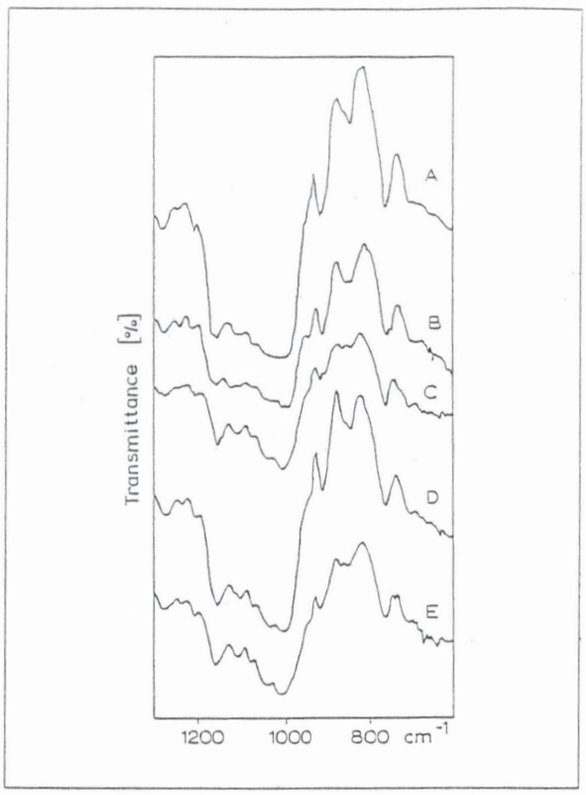

Fig. 1. Low frequency region of IR spectra of the amorphous dextran powder (A), the insoluble particle from the dextran solution (B), the induced dextran particulate matter (C), the dextran powder dried (D), and the dextran precipitate obtained from the amorphous dextran solution by water evaporation followed by drying (E)

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Study on dextran particulation in bottled dextran solutions

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The insoluble particles in bottled dextran solutions sometimes formed during sterilization and long-term storage has drawn the attention of a number of investigators because of the great commercial and practical importance of the solution [1]. The insoluble particles are very closely related to the dextran used for the solution preparation [2]. Recently, it has been shown that the particulation occurs *via* a three-step mechanism: the isolation of a small amount of solution out of the main solution, the evaporation of water from the isolated droplets and the fall of dextran precipitate into the solution [3]. The water evaporation gives rise to the concentration of the isolated droplets, creating the favourable conditions for the phase transformation of dextran due to crystallization: the amorphous dextran from the solution becomes crystalline in the precipitate which is therefore insoluble [4].

In the present work the IR spectra and the X-ray powder diagrams of several dextran samples (amorphous dextran powder; dextran powder dried at 130 °C; and dextran precipitate obtained by water evaporation from the solution of the dextran and dried at 130 °C), the dextran particles isolated from commercial dextran solutions and the dextran particulate matter formed according to the mechanism described elsewhere [3] were studied. The main goal was to check the mechanism of formation and crystalline qualities of the insoluble particles.

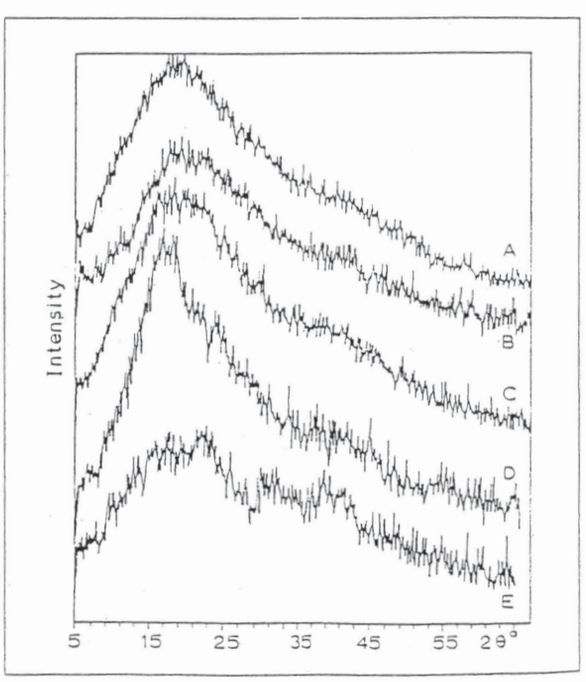

Fig. 2. X-ray powder diagrams. Key: see Fig. 1

The low-frequency region of the IR spectra of the amorphous dextran powder (A), the insoluble particle from the dextran solution (B), the induced dextran particulate matter (C), the dextran powder dried (D), and the dextran precipitate obtained from the amorphous dextran solution by water evaporation followed by drying (E) are shown in Fig. 1. Although the spectra are very similar to each other, an obvious difference can be seen at 1047 cm^{-1}. Namely, the new clearly observed absorption band appears around 1047 cm^{-1} in the spectra of the dextran samples B, C, D and E compared to that of the amorphous dextran (curve A in Fig. 1) in the same spectral region.

The X-ray powder diagrams of the samples investigated are presented in Fig. 2. Contrary to the diagrams of the amorphous dextran powder (A), the curves for dextran samples B, C, and especially D and E indicate the existence of a somewhat higher degree of crystallization. There is some similarity with that reported for crystaline dextran [5].

In fact, the various levels of the crystallization of dextran are expected because dextran is a conformationally labile polymer with very close free conformation energy levels [6].

Thus, the existence of both the "naturally" formed and "induced" insoluble crystalline dextran particles indirectly confirms the mechanism of particle formation and explains the insolubility of the particles.

Experimental

1. Materials

The amorphous dextran (m.wt. = 40000) powder (sample A) from Zdravlje (Leskovac, Yugoslavia) was used. The insoluble particles (sample B) were isolated by membrane filtration (0.9 μm) from the sterile glass-bottled solution (10%) prepared from the same amorphous dextran and dried by lyophilization. the induced insoluble particles (sample C) were prepared by treating the glass-bottled dextran solution at 130 °C for 30 min, according to the mechanism reported elsewhere [3]. The sample D was obtained by heating the amorphous dextran powder at 130 °C for 30 min. Sample E was, similarly, prepared by evaporation of the 10% dextran solution at 130 °C followed by heating at the same temperature for 30 min.

2. Measurements

The IR spectra were recorded on an IR spectrophotometer Perkin Elmer, model 580, using the KBr technique. The X-ray powder diagrams were obtained on a Jeol diffractometer using CuK_α radiation (λ = 154.178 pm).

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Di(acyloxy)dialkyl- und Di(acyloxy)diphenylsilane — neue artige Vesikelbildner

Teil 4[3]: Einschluß von Insulin in Siosomen

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Liposomal verkapseltes Insulin ist schon von zahlreiche Forschungsgruppen untersucht worden [1–7], jedoch gelan es bisher noch nicht, Insulin als vesikuläre Arzneiform zu Anwendung zu bringen.

Nachfolgend wird über den Einschluß von Insulin in Vesike aus Di(acyloxy)dialkyl- und Di(acyloxy)diphenylsilanen, vor uns erstmals eingesetzte Strukturbildner, berichtet. Die Herstellung der Siosomen erfolgte nach einer speziellen Injektionsmethode, die sich bereits bei anderen Einschlußuntersuchungen bewährt hat [8]. Zur Bestimmung des Insulins diente ein Radioimmunoassay (RIA).

Die Siosomenpräparation erfolgte stets unter konstanten Bedingungen: Ethanolphase: 0,01 mol/l Diacyloxysilan; wäßrige Phase: 3 ml Insulinlösung 0,01 mol/l; Rührgeschwindigkeit: 2000 ± 200 U/min; Temperatur: 50 °C ± 0,1 K. Der Überschuß an nichteingeschlossenem Arzneistoff wurde durch Dialyse an einer Nephrophan®-Membran abgetrennt. 1 ml der verdünnten Siosomendispersion (1 : 8) wurde für mindestens 1 h unter ständiger Aufrechterhaltung des Konzentrationsgefälles dialysiert. Als Dialyseflüssigkeit kam z. B. isotonische Natriumchloridlösung zum Einsatz, andere Lösungen (Kaliumchlorid-, Phosphat-, Phosphat-Albumin-, Krebs-Ringer-Puffer; alle unter Berücksichtigung der Isotonie) wurden ebenfalls in die Untersuchungen einbezogen, wobei die ermittelten Einschlußraten keine wesentlichen Veränderungen zeigten. Die dialysierte Siosomensuspension wurde quantitativ von der Membran gespült und mit Puffer auf 25,0 ml verdünnt. 200 μl wurden zur Bestimmung mittels RIA verwendet [9]. Eine hohe Verdünnung ist wegen der sehr geringen Nachweisgrenze für Insulin (0,1 ng/ml) möglich und erforderlich. Es wurden mindestens 10 identische Versuchsreihen aufgenommen (wegen der relativ hohen Streuung z. T. mehr als 50 Versuchsreihen). Eine Zerstörung der Siosomen ist im Falle des Insulins nicht notwendig, da bereits bei der Aufbereitung der Proben für den RIA die Vesikel wegen der drastisch geänderten osmotischen Verhältnisse (durch Tracerzugabe von 5 : 1) zerstört werden. Mit Ethanol behandelte Liposomen ergaben deutlich niedrigere Resultate, was auf eine teilweise Denaturierung des Insulins schließen läßt.

Tabelle

Acyloxykette	Einschlußkapazität	
	[%]	s [%]
Di(acyloxy)dimethylsilane		
decanoyloxy	63.53	5,97
tetradecanoyloxy	62.74	8,87
octadecanoyloxy	79.51	6,29
Di(acyloxy)diphenylsilane		
decanoyloxy	69.67	8,65
tetradecanoyloxy	66.60	7,74
octadecanoyloxy	74.10	10,30
Di(acyloxy)diethylsilane		
decanoyloxy	67.53	8,52
tetradecanoyloxy	66.30	4.85
octadecanoyloxy	54.15	11.30