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DISINTEGRATION OF DEXTRAN SULFATE TABLET PRODUCTS: EFFECT OF PHYSICOCHEMICAL PROPERTIES

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ABSTRACT

Disintegration characteristics of three lots of enteric-coated dextran sulfate tablets (250 or 300 mg dosage formulations) from two manufacturers (*A* and *B*) were determined in 0.1M phosphate buffer at various pH levels between 5.0 and 7.5. Differences in disintegration times within- and between-lots were observed and appear to relate to differences in the nature and thickness of their enteric coatings. The composition of tablets and coatings was examined by Fourier-transform infrared spectroscopy. Lactose and a form of cellulose were the predominant excipients in the *A* and *B* formulations, respectively. The yellow coating on *A* tablets consisted mainly of a phthalic alkyd polyester modified with soya oil, whereas the white coating on *B* tablets contained mostly hydroxypropyl methylcellulose, modified with di-2-ethylhexylphthalate. Some yellow tablets appeared darker than the rest, attributable to the larger film thickness of dark yellow tablets (0.14 mm) compared with that of lighter tablets (0.06 mm). The more than twofold greater film thickness of dark yellow tablets was consistent with the near doubling of disintegration times at pH 6.8, from about 62 minutes for light yellow tablets to about 109 minutes for dark yellow tablets.

INTRODUCTION

Dextran Sulfate (DS) has been available since the 1950's and used occasionally as an anticoagulant or antilipemic agent by the oral route, principally in Japan [1]. However, it was

only after 1987 when it was found to be a potent agent against human immunodeficiency virus (HIV) *in vitro* that the need for extensive study was provoked [2,3]. Although its place in AIDS therapy as a single active ingredient is doubtful, since early trials have not been promising [4,5], there was a need for oral dosage forms of consistent quality for trials. In addition, the U.S. Food and Drug Administration allowed people to import this unapproved AIDS drug for personal use, and DS tablets were imported from Japan and Canada [6-8].

The current study of physicochemical and disintegration properties of various DS preparations [9] arose from review of a new drug submission, which indicated a need for qualitative procedures to assess the within- and between-lot quality of drug product.

EXPERIMENTAL

Dextran Sulfate Tablets

Yellow enteric-coated, oblong, biconvex tablets containing 250 mg DS were obtained from manufacturer *A*. The tablets were formulated for *A* by another manufacturer. They originated from two different drums (hereinafter denoted as Drum 1 and Drum 2) within the same lot and at least 6% of the tablets were darker yellow than the rest. All dark yellow tablets were from the same drum. Two lots (hereinafter designated as Lot 1 and Lot 2) of white enteric-coated, round, biconvex tablets containing 300 mg DS were obtained from manufacturer *B*.

Tablet Sizing

Tablet dimensions were measured with a micrometer for diameter and thickness for *B* tablets, and for length, width and thickness for *A* tablets. Film thickness was measured with a stereo microscope (80x), equipped with a reticule, from tablet sections cleaved across diameter (*B* tablets) and both transversely and longitudinally (*A* tablets). Four to six measurements were taken at various points of each cleaved tablet face. The reticule of the microscope was calibrated using a stage micrometer (2 mm division into units of 0.01 mm).

Fourier-Transform Infrared Spectroscopy (FTi.r.) Characterization of Tablets

The yellow coating on *A* tablets was removed, without apparent alteration of the remaining core, by immersing a tablet in a solution of dichloromethane:methanol (1:1, v/v). A portion of solution was evaporated on a NaCl plate for FTi.r. spectral recording. The coating could also be removed in layers by submerging a tablet in water for 24 h. The coating on *B* tablets was removed with a scalpel, and an acetone solution of coating was evaporated on a NaCl plate for FTi.r. analysis.

Decoated tablets from *A* (light and dark yellow samples) were separately pulverized to fine powders with a mortar and pestle. Portions of these powders were prepared as potassium bromide (KBr) discs (0.3% analyte) for FTi.r. determination using i.r. spectral grade KBr. Spectral subtraction of these tablet spectra was performed using the spectrum of a reference bulk DS to determine the major excipient in each formulation. Reference DS was obtained from both *A* and *B* manufacturers.

Decoated samples from the two lots of *B* tablets were separately dissolved in water to obtain an insoluble excipient material. In each instance, the material was collected, washed with water, and dried in a drying pistol before being admixed (10%) with spectral grade potassium chloride for examination by diffuse reflectance infrared Fourier-transform spectroscopy (DRIFTS).

FTi.r. spectra were determined from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1} using a Nicolet 60SX instrument. Spectra were compared to computerized library spectra (Sprouse Polymer Spectral Library) to help identify the coatings and excipients of the DS tablets.

Tablet Disintegration Testing

Disintegration tests were done following methods similar to British Pharmacopoeia (BP) [10] and United States Pharmacopeia (USP) [11] disintegration procedures for enteric-coated tablets. The method consisted of raising and lowering the basket-rack assembly (30 strokes/min) containing 6 tablets in 0.1M HCl at 37°C for 60 min (no discs), rinsing with water, replacing the HCl with 0.1M phosphate buffer (pH 5.0, 6.8, 7.2 or 7.5) and then operating the assembly (with disks) until all tablets had disintegrated. The disintegration time (DT) and the time interval (TI) from complete removal of the enteric coat to the DT were recorded for all samples.

Phosphate Buffer Preparation

Aqueous phosphate buffers of pH 5.0, 6.8, 7.2 and 7.5 were prepared by adding the appropriate amount of solid sodium hydroxide pellets to a solution of 0.1M potassium dihydrogen phosphate.

Statistical Analysis

All results in the text and tables are expressed as either mean $\pm$ SD or as the 99.5% confidence limits of the difference between two means. Differences between means were assessed by a *t* test for unpaired samples with equal variances, with a *p*-value of ≤ 0.05 considered significant. Correlations between tablet weight and DT and between pH and DT were determined by linear regression analysis, with DT as the dependent y-variable.

TABLE 1

Physical Characteristics of Dextran Sulfate Tablet Specimens[1].

Specimen	Length (mm)	Thickness (mm)	Weight[2] (mg)	Width (mm)	Film[3] Thickness (mm)
Manufacturer *A*					
Dark Yellow	17.94 ± 0.03	6.51 ± 0.04	1089.6 ± 12.0	10.72 ± 0.03	0.14
Light Yellow	17.73 ± 0.04	6.40 ± 0.04	1039.8 ± 11.9	10.51 ± 0.02	0.06
D ± CL[4]	0.21 ± 0.05	0.11 ± 0.05	49.8 ± 9.2	0.21 ± 0.04	0.08
Manufacturer *B*					
Lot 1	10.45 ± 0.04	5.23 ± 0.05	438.4 ± 17.4	-	0.10
Lot 2	10.92 ± 0.03	5.61 ± 0.04	504.8 ± 12.0	-	0.10
D ± CL[4]	0.47 ± 0.05	0.38 ± 0.07	66.4 ± 14.1	-	0.00

[1] Tablet measurements are mean ± SD.

[2] The following numbers of tablets were selected to determine weights: Lot 1 (20), Lot 2 (20), dark yellow (22) and light yellow (40).

[3] For each tablet type, four tablets were measured for film thickness at various points along the cleaved face, and 10 tablets were measured for the other dimensions. No variation in film thickness was observed among like tablets.

[4] D ± CL refers to the 99.5% confidence limits (CL) of the absolute difference (D) in mean measurements.

RESULTS

Physical and Chemical Characteristics

General features of the three lots of DS tablets examined in this study are summarized in Table 1. Yellow-coated tablets from *A* consisted of a mixture of dark and light yellow tablets and were much larger and about twice as heavy as white tablets from *B*.

Differences between mean tablet measurements for the two *B* lots and for the two types of yellow *A* tablets are tabulated with their 99.5% confidence limits in Table 1. All physical measurements showed small but statistically significant differences ($p < 0.0001$) between light and dark yellow tablets from *A* and, except for film thickness, between the two lots of *B* tablets. Tablets sampled from the two *B* lots appeared to be physically identical within the same lot.

The enteric coating was more than twice as thick on four dark yellow tablets (0.14 mm) compared with four light yellow tablets (0.06 mm), and was 0.10 mm on four tablets tested from each *B* lot. Some dark yellow tablets displayed "chipping" or loss of small fragments of the enteric coating at edges, exposing the white to very pale yellow color of the compressed inner

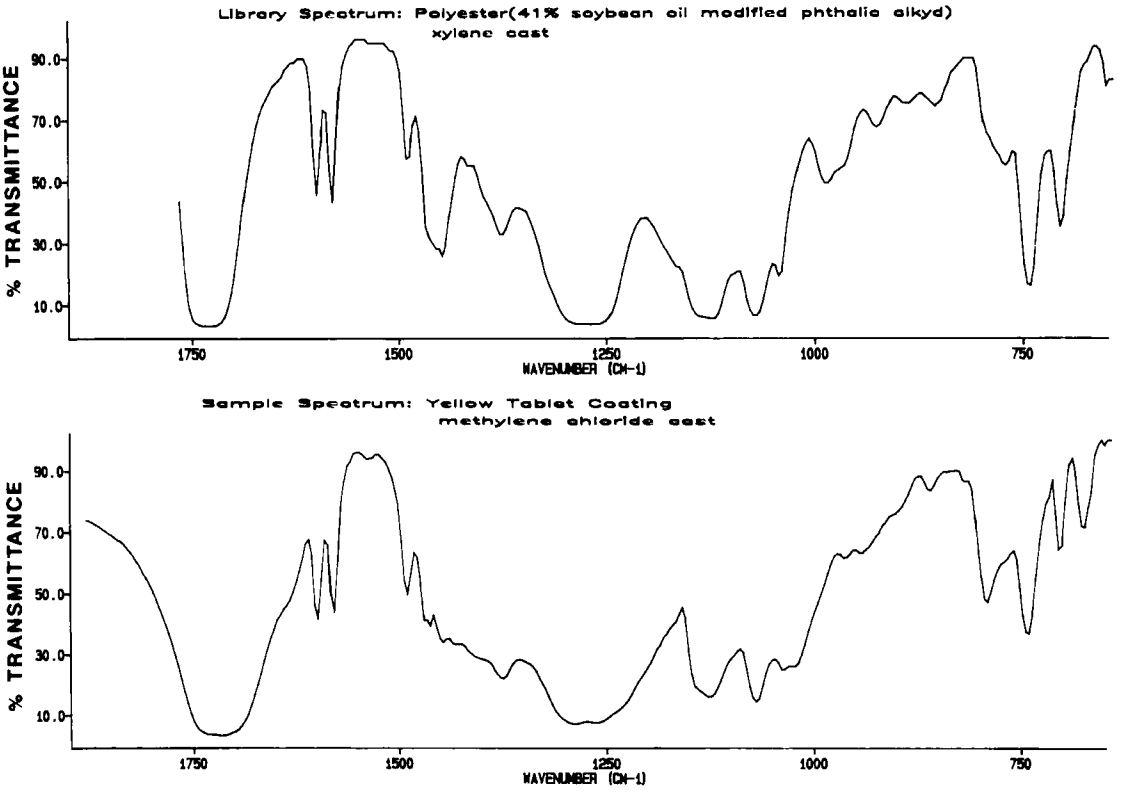

FIGURE 1

Infrared spectrum of the yellow film coating on tablets from manufacturer *A* (bottom) and a library spectrum (top) of a phthalic alkyd polyester modified with soya oil.

tablet material. Except for the chips, all tablets from both manufacturers displayed uniform film thickness.

Figure 1 shows the i.r. spectrum determined for the yellow enteric-coating material compared with a good i.r. library match spectrum. The coating appears to be a phthalic alkyd polyester modified with soya oil. Figure 2 shows a series of four i.r. spectra demonstrating how the pulverized (and coating free) tablet material from *A* was found to contain lactose as its major excipient. The net spectral result (Figure 2C) compared well with an i.r. library reference spectrum (Figure 2D) for hydrous lactose powder.

The white enteric coating on *B* tablets was physically and chemically identical for both lots and was determined by i.r. spectral comparison to consist mainly of hydroxypropyl

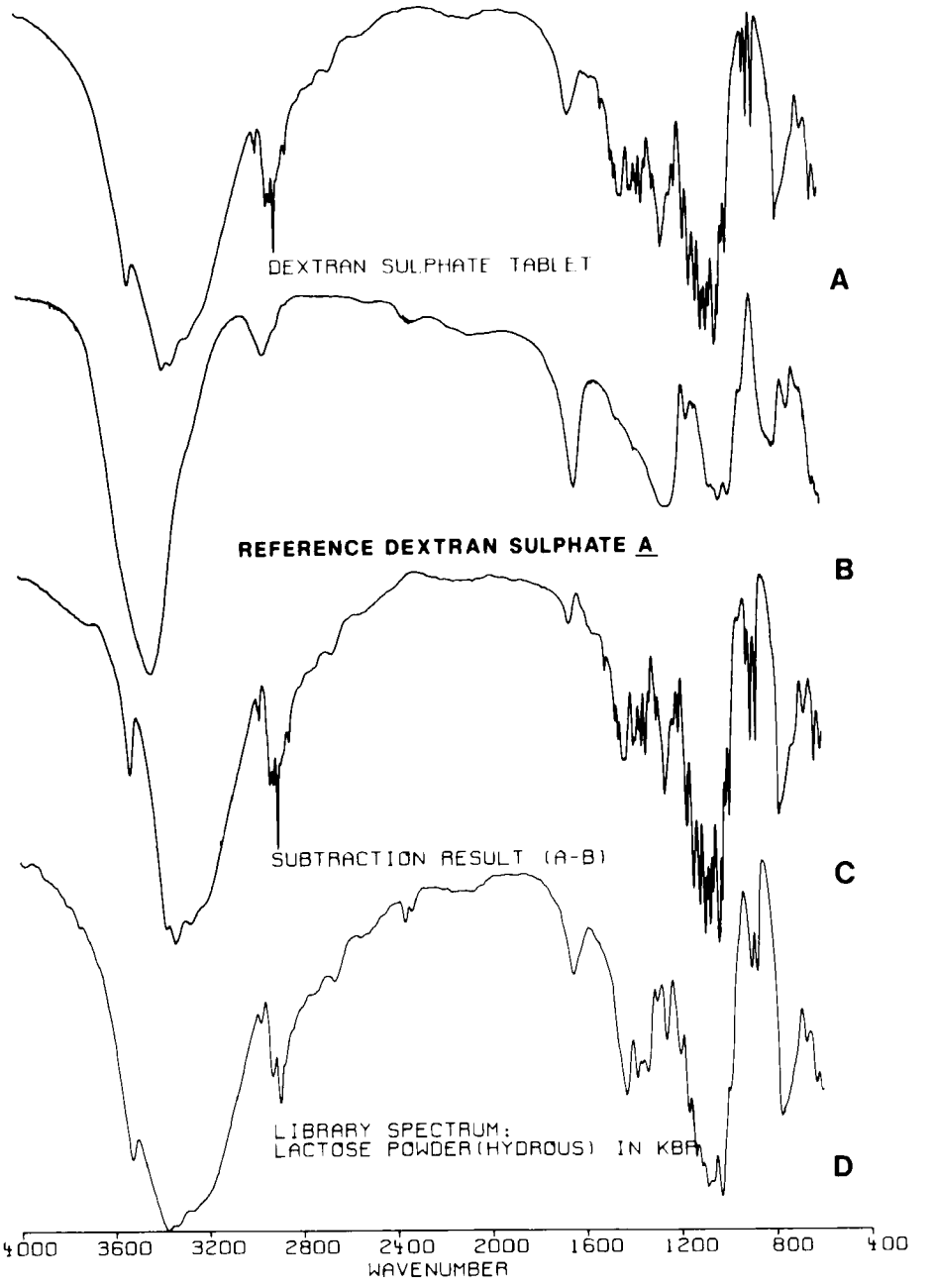

FIGURE 2

Characterization of excipient in tablets from manufacturer *A*. A montage of infrared spectra showing changes arrived at by spectral subtraction of reference dextran sulfate (B) from the spectrum of a pulverized tablet (less its coating) (A). The difference spectrum (C) compared with a library spectrum (D) showed lactose to be the main excipient.

methylcellulose containing di-2-ethylhexylphthalate (Figure 3). Although the inner core of tablets from Lot 2 was white whereas that of tablets from Lot 1 was off-white, a water insoluble material, characterised as a form of cellulose by the DRIFTS technique, was nevertheless found to be the major excipient in both types of *B* tablets (Figure 4). Examination of pulverized decoated material by the infrared KBr disc method revealed that no lactose was present in either *B* tablet formulation.

Disintegration Characteristics

Morphological changes of tablets from the two manufacturers were noticeably different during the disintegration process. The enteric coating on all tablets showed no tendency to crack after 60 min in 0.1M HCl, although slight leaching of the yellow dye from tablets supplied by *A* was indicated by UV spectrophotometry. Even at pH 5.0 for 120 min no discernible cracking or softening of enteric coatings was observed. However, at pH $\geq$ 6.8 the enteric coating from *A* tablets gradually became released as thin flexible sheets from the tablet inner core. This process was very distinct for the yellow tablets, with complete removal of the coating occurring before total disintegration. On the other hand, white tablets from *B* disintegrated into fine particles at pH $\geq$ 6.8, with no apparent discarding of the enteric coat and hence no observable TI measurements.

Tables 2 and 3 present disintegration results of DS tablets from *A* and *B*, respectively. Disintegration profiles of dark and light yellow tablets were distinctly different at pH 6.8. Dark yellow tablets had smaller TI values (2.6 $\pm$ 2.2 vs 17.7 $\pm$ 2.4 min) and longer DTs (109 $\pm$ 10.2 vs 61.9 $\pm$ 4.8 min) than those of light yellow tablets from the same drum. Dark yellow tablets with chipped coating did not disintegrate noticeably faster than those without chips. There was no significant correlation between individual weight and DT for either light (r = 0.258, n = 24) or dark (r = 0.136, n = 12) yellow tablets. Also, there was no significant difference in the disintegration profile at pH 6.8 for light yellow tablets from different drums (p = 0.207, n = 36), the TI averaging 17.7 min for both drums and the mean DT occurring at 61.9 min for one drum and 59.9 min for the other drum.

Further testing of light yellow tablets at higher pH indicated that DT decreased from 61.9 $\pm$ 4.8 min at pH 6.8 to 55.3 $\pm$ 2.9 min at pH 7.2 and to 48.1 $\pm$ 1.7 min at pH 7.5. Although only three pH levels were studied, the decrease in DT with increase in pH appears to be linearly related (r = 0.994). The TI values averaged 18.7 min and were relatively invariant at the three pH levels. All coefficients of variation (CV) were < 8% for DT values and < 14% for TI values.

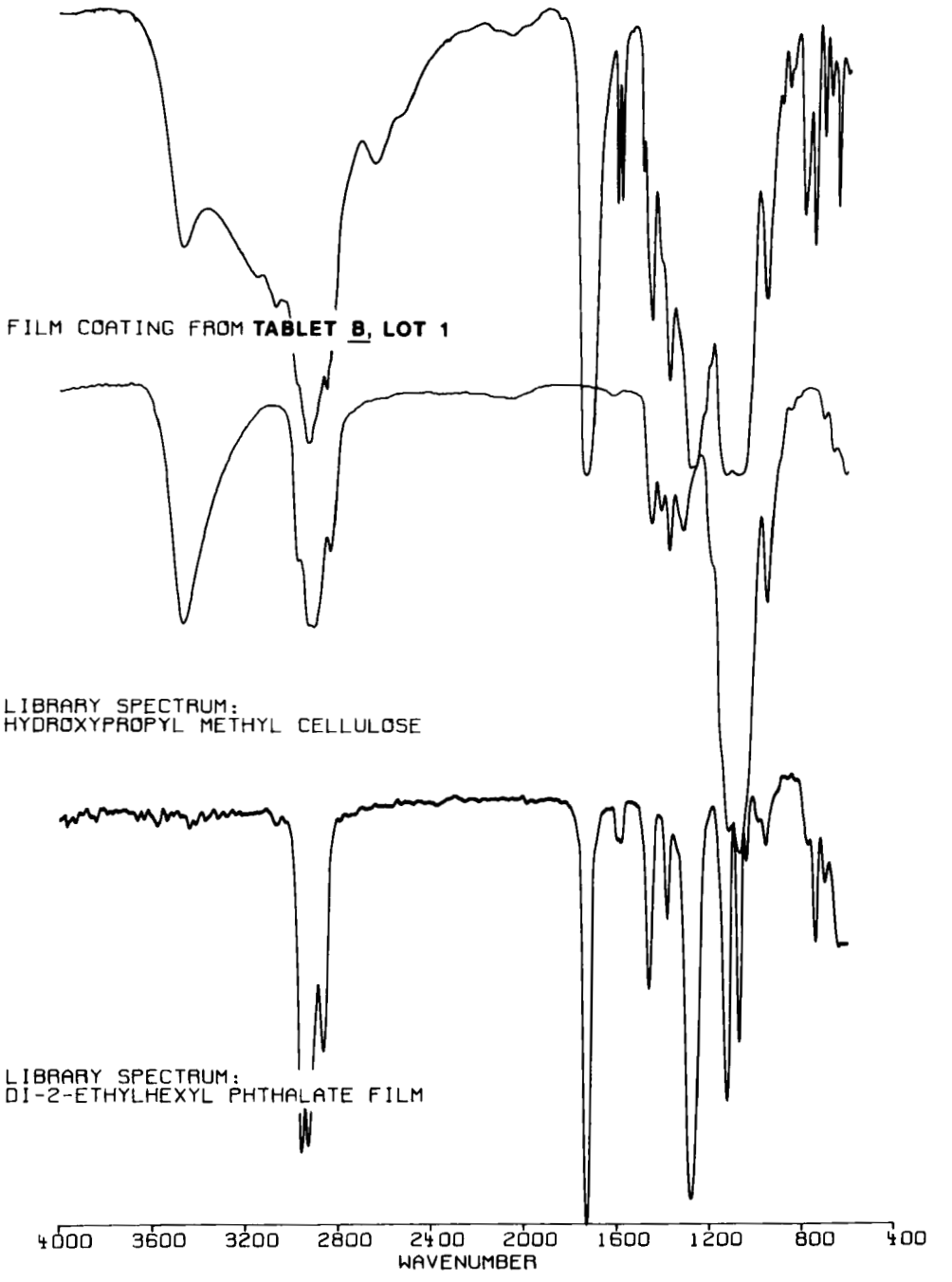

FIGURE 3

Infrared spectrum of the white film coating on tablets from manufacturer *B* (top) and library spectra of its principal components, hydroxypropyl methylcellulose (middle) and di-2-ethylhexyl phthalate (bottom).

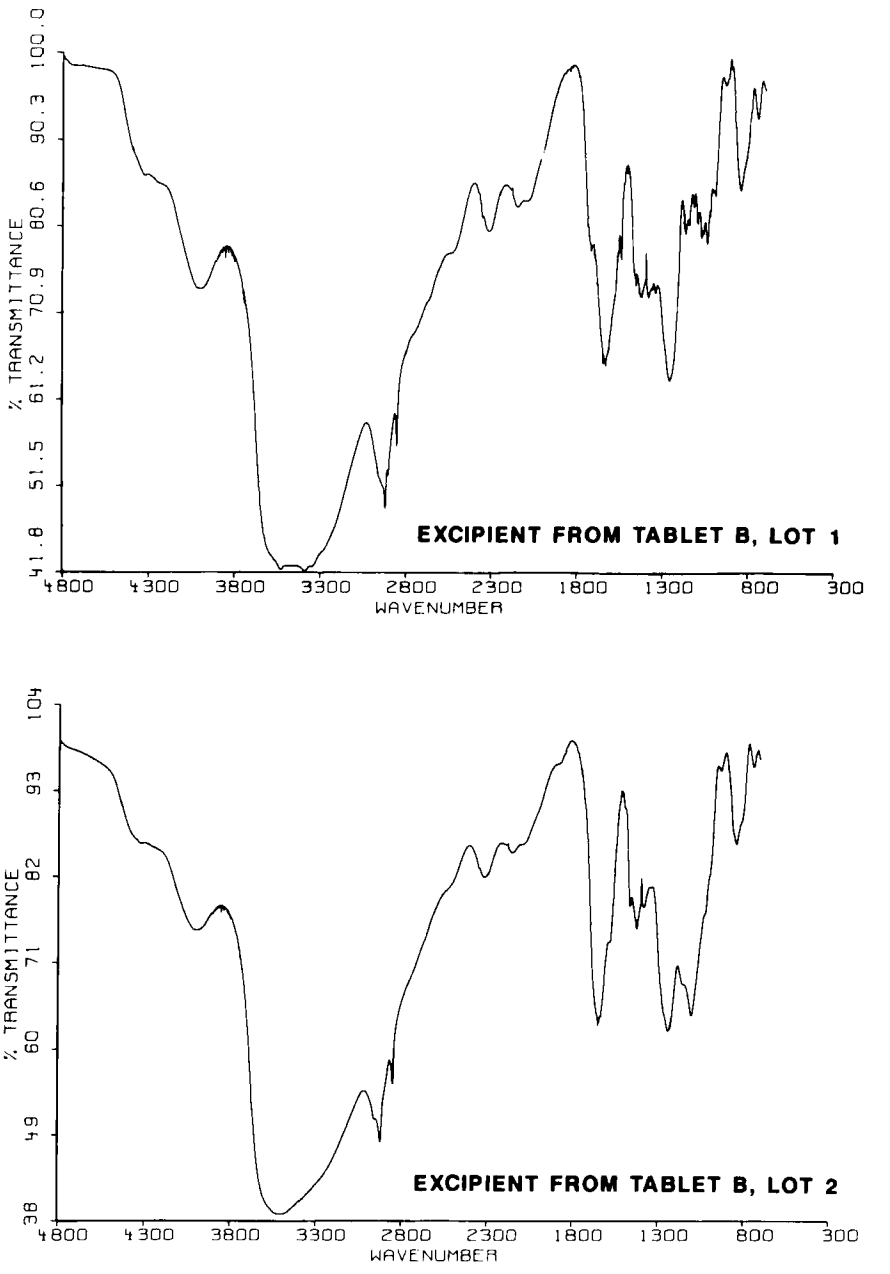

FIGURE 4

DRIFTS infrared spectra of the major excipient material recovered from tablets from manufacturer *B*, deduced by spectral searching to be a form of cellulose.

TABLE 2

Disintegration Profile of Yellow Dextran Sulfate Tablets (Manufacturer *A*) in Phosphate Buffer (0.1M, 37°C) of Different pH.

	LIGHT YELLOW					DARK YELLOW
	pH 5.0	**pH 6.8**	**pH 6.8**	**pH 7.2**	**pH 7.5**	**pH 6.8**
Drum #	1	1	2	1	1	1
n	6	24	12	6	6	15
TI (min)[1]	> 120	17.7 ± 2.4	17.7 ± 1.8	18.5 ± 2.1	21.0 ± 0.5	2.6 ± 2.2
DT (min)[1]	> 120	61.9 ± 4.8	59.9 ± 3.2	55.3 ± 2.9	48.1 ± 1.7	109 ± 10.2

Note. DT, disintegration time; TI, time interval from complete removal of the enteric coat to DT.
[1] TI and DT values are mean ± SD.

TABLE 3

Disintegration Profile of Dextran Sulfate Tablets (Manufacturer *B*) in Phosphate Buffer (0.1M, 37°C) of Different pH.

	pH 5.0	**pH 6.8**	**pH 7.5**
Lot 1			
n	6	17	6
DT (min)[1]	> 120	25.5 ± 1.5	20.3 ± 1.6
Lot 2			
n	6	12	6
DT (min)[1]	> 120	27.3 ± 2.0	21.5 ± 1.4

[1] Disintegration time (DT) values are mean ± SD.

The mean DT at 37°C and pH 6.8 of Lot 2 tablets from *B* (27.3 ± 2.0 min, n = 12) was similar yet significantly longer ($p = 0.0043$) than that of Lot 1 tablets (25.5 ± 1.5 min, n = 17). The DTs decreased at pH 7.5 (Lot 2: 21.5 ± 1.4 min, n = 6; Lot 1: 20.3 ± 1.6 min, n = 6) but the difference between lots was not statistically significant ($p = 0.2004$).

DISCUSSION

The physical, chemical and disintegration characteristics of the three lots of DS tablets showed distinct within- and between-lot variability. Although the yellow tablets from *A* showed

obvious color differences within the same lot and from the two lots of white *B* tablets, the physical differences between the two types of yellow tablets, like those of the *B* tablets, could only be distinguished by measurements of tablet dimensions and weight.

The two shades of yellow enteric coat were easily discernible to the naked eye. The darker yellow colour is most likely due to the thicker enteric coat on these tablets, 0.14 mm compared with 0.06 mm. The greater film thickness of dark yellow tablets, combined with the uniformity of thickness of both light and dark yellow coatings, probably accounts for the slightly larger physical dimensions and weight of dark yellow tablets.

The more than twofold higher DTs at pH 6.8 for light yellow tablets compared with *B* tablets is not related to the thickness of enteric coat, because film thickness is less in light yellow tablets, 0.06 mm compared with 0.10 mm. Instead, it is probably related to differences in enteric-coat composition (alkyd polyester {*A*} versus a methylcellulose derivative {*B*}), and perhaps to differences in amount and type of excipient (lactose {*A*} compared with a form of cellulose {*B*}) and compression force used to manufacture the tablets. On the other hand, the near doubling of DTs at pH 6.8 for dark yellow compared with light yellow tablets is consistent with the more than twofold thicker film on the former. However, the longer DTs of Lot 2 tablets from *B* compared with those of Lot 1 tablets, albeit only by about 2 min, may be attributed to the larger physical dimensions and weight of the Lot 2 tablets, since the enteric coatings are the same thickness in the two lots.

The enteric-coating of all tablets tested was resistant to cracking and softening for at least 2 h in aqueous solution of pH 1 to 5. However, most tablets completely disintegrated within 2 h at pH 6.8 and small decreases in DTs were observed upon raising the pH from 6.8 to 7.5. Since there are no published procedures for either dissolution or disintegration testing of DS, our results indicate that a disintegration method based on either the BP [10] or USP [11] procedures for enteric-coated tablets would be suitable for testing these DS tablets. BP requires that tablets disintegrate within 1 h in pH 6.8 phosphate buffer after 2 h in 0.1M HCl, whereas USP requires complete disintegration within 2 h in simulated intestinal fluid TS (pH 7.5) after 1 h in simulated gastric fluid TS (pH 1.2). Both procedures specify that the enteric coating on all tablets must show no signs of cracking during submersion in acid.

Although dissolution testing is generally more sensitive than disintegration testing for detecting differences in tablet formulation, the lack of a UV absorbing chromophore above 200 nm in DS and the absence of feasible analytical methods [5,12-14] for measuring DS make dissolution testing of this drug difficult. Nonetheless, the combination of disintegration testing, physical measurements, and FTi.r. spectroscopy on DS tablets from different lots provided a reasonable means of discriminating differences in tablet formulations. However, even if these

within- and between-manufacturer differences affect the rate of release of DS from the gastrointestinal tract after oral administration, the overall effect on oral bioavailability (< 20% in rats [15,16]) will be minimal, since the drug appears to be rapidly metabolized before entering the systemic circulation.

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