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Dissolution rates of sulfamethoxazole utilizing sugar glass dispersions

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Solid glass dispersions of sulfamethoxazole have been prepared by fusion using different classes of sugars, A marked increase in the dissolution rate of sulfamethoxazole in the solid dispersions was observed compared with that of the drug alone. During the fusion process, interaction took place between sulfamethoxazole and those sugars with carbonyl groups. The bacteriological activity of sulfamethoxazole was not changed by the interaction compared with dispersions in which the interaction did not occur.

Sulfamethoxazole is widely used in combination with trimethoprim for treating systemic infections (Septrin, Burroughs Wellcome & Co., London). It is slightly soluble in water (B.P.C., 1973). To increase solubility of insoluble or slightly soluble drugs, Chiou & Riegelman (1969) proposed the use of organic glass-forming compounds to form binary glass systems with water-insoluble drugs. They demonstrated the increased dissolution rate of griseofulvin in a citric acid glass. The glass system gave faster drug release than other solid dispersion systems studied. Reserpine and digitoxin (Stupak & Bates 1972, 1973) and methisazone (Gidwani & Anderson 1976) have been prepared as glass solutions with polyvinylpyrrolidone (pvp). The mechanism involved in increasing the solubility with pvp has been extensively studied by Simonelli et al (1976).

Recently, Allen et al (1977) used the sugar glass dispersion technique to increase the dissolution rate of some orally administered corticosteroids. The sugars used were dextrose galactose and sucrose. Sugars as carriers in solid dispersions are non-toxic, inexpensive and physiologically acceptable. We have applied the glass dispersion technique to sulfamethoxazole using different classes of sugars.

MATERIALS AND METHODS

Materials

Sulfamethoxazole (Kahira Pharm. & Chem. Ind. Co., Egypt), glucose, sorbitol and mannitol (El-Nasr Chem. Co., Egypt), galactose (E. Merk), Maltose (spolek, Czechoslovakia), and sucrose (purchased).

Preparation of the dispersion systems

All dispersion systems were prepared by fusion as follows: a suitable amount of the drug-carrier mixture (1 : 1 w/w), was placed in an aluminium dish (ca 10 cm diam.) which was placed on a wire screen positioned on a preheated electric hot plate. Heat was applied and stirring was constant until a melt was obtained. All melts were rapidly solidified by placing the dish immediately in ice. The heating temperatures for the solid dispersions were: sucrose 165 °C, mannitol 167 °C, sorbitol 115 °C, glucose 160 °C, galactose 168 °C, maltose 110 °C and fructose 135 °C.

After solidification, the dispersion system was stored in a desiccator ($CaCl_2$) for 24 h, pulverized and the 100–200 μm particle size used. Sulfamethoxazole of the same particle size was used for comparison.

Dissolution rate study

Sulfamethoxazole (100 mg) or the equivalent of solid dispersion was introduced into 500 ml water at 37° ± 0·1 °C and the solution stirred at 60 rev min^{-1}. Two ml samples, taken at intervals and replaced by fresh solvent, were filtered through Whatman filter paper and the drug content of dispersions with non-reducing sugars was determined spectrophotometrically at 265 nm after diluting with 0·1 M HCl (colourimetric assay gave similar results). Each experiment was done at least in duplicate. For solid dispersions with reducing sugars (glucose, galactose and maltose), the absorbance values were higher than expected from the concentration present, so the drug content was determined (Bratton & Marshall 1939).

Spectra

The ultraviolet spectra of sulfamethoxazole alone or of the solid dispersions were determined in 0·1 M HCl in the range of 230–300 nm. Infrared spectra of drug sugars and solid dispersions were determined using potassium bromide pellets.

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Thin layer chromatography

Ethanolic solutions of sulfamethoxazole, solid dispersions and physical mixtures (1 : 1 w/w), were each spotted on 0·25 mm fluorescent silica gel G plates. The plates were developed with chloroform–methanol 100 : 10 (Stahl 1969), air dried and visualized under u.v. light.

Solubility determination

An excess of sulfamethoxazole was added to either 15 ml water or of solutions of the sugars, in 30 ml glass-stoppered bottles which were rotated on a water bath at 37° ± 1 °C until equilibrium. Samples were filtered and assayed as described.

Bacteriological study

Double strength nutrient broth casamino acid 2 g, glucose 2 g, beef extract 0·6 g and distilled water to 100 g was seeded with 0·1 ml of *Bacillus subtilis* spores. Two-fold serial dilutions were prepared from sulfamethoxazole alone (500–0·244 μg ml^{-1}), and of equal concentrations from the solid dispersions as well as the physical mixture of sorbitol and glucose as representatives of the classes of sugars. One ml of each was mixed with one ml of the seeded nutrient broth. The tubes were incubated at 37°C and the minimum effective concentrations of each preparation was noted at 24 and 48 h. The drug sugar ratios used were 1 : 1 and 1 : 70 for glucose and 1 : 1 for mannitol.

RESULTS AND DISCUSSION

The temperatures used in preparing the solid dispersions were slightly higher than the melting point of the sugar but less than the melting point of sulfamethoxazole to prevent decomposition of both components. The easily prepared systems were glassy, with sulfamethoxazole dispersed as solid particles, hygroscopic and slightly amber.

Figs 1 and 2 show the dissolution rates of sulfamethoxazole from solid dispersions in different classes of sugars. Glucose, maltose and sorbitol showed nearly the same release rate which was the fastest of all solid dispersions (complete release in about 5 min). Galactose solid dispersion (monosaccharide) had the lowest release rate. Sucrose and mannitol had intermediate dissolution rate values. The 50 and 100% dissolution times are shown in Table 1. (The rate of solution of the drug at a smaller particle size (32·63 μm) was 14 mg at 5 min, 34 mg at 10 min, 78 mg at 30 min and 97 mg litre^{-1} at 60 min.)

From the Figures it can been seen that the dissolution curves show two phases, an initial rapid phase and a slow and more prolonged phase. The

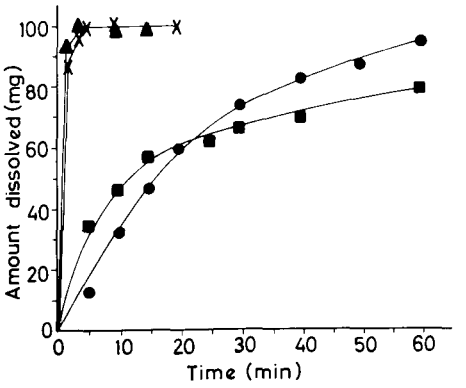

FIG. 1. Dissolution rate of 1 : 1 drug sugar solid dispersions in water using ▲ maltose, × glucose, ■ galactose and ● sulfamethoxazole alone (drug was assayed by diazotization).

first could be due to rapid solubility of the fraction of sulfamethoxazole present in a state of molecular dispersion in the molten mass and the slow phase to the release of sulfamethoxazole present as dispersed particles. The sugars, being hydrophilic would be expected to increase the wettability of the drug particles and hence its dissolution compared with the drug alone. An exception is galactose solid dispersion which formed a round mass with slow release when added to water. The dissolution rates of samples of solid dispersions stored over 30 days and 1 year showed no change. The ultraviolet spectra with the non-reducing disaccharide, sucrose, as well as the alcoholic sugars mannitol and sorbitol showed no change in λ_{max} of the spectrum (265 nm). Slight hyperchromic changes occurred only when the reduc-

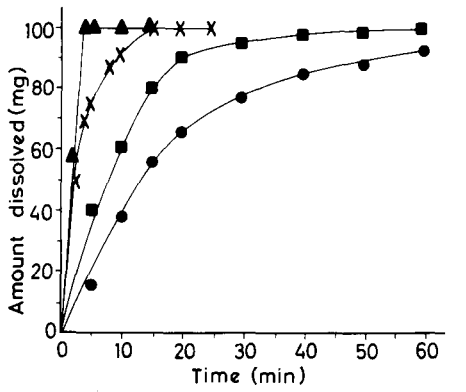

FIG. 2. Dissolution rate of 1 : 1 drug sugar solid dispersions in water using ▲ sorbitol, × sucrose, ■ mannitol and ● sulfamethoxazole alone (drug was assayed spectrophotometrically).

Table 1. Time of 50 and 100% dissolution of the solid dispersions.*

Sugar used	T 50% (min)	T 100% (min)
Maltose	< 2	4
Sorbitol	< 2	4
Glucose	< 2	5
Sucrose	2	15
Mannitol	< 10	60
Galactose	< 15	> 90

* Average of duplicate determinations.

Table 2. Solubility of sulfamethoxazole in different concentration of the sugars in water at 37° ± 1° C.

	Solubility in different concentrations of sugars[1] g litre^{-1}		
Sugar	0·5%	1%	1·5%
Maltose	0·66	0·79	0·83
Sorbitol	0·60	0·595	0·60
Glucose	0·67	0·755	0·76
Sucrose	0·615	0·605	0·615
Mannitol	0·615	0·605	0·603
Galactose	0·67	0·775	0·80

[1] Average of duplicate determinations—Solubility of sulfamethoxazole alone in water at 37° ± 1 °C = 0·6 g litre^{-1}.

ing sugars glucose, galactose and the disaccharide maltose were used (268 nm), indicating interaction between the drug and the sugar.

Solid dispersions prepared from the non-reducing sugars, sucrose, mannitol and sorbitol showed only one spot with R_F value equal that of sulfamethoxazole alone. Dispersions prepared from the reducing sugars glucose, galactose and maltose together with fructose (included only for t.l.c.) showed two spots under u.v. light, one of which corresponded to that of sulfamethoxazole and the other remained at the origin. It seems that a fraction of sulfamethoxazole occurs as free drug and another fraction as complex with the reducing sugars. A gradual increase of the weight fraction of the sugars, e.g. glucose, resulted in a gradual decrease in the intensity of the spot corresponding to the free drug. At a weight ratio drug: glucose 1:50, this spot disappeared. The reaction between the sugars and sulfamethoxazole occurs only on fusion of the sugars containing a carbonyl group since physical mixtures of both sugar and drug in ethanol gave only one spot for free sulfamethoxazole.

The solubility of sulfamethoxazole in aqueous solutions of the sugars increased slightly only with those sugars having a free carbonyl group (Table 2). On t.l.c. of the resulting solutions only one spot, corresponding to free sulfamethoxazole, was obtained showing the absence of any chemical interaction between drug and sugar. No change in λ_{max} of drug was noticed in any of the resulting solutions.

The minimum effective concentrations for the solid dispersions, as well as the physical mixture with the two different classes of sugars–glucose and mannitol —in the different drug sugar ratios used, were the same, 0·97 and 1·95 μg ml^{-1} after 24 and 48 h respectively. The physical mixture was included as a control. The minimum effective concentration for sulfamethoxazole alone was 0·48 and 0·97 μg ml^{-1} after 24 and 48 h respectively. The difference in the results between drug alone and solid dispersions is due to the nutrient effect of the sugars in increasing growth of the organism. The results showed that the bacteriological activity of the drug dispersions was not changed by interaction with sugars.

There is no doubt that interaction took place between the sugars with a free carbonyl group and sulfamethoxazole. Unfortunately the i.r. spectra of the solid dispersions were inconclusive since the spectrum of sulfamethoxazole alone showed a band at 1650 cm^{-1} where C = N band should appear (interaction of carbonyl group and amino group).

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