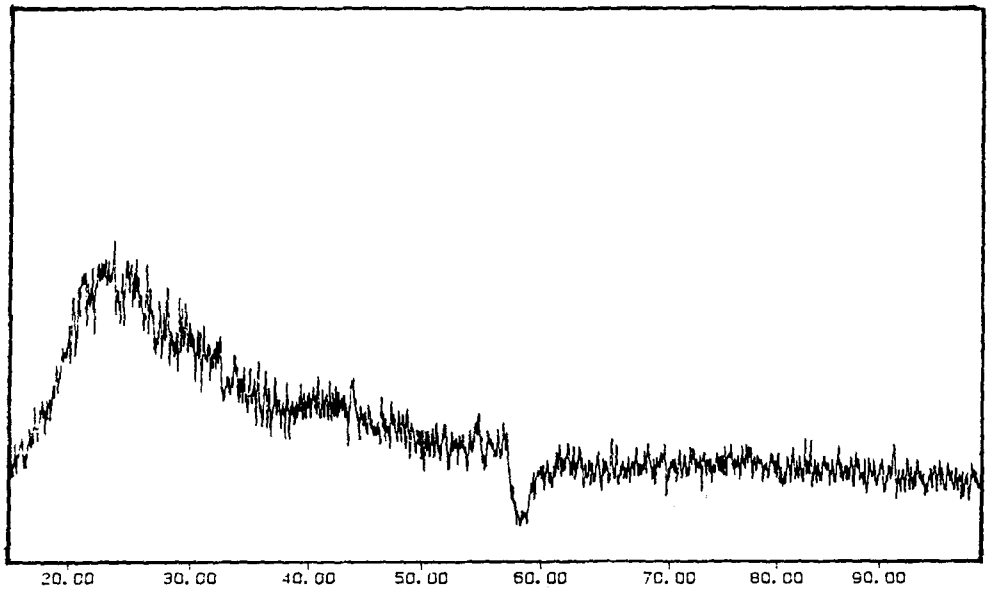

Fig. 1. Scleroglucan X-ray scan.

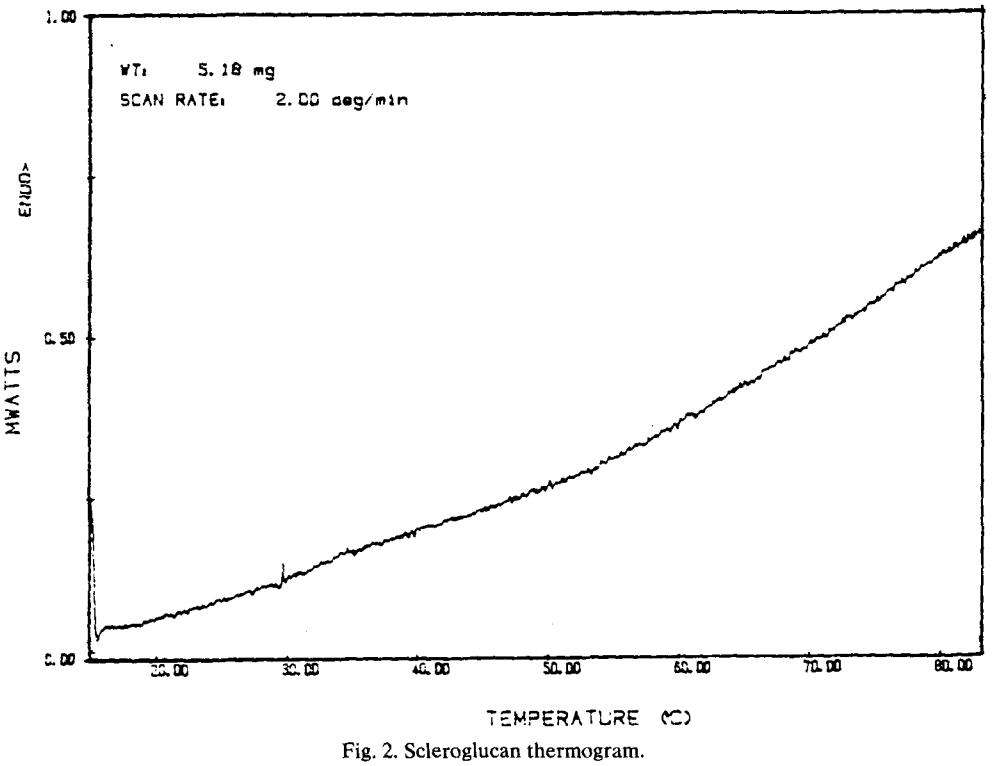

Fig. 2. Scleroglucan thermogram.

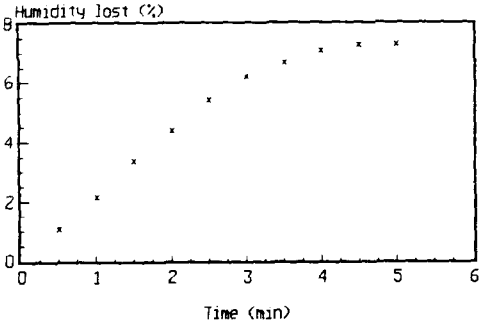

Fig. 3. Plot of humidity lost.

mean of three replicates (C.V. less than 3%). Scleroglucan presents the largest specific surface area.

3.1.5. Water uptake measurements

In Fig. 5 the mean water uptake profiles, normalised per g of powder, of the three polysaccharides are given. Each profile is the mean of three replicates (C.V. less than 5%).

Actigum CS11, similarly to xanthan CX90, is characterised by low water uptake over a relatively long period of time, whereas xanthan SM, showing more hydrophilic properties, is characterised by greater water uptake over a short period of time.

The water uptake parameters obtained by fitting the water uptake profiles by the Weibull equation are given in Table 2. The coefficient of variation of estimated parameters was always less than 5%.

As anticipated, xanthan CX90 looks similar to Actigum CS11. Xanthan SM is characterized by a much higher water penetration rate which explains its disintegrating properties.

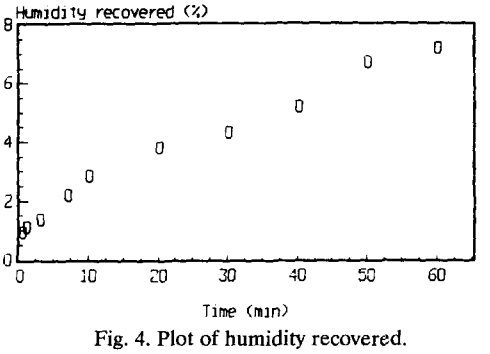

Fig. 4. Plot of humidity recovered.

Table 1
Specific surface area of polysaccharides samples

	Specific surface area ($m\ g^{-1}$)
Actigum CS11	0.67
Xanthan CX90	0.52
Xanthan SM	0.44

Water uptake measurements would indicate that scleroglucan (similarly to xanthan CX90) interacts very slowly with water and may therefore be used as a matrix carrier for slow release preparations.

During hydratation, the formation of a gel layer, which slows down the penetration of the dissolution medium, has been observed.

The specific surface area does not seem to influence the rate of water penetration of slowly hydrating polymers (Actigum CS11 and xanthan CX90). In fact, the largest specific surface area corresponds to the slowest water uptake. This indicates that the formation of the gel-layer at the surface of the polymer is the rate-limiting step of water penetration.

On the other hand, the smallest specific surface area of xanthan SM does not limit its hydrophilicity. In fact, no gel layer is formed and the material can therefore be used as disintegrating agent.

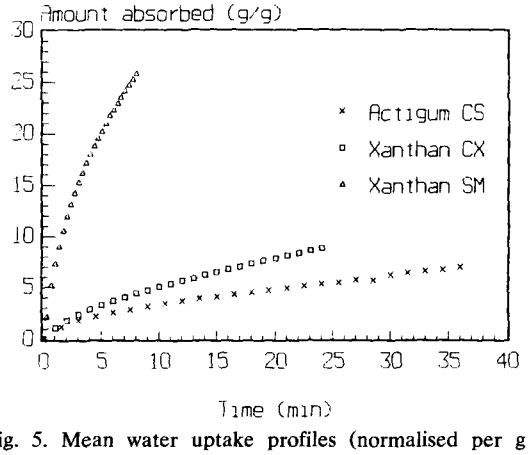

Fig. 5. Mean water uptake profiles (normalised per g of powder) of the three polysaccharide samples.

Table 2
Water uptake parameters of polysaccharides samples

	Q_{max} (g/g)	Water penetration rate (g/min)
Actigum CS11	6.85	0.16
Xanthan CX90	8.77	0.32
Xanthan SM	25.72	3.18

3.2. Scleroglucan pharmacotechnical properties

3.2.1. Scleroglucan raw material

In Table 3 the results of preformulation studies carried out on scleroglucan powder (namely, granulometry, rheology and compressibility) and tablets are given (Rizk et al., 1993b).

Scleroglucan can be considered as a fine powder ($d_m = 15$ μm). Its particle size is compatible in dimensions with those of most base materials used for direct compression. Its flow rate (according to the French Phamacopoeia (1991) Xth Edn, V.5.G.) is satisfactory (lower than 10 g/s^{-1}); its high packing volume (French Phamacopoeia (1991) Xth Edn, V.5.F.), would suggest that scleroglucan might be mixed with a base material characterized by a higher density.

The low correlation coefficient of the plot ($D = f(Y_1)$ (D, tablet hardness; Y_1, compression force) indicates that scleroglucan must be formulated together with another excipient in order to reduce the high compression energy.

The lack of disintegration (European Phamacopoeia (1991) IInd Edn, V.5.1.1) over a 6 h period confirms the suitability of scleroglucan for use as a matrix carrier.

Table 3
Scleroglucan pharmacotechnical properties

Powder	
Particle size distribution	normal law distribution $d_m = 0.15$ $\sigma = 0.06$
Flow rate	8 s/100 g
Packing volume ($V_{10} - V_{500}$)	32 ml/100 g
Tablets	
Hardness (D) vs compression force (Y_1) plot (linear regression coefficient)	$D = -0.434 + 0.0005Y_1$ $r = 0.9998$
Disintegration time	$T > 6$ h

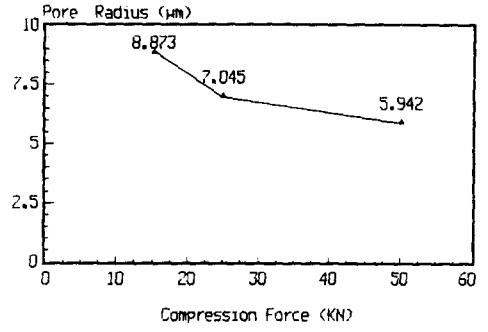

Fig. 6. Tablet pore radius at different compression force levels.

3.2.2. Scleroglucan tablet properties

Fig. 6 and 7 show the patterns of mean pore radius and pore volume, respectively, as a function of the compression force levels.

An inverse relationship seems to exist between compression force and mean pore radius (Fig. 6) as well with pore volume (Fig. 7).

At the maximum force level (50 kN), zero porosity is not yet reached, which otherwise could lead to tablet decapping with no additional bonds (Rime and Doelker, 1993).

X-ray thermograms performed on scleroglucan tablets show the tablet structure is similar to that observed for Actigum CS11 powder: this fact point out the absence of crystalline structure formation even under high compression forces (50 kN).

Scleroglucan can be used as a directly compressible material yelding non-disintegrating, porous, swellable matrices for sustained release tablets.

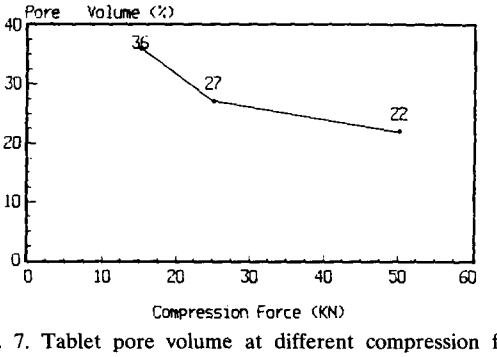

Fig. 7. Tablet pore volume at different compression force levels.

4. Conclusions

The following observations can be drawn from the tests performed: (i) Scleroglucan (Actigum CS11) has a completely amorphous structure; (ii) no thermal event was found between 10 and 90°C; (iii) the dried sample, obtained after a 5 min desiccation at 90°C, recovers within 1 h the entire humidity lost; (iv) Actigum CS11 water uptake capacity is similar to that of xanthan CX90 which is known for its matrix forming properties; (v) Actigum CS11 tablets disintegrate very slowly, even when prepared at low compression forces ($F = 15$ kN): even at high compression forces, the tablets maintain a relatively high porosity; (vi) whatever the force exerted (15–50 kN), the structure of Actigum CS11 remains amorphous; (vii) the physico-chemical properties of Actigum CS11 suggest its suitability as a gelling polymer carrier matrix for slow release matrices.

Acknowledgements

The authors would like to thank Micromeritics S.A.-France, for porosity measurements and Sanofi Bio Industries-France, for providing polysaccharide samples.

References

Brigand, G., *The Scleroglucan,* Technical Bulletin, CECA SA Research Laboratory, Baupte, France, 1988.

Caramella, C., Ferrari, F., Gazzaniga, C., Conte, U., La Manna, A. and Gedde, M., A new computer aided apparatus for simultaneous measurements of water uptake and swelling force in tablets. *Proc. Pharm. Technol. Conf.,* 7 (1988) 194–204.

Duru, C., Abramovici, B., Jacob, M., Puech, A. and Baylac, G., Etude en compression directe de gélatines hydrolysées: Evaluation de leur influence sur la comprimabilité du lactose cristallisé par mesures extensiométriques. *Pharm. Acta Helv.,* 62 (1987) 145–153.

Duru, C., Colombo, P., Gaudy, D., Massimo, G., Santi, P., Catellani, P.L. and Barthelemy, P., A comparative study of the disintegrating efficiency of polysaccharides in a directly-tabletable formulation. *Pharm. Technol. Int.,* 4 (1992) 15–23.

Ferrari, F., Geddo, M., Cazzaniga, A., Caramella, C. and Conte, U., Water uptake to fast disintegrating tablets and Weibull function. *STP Pharm.,* 4 (1988) 481–484.

Ingani, H.M. and Moes, A.J., Utilisation de la gomme de xanthane dans la formulation des matrices hydrophile de théophylline. *STP Pharm.,* 4 (1988) 188–195.

Johnson, J., Kirkwood, S., Misaki, A., Nelson, T.E., Scaletti, J.V. and Smith, F., Structure of a new glucan. *Chem. Ind.,* (1963) 820–822.

Rime, A.F. and Doelker, E., Caractéristiques de compression et comprimabilité des poudres de polymères à usage pharmaceutique. *STP Pharm. Sci.,* 2 (1993) 109–129.

Rinaudo, M. and Vincendon, M., ^{13}C NMR structural investigation of scleroglucan. *Carbohydr. Polym.,* 2 (1982) 135–144.

Rizk, S., Duru, C., Bardet, L., Fortunet, R. and Jacob, M., Etude des caractéristiques rhéologiques d'un polymère naturel, le scléroglucane. *J. Pharm. Belg.,* 48 (1993a) 1–12.

Rizk, S., Duru, C., Sabatier, R. and Jacob M.. Matrices hydrophiles à base de Scléroglucane:choix de l'excipient diluant. *J. Pharm. Belg.,* 48 (1993b) 197–207.

Salemis, P. and Rinaudo, M., Gel permeation chromatography of starch and other uncharced polysaccharides. *Polym. Bull.,* 11 (1984) 397–400.

Van Kamp, H.V., Bolhius, G.K., De Boer, A.H., Lerk, C.F. and Lie-a-Huen, L., The role of water uptake on tablet disintegration. *Pharm. Acta Helv.,* 61 (1986) 22–29.

Yanaki, T., Kojima, T. and Norisuye, T., Triple helice in dilute aqueous sodium hydroxide. *Polym. J.,* 13 (1981) 1135–1143.