Dissolution Rates of Hydrocortisone and Prednisone Utilizing Sugar Solid Dispersion Systems in Tablet Form

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Abstract □ The utilization of ternary sugar solid dispersion systems and the incorporation of these systems into tablet dosage forms were investigated. The dispersion systems were prepared by the fusion method using 50% sucrose–50% mannitol and 50% sorbitol–50% mannitol. Other systems investigated utilized sorbitol, mannitol, and polyethylene glycol 6000 for comparison. The drug component was hydrocortisone or prednisone. The results from a modified NF XIII dissolution rate determination revealed that the mannitol system had the fastest dissolution rate, followed by sorbitol–mannitol, sucrose–mannitol, sorbitol, and, finally, polyethylene gylcol 6000. The corticosteroids were stable and did not decompose during preparation of the dispersion systems or direct compression of the tablets. A short-term stability study revealed that the tablets retained their fast dissolution rates and that the tablet characteristic tests, *i.e.*, tablet hardness, remained unchanged. The use of sugar combinations overcame some difficulties previously reported with single sugar systems.

Keyphrases □ Hydrocortisone—sugar solid dispersions in tablets, dissolution rates and stability □ Prednisone—sugar solid dispersions in tablets, dissolution rates and stability □ Sugar solid dispersions—sucrose, mannitol, and sorbitol in tablets with hydrocortisone and prednisone, dissolution rates and stability □ Dissolution rates—hydrocortisone and prednisone sugar solid dispersions in tablets □ Stability—hydrocortisone and prednisone sugar solid dispersions in tablets □ Tablets—hydrocortisone and prednisone sugar solid dispersions, dissolution rates and stability □ Glucocorticoids—hydrocortisone and prednisone, sugar solid dispersions in tablets, dissolution rates and stability

The corticosteroids are poorly water soluble and have demonstrated unpredictable, irregular dissolution rates (1–5). Solid dispersion techniques have been utilized to reduce the particle size of drugs and to increase their dissolution and absorption rates.

Sugar glass dispersions were used to increase the dissolution rates of some orally administered corticosteroids (6, 7). Some of the most effective sugars used (*e.g.*, sucrose), however, became discolored during the preparation of the melt. This amber discoloration did not appear to affect the dissolution rates of the dispersion systems. Some systems were also hygroscopic and required storage of the prepared materials in a desiccator.

The purposes of the present investigation were to study sugar combinations and other individual sugars in an attempt to overcome discoloration and hygroscopicity and to incorporate the resulting sugar solid dispersion systems into tablet dosage forms and to determine their dissolution rates.

EXPERIMENTAL

Mannitol, sorbitol, and mixtures of 50% sorbitol–50% mannitol and 50% sucrose–50% mannitol were used as the sugar carriers for the dispersion systems. These systems were compared to polyethylene glycol 6000 as a model system. Two orally administered corticosteroids, hydrocortisone and prednisone, were studied.

Preparation of Dispersion Systems—The dispersion systems were parpared by the fusion method as previously described (6). They were prepared in a ratio of 5 mg of the hydrocortisone or prednisone to 95 mg of the individual carrier. The hydrocortisone and prednisone controls were prepared in the same manner, without the melting and quenching procedures. The dispersion systems were stored for 48 hr at 25° in a desiccator before tableting.

A single-punch tablet machine[1] was used to prepare the tablets. The punch faces and die cavity were polished, and the compression pressure was adjusted to produce tablets that would meet USP standards. The formulation for the 200-mg tablets consisted of 2.5% corticosteroid, 47.5% sugar carrier (or 50% dispersion system), 35% dextrose and corn syrup solids[2], 7.5% microcrystalline cellulose[3], and 7.5% stearic acid–palmitic acid derivative[4]. Two batches were prepared for each dispersion system, and two lots of tablets were made from each batch. Therefore, for each dispersion, four lots of tablets were made with 80 tablets in each lot. The tablets were made by the direct compression method.

Tablets from each lot were analyzed for tablet hardness[5], thickness[6], weight[7], disintegration[8], and dissolution[8] and were required to meet the following criteria: hardness, 5–6 kg; thickness, 2.0 mm; weight, 200 mg ± 5%; content uniformity, 95–102%; and disintegration, <5 min.

The prepared tablets and the powdered dispersion systems were individually placed in a modified NF XIII dissolution rate apparatus (6). A 200-mg tablet or 100 mg of powdered sample was placed in the wire basket and lowered into the flask containing 1000 ml of deionized water. The basket was rotated at 100 rpm with a constant temperature of 25°.

A 10-ml volumetric pipet with an attached filter was used to remove a 10-ml sample of the dissolution fluid at 0, 2, 4, 6, 8, and 10 min. The sample was obtained from the same location in the container and transferred to labeled containers. Deionized water, 10 ml, was added to the dissolution container after sampling. Appropriate calculations were made to compensate for replacement of the sample fluid.

The corticosteroid concentration of each sample was analyzed using a UV spectrophotometer[9] (6). The concentrations were converted to percent dissolved and plotted against time t. All determinations were done at least in duplicate.

Short-Term Stability Study—The powdered and tableted dispersion systems were subjected to a short-term stability study at room temperature.

After 30 days of storage, the tablets were subjected to tablet characteristic tests; the dissolution rates of both the powdered melts and the tablets were determined. The results were compared to those obtained from previous experiments.

Corticosteroid Stability Studies—The stability of the corticosteroids during the preparation of the dispersion system and the tablets was studied as previously described (6).

RESULTS

Solid Dispersion Formation—All dispersion systems were relatively easy to prepare. Hydrocortisone and prednisone were miscible with mannitol in the melted state at the preparation temperature (200°). The mannitol dispersion systems were not hygroscopic, did not discolor, were very easy to manipulate, and possessed excellent flow characteristics.

The corticosteroids were only partially miscible with the sorbitol. These

[1] Stokes, Pennsalt Chemical Corp., Warminster, Pa.
[2] Celutab, Penick and Ford Co., Cedar Rapids, Iowa.
[3] Avicel-PH-101, FMC Corp., New York, N.Y.
[4] Sterotex, Capitol City Products Co.
[5] Stokes hardness tester, Pennsalt Chemical Corp., Warminster, Pa.
[6] Ames thickness gauge, Ames Co., Elkhart, Ind.
[7] Mettler H-8 analytical balance, Mettler Instrument Corp., Hightstown, N.J.
[8] Modified NF XIII dissolution rate apparatus, Hansen Research Corp., Los Angeles, Calif.
[9] Beckman ACTA III, Beckman Instruments, Fullerton, Calif.

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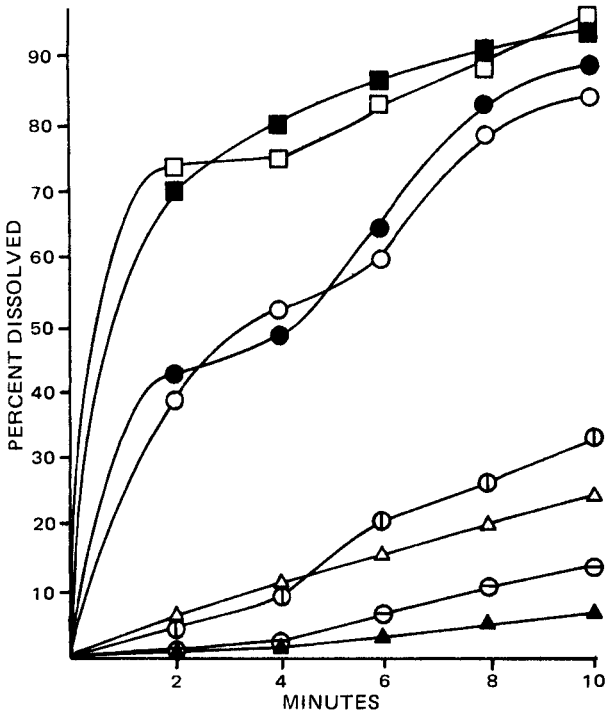

Figure 1—*Dissolution rates of hydrocortisone and prednisone in a sorbitol dispersion. Key for hydrocortisone: △, control powder; ⊖, control tablets; □, dispersion powder; and ○, dispersion tablets. Key for prednisone: ▲, control powder; ⊖, control tablets; ■, dispersion powder; and ●, dispersion tablets.*

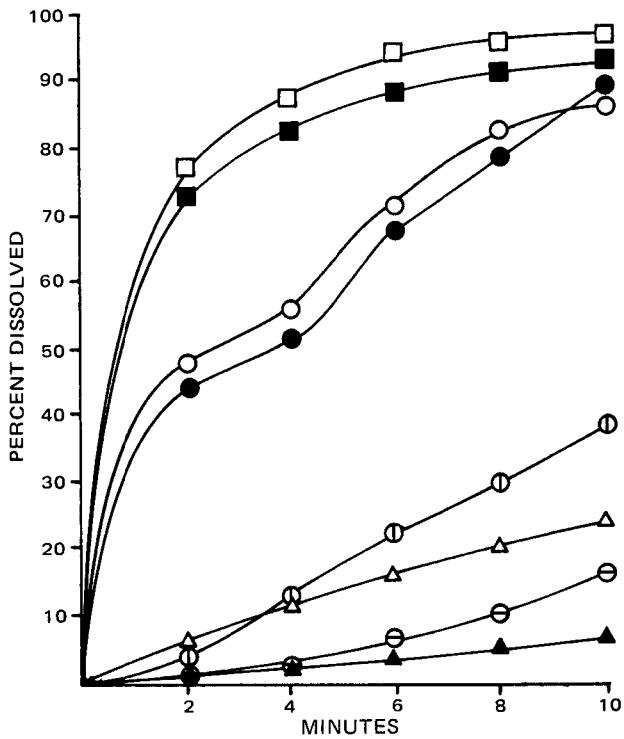

Figure 3—*Dissolution rates of hydrocortisone and prednisone in a sorbitol–mannitol dispersion. Key for hydrocortisone: △, control powder; ⊖, control tablets; □, dispersion powder; and ○, dispersion tablets. Key for prednisone: ▲, control powder; ⊖, control tablets; ■, dispersion powder; and ●, dispersion tablets.*

mixtures were hygroscopic and not as easily manipulated but did not discolor.

Both corticosteroids were miscible with the 50% mannitol–50% sorbitol mixture in the melted state. The addition of the mannitol to the sorbitol greatly improved the properties of these systems because they were easily manipulated, did not discolor, and were only slightly hygroscopic. A slight clumping of the particles could be broken up by a gentle tapping of the sample container; the powder could be seen to flow freely.

The 50% mannitol–50% sucrose mixture had a melting point of 154°, or approximately 14° lower than mannitol alone and about 20° lower than sucrose alone. This melting point resulted in a reduction of the sucrose

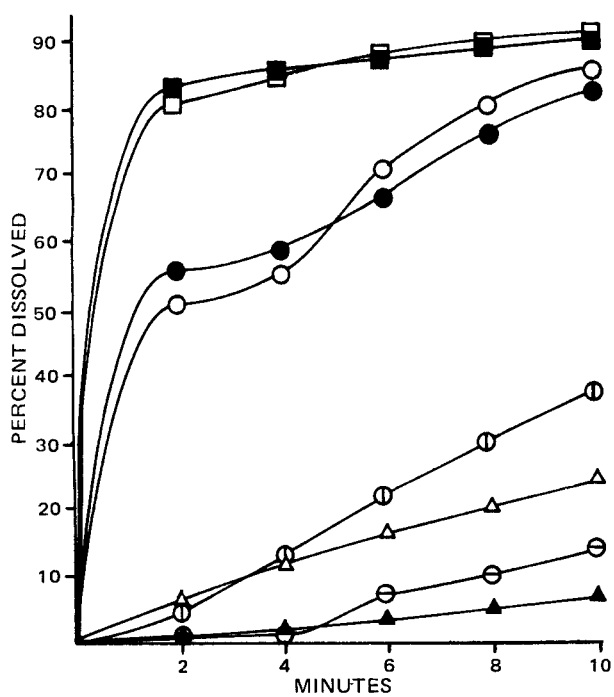

Figure 2—*Dissolution rates of hydrocortisone and prednisone in a mannitol dispersion. Key for hydrocortisone: △, control powder; ⊖, control tablets; □, dispersion powder; and ○, dispersion tablets. Key for prednisone: ▲, control powder; ⊖, control tablets; ■, dispersion powder; and ●, dispersion tablets.*

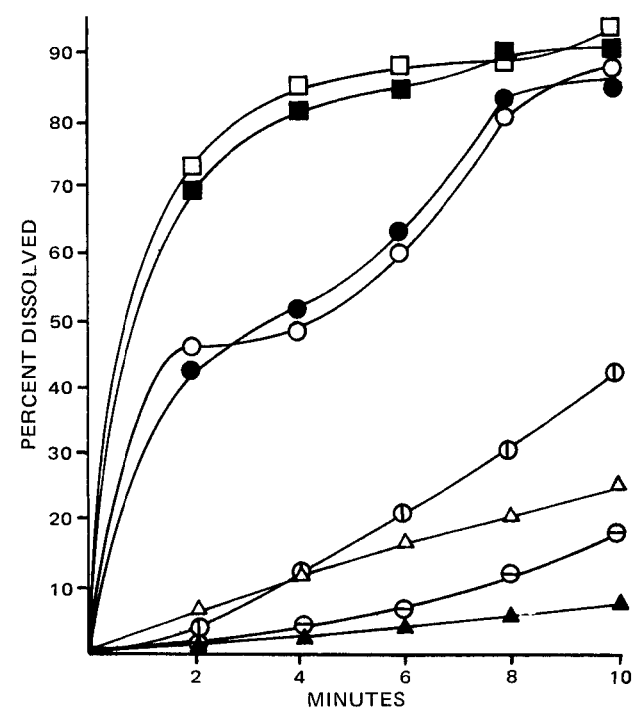

Figure 4—*Dissolution rates of hydrocortisone and prednisone in a sucrose–mannitol dispersion. Key for hydrocortisone: △, control powder; ⊖, control tablets; □, dispersion powder; and ○, dispersion tablets. Key for prednisone: ▲, control powder; ⊖, control tablets; ■, dispersion powder; and ●, dispersion tablets.*

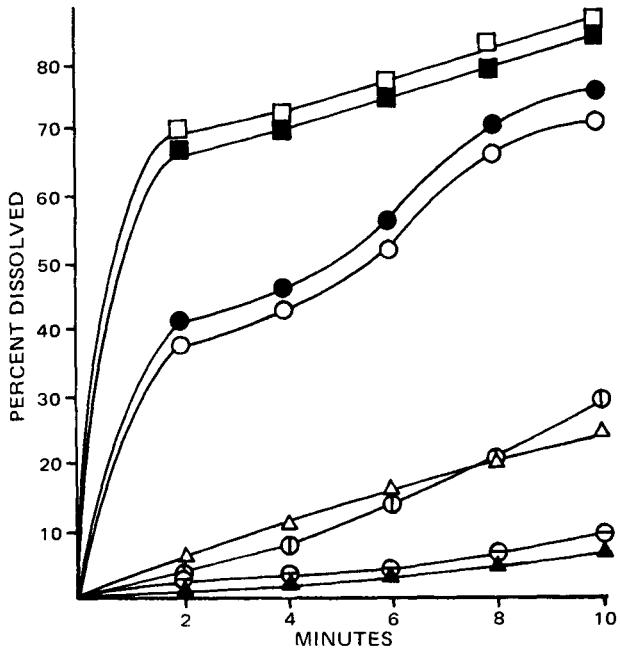

Figure 5—*Dissolution rates of hydrocortisone and prednisone in a polyethylene glycol 6000 dispersion. Key for hydrocortisone: △, control powder; ◑, control tablets; □, dispersion powder; and ○, dispersion tablets. Key for prednisone: ▲, control powder; ⊖, control tablets; ■, dispersion powder; and ●, dispersion tablets.*

discoloration during the preparation of this dispersion system. This mixture was, however, still slightly hygroscopic, but its flow properties were good, resulting in easy manipulation and workability similar to the mannitol–sorbitol mixture.

Hydrocortisone and prednisone were miscible with polyethylene glycol 6000 in the melted state. The physical properties of this dispersion system were very good. The system was heat stable, nonhygroscopic, and easy to manipulate, and it had excellent flow properties.

Dissolution Rate Determinations—As shown in Figs. 1–5, the dissolution rates of both corticosteroids increased markedly in all systems. The mannitol system had the fastest dissolution rate, followed by sorbitol–mannitol, sucrose–mannitol, sorbitol, and, finally, polyethylene glycol 6000.

Samples of the various lots of the powders and the tablets gave similar results. There was no alteration in the dissolution rates of samples subjected to the 30-day short-term stability test.

Stability Studies—Neither hydrocortisone nor prednisone showed any decomposition during the preparation of the melts or the tablets according to the analytical methods used. The tablet characteristic test results remained unchanged after 30 days of storage.

DISCUSSION

The solid dispersion systems demonstrated a fast initial release, followed by a slower, prolonged release of hydrocortisone and prednisone. Similar profiles previously were reported and discussed (6). As expected, the tablets produced slower dissolution rates than the powders.

After about 8 min in the dissolution fluid, the slope of the dissolution curve approached that of the powdered sample. This result indicated that the tablet formulation was effective in breaking up and exposing the system to the dissolution medium.

The control tablets possessed slightly faster dissolution rates than the control powders, probably because of the easier wettability of the steroid particles when encompassed by the hydrophilic tablet excipients. During tablet compression, the adsorbed or entrapped air was removed and, since the excipients were mostly hydrophilic in nature, they assisted in wetting the steroid particles.

The popularity of polyethylene glycol as a carrier was the main reason that the polyethylene glycol 6000 dispersion systems were used as a reference model when comparing the dissolution rates of the sugar dispersions. The sugar dispersions had a faster dissolution rate than the polyethylene glycol dispersions.

The data indicate that mannitol is one of the better sugar carriers, especially since it forms a stable, nonhygroscopic, free-flowing dispersion system. It revealed no discoloration during the preparation of the melt and was miscible with two steroids in the concentration range used.

The use of sugars in dispersion systems is advantageous over other solid dispersion carriers because they are nontoxic, inexpensive, and physiologically acceptable.

REFERENCES

(1) B. E. Ballard and J. A. Biles, *Steroids*, **4**, 273 (1964).

(2) G. Levy, N. A. Hall, and E. Nelson, *Am. J. Hosp. Pharm.*, **21**, 402 (1964).

(3) G. H. Schneller, *Drug Inform. Bull.*, **3**, 100 (1969).

(4) H. C. Shirkey, *J. Pediatr.*, **76**, 774 (1970).

(5) W. E. Hamlin, E. Nelson, B. E. Ballard, and J. G. Wagner, *J. Pharm. Sci.*, **51**, 423 (1962).

(6) L. V. Allen, Jr., V. A. Yanchick, and D. D. Maness, *ibid.*, **66**, 494 (1977).

(7) T. Otto, M.S. thesis, University of Oklahoma, Norman, Okla., 1976.

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