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INFLUENCE OF A MONTMORILLONITE CLAY ON THE PROPERTIES OF GRISEOFULVIN TABLETS

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ABSTRACT

Direct compression techniques were used to prepare tablets containing griseofulvin-montmorillonite adsorbates. The resulting tablets displayed uniform and consistent properties which compared quite favorably with commercial dosage forms containing micronized griseofulvin. Dissolution studies were conducted on powdered samples from the various tablets and these studies indicated that the highest levels of griseofulvin in solution after twenty minutes were found with the griseofulvin-montmorillonite samples.

INTRODUCTION

The absorption and therapeutic efficacy of griseofulvin are generally recognized as being rate-limited by the dissolution process in the gastrointestinal fluids. Due to the poor aqueous solubility of griseofulvin, 15 μg/ml at 37° (1), this antifungal

drug has been selected for many studies aimed at improving its dissolution rate and absorption (2-9). Crounse (10) reported that human blood levels of griseofulvin were variable and could be enhanced when the drug was administered in conjuction with high fat meals. Micronization of griseofulvin to increase the surface area and dissolution rate has resulted in a reduction of the recommended dose necessary for therapeutic effectiveness. Krami et al. (3) found that a 0.5 g dose of micronized griseofulvin produced serum levels indistinguishable from those produced by a 1.0 g dose of the nonmicronized drug. Chiou and Riegelman (7) reported that a ten percent dispersion of griseofulvin in a solid matrix of polyethylene glycol 6000 gave rise to a much higher and more consistent absorption than that of a micronized commerical product. Tablets containing micronized griseofulvin and glycol dispersions of the drug, are currently the most popular dosage forms for this antifungal agent.

However, the formulation of griseofulvin tablets continues to present several formulation challenges due to the high dosage needed, the fine particle size of the drug and the hydrophobic nature of griseofulvin (11). Harwood and Pilpel (12) proposed bowl granulation of griseofulvin using polyvinylpyrrolidone as a granulating agent for the preparation of griseofulvin tablets. Using a mixture of dicalcium phosphate dihydrate and calcium phosphato-carbonate complex as the tablet matrix, Khan and Rhodes (11, 13) successfully prepared a number of griseofulvin tablet

formulations by direct comprossion, recompression and wet granulation techniques.

The authors have previously reported that surface adsorption of griseofulvin onto a micronized montmorillonite clay was an effective method of increasing the dissolution rate of the drug (9). In the present study, the properties of tablets containing griseofulvin-montmorillonite adsorbates are investigated and compared to five marketed tablets containing micronized griseofulvin.

EXPERIMENTAL

Materials - The following materials were used: colloidal magnesium aluminum silicate[1], griseofulvin[2], starch[3], sodium starch glycolate[4], dicalcium phosphate dihydrate[5], magnesium stearate[6]. All other chemicals and solvents were reagent grade and were used as received.

Methods - Griseofulvin tablets containing griseofulvin-montmorillonite (1:1) adsorbates, were compressed with a Stokes Model F single punch tablet machine, using 7/16" flat face bevel edge punches. The preparation of the drug-clay adsorbates (equilibrated in acetone) has been previously described (9). Four tab-

[1]Veegum F®, R.T. Vanderbilt, Norwalk, CT 06855
[2]Ayrest Laboratories, Inc., Rouses Point, NY 12979
[3]StaRx 1500, Colorcon Co., West Point, PA 19486
[4]Explotab, Edward Mendell Co. Inc., Carmel, NY 10512
[5]Emcompress, Edward Mendell Co. Inc., Carmel, NY 10512
[6]Alfa Division, Ventron Corp., Danvers, MA 01923

let formulations were prepared. The formulas for products A and C appear in Table I. Ingredients were blended for 20 minutes and then directly compressed into tablets. Products B and D were prepared by recompression of formulas A and C respectively. The physical and chemical properties of the tablets were compared with five commerical griseofulvin tablets, (Products I, II, III, IV, and V) containing micronized drug. Since no official dissolution apparatus is currently available to test griseofulvin tablets, a comparison test was made of the crushed tablets containing 5 mg of the drug. Powders from the crushed tablets were passed through

TABLE I

COMPOSITION OF TABLETS CONTAINING

GRISEOFULVIN-MONTMORILLONITE (1:1) ADSORBATES

	Product A	Product C
Griseofulvin-Montmorillonite 1:1 Adsorbate	250 mg	250 mg
Starch	25 mg	25 mg
Sodium starch glycolate	25 mg	30 mg
Dicalcium phosphate dihydrate	291 mg	91 mg
Magnesium stearate	9 mg	4 mg

a 100 mesh screen prior to the test. The dissolution apparatus has been described previously (9).

RESULTS AND DISCUSSION

Four directly compressed tablet formulations were prepared and their properties were examined and compared to commercial tablets containing micronized griseofulvin. The formulas for Products A and C are shown in Table I. Products B and D consisted of recompressed tablets made from A and C respectively. Studies by Khan and Rhodes (11, 13) showed that dicalcium phosphate dihydrate was an excellent diluent for griseofulvin tablets and a similar conclusion was reached from this present study. The properties of the tablets containing the drug-clay adsorbates are found in Table II.

Although both formulas A and C contained in excess of 50% fines, both powder mixes exhibited good flow properties and the resulting tablets showed excellent weight uniformity. The bevel edged tablets for all formulas showed low friability values and no capping was found despite the high pressure used to compress the tablets. Disintegration was faster in dilute hydrochloric acid (0.1 N) than in purified water and Products C and D were found to disintegrate in less than one minute. Slightly faster disintegration times were found with softer tablets. For all the parameters studied excellent reproducibility in tablet properties was seen. This was probably due to the uniformity of mean

TABLE II

PROPERTIES OF TABLETS CONTAINING GRISEOFULVIN-MONTMORILLONITE (1:1) ADSORBATES

	Product A	Product B	Product C	Product D
Tablet weight, mean ± S.D. (mg) n = 20	613.2 ± 1.4	640.2 ± 3.5	416.9 ± 2.3	399.2 ± 1.8
Hardness (kg)*	13.7 ± 0.8	15.3 ± 0.5	12.9 ± 0.6	13.4 ± 0.6
Disintegration time, mean ± S.D. (sec), in purified water at 37°**	71.3 ± 2.1	86 ± 4.2	48.3 ± 2.9	53.2 ± 2.1
Disintegration time, mean ± S.D. (sec), in 0.1 N HCl at 37°**	63.7 ± 2.3	72.7 ± 1.4	41.8 ± 1.9	49.2 ± 1.7
Friability (%)	0.3	0.19	0.05	0.05
Apparent tablet density ($g.cm^{-3}$)	1.70	1.73	1.65	1.73

*Herberlien hardness tester.
**USP Disintegration apparatus

weights of the tablets. Recent studies by the authors (14) have shown that high levels of colloidal magnesium aluminum silicate in sulfathiazole tablets produced slow-release dosage forms. However, since the clay was coated with griseofulvin in the present study, the sodium starch glycolate was added to disintegrate the tablets. Swelling of the individual clay particles resulted in the displacement of the weakly bound drug (9).

Table III contains a comparison of the properties of commercial griseofulvin tablets containing micronized drug in conventional tablet formulations and as a polyethylene glycol solid dispersion. Tablet disintegration times varied from 32 secs. for Product I to a mean time of 708 secs. for Product IV which showed the slowest and most variable disintegration times. Although both Products I and V displayed rapid disintegration times, aggregates were formed as the tablet passed through the disintegration baskets. This suggested that the dissolution rates of the micronized drug may have been reduced by the clumping of the tablet components.

Due to the poor solubility of griseofulvin no official dissolution test is currently available for tablet dosage forms of the drug. Walkling *et al.*, (1) have used a hydroalcoholic dissolution media and found that convenient volumes of dissolution fluid could be used, intact dosage forms could be tested and formulations could be compared without concern for non-sink effects. However, other studies in our laboratory have shown that the disintegrating properties of the griseofulvin tablets

TABLE III

PROPERTIES OF COMMERCIAL MICRONIZED GRISEOFULVIN TABLETS*

	Product I	Product II	Product III	Product IV	Product V
Tablet weight, mean ± S.D. (mg) n = 20	599.6 ± 3.79	320.8 ± 3.25	613.5 ± 3.70	922 ± 10.6	667 ± 6.99
Hardness**	10.12 ± 1.61	5.625 ± 0.63	5.92 ± 0.14	15.75 ± 0.35	9.9 ± 0.25
Disintegration time, mean ± S.D. (sec), in purified water at 37° ***	32.0 ± 0.2	156.5 ± 11.9	114.5 ± 4.37	708.0 ± 67.6	36.5 ± 2.6
Disintegration time, mean ± S.D. (sec), in 0.1 N HCl at 37°***	37.50 ± 1.5	115.3 ± 15.3	56.5 ± 1.64	454.3 ± 146	34.5 ± 3.5
Friability (%)	0.639	0.39	0.628	0.017	0.553
Apparent tablet density (g cm^{-3})	1.153	1.095	0.952	0.922	1.208

*Tablets contained 125 mg, 250 mg or 500 mg griseofulvin
**Herberlien hardness tester
***USP Disintegration apparatus

shown in Table I were considerably different in aqueous and hydroalcoholic media.

The dissolution profiles in Fig. 1 show a comparison of drug release from powdered samples of griseofulvin tablets. Aliquots of powder containing 5 mg of griseofulvin were used for the dissolution studies. The profiles in Fig. 1 show that the dissolution rate of griseofulvin was slowest from Product II with only 31 percent drug of the available drug in solution after 20 minutes. Product IV after 20 minutes had 48 percent drug in solution. The powdered sample from the griseofulvin-montmorillo-

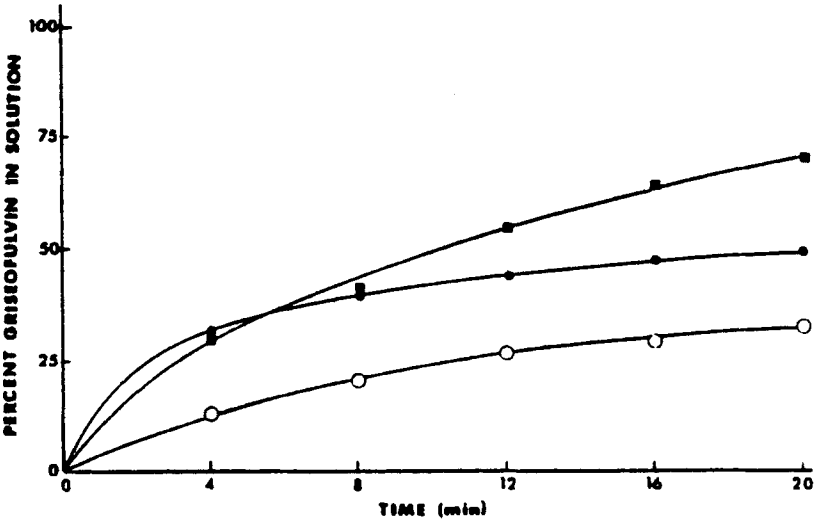

Figure 1

Dissolution profiles from powdered tablets containing 5 mg griseofulvin, in 900 ml aqueous polysorbate 80 solution (0.02%) maintained at 37° and stirred at 150 rpm. Key: ■ , Tablet C (Table I); ●, Product IV; ○, Product II.

nite tablet (Tablet C, Table I) exhibited 72 percent drug in solution after the same time period. The dissolution profiles for Products I, III and V fell into the region between the curves for Products II and IV. It should also be pointed out that dissolution tests employing crushed powdered samples of the various tablets do not take into account the disintegration times of the respective dosage forms, which are reported in Tables II and III.

Although the powdered montmorillonite tablets containing adsorbed griseofulvin produced the highest amount of drug in solution after a 20 minute period, the dissolution rate was considerably less than previously seen with adsorbate powders. This decrease appears to be due to the physical displacement of weakly bound drug from the clay particles by the pulverization process used prior to the dissolution test. Recent studies by the authors have shown that the dissolution rates of griseofulvin from montmorillonite adsorbates were reduced significantly by grinding the adsorbate prior to the dissolution test (14).

In conclusion, it has been shown that tablets containing griseofulvin-montmorillonite adsorbates can be prepared using direct compression techniques. The resulting tablets displayed uniform and consistent properties which compared quite favorably with commercial dosage forms. Since no official dissolution test is available to compare the intact dosage forms, powdered samples from the various tablets were used. These studies in-

dicated that the highest levels of griseofulvin in solution after 20 minutes were found with the griseofulvin-montmorillonite samples. Further studies in vivo are necessary to verify the significance of these results.

REFERENCES

1) W.D. Walkling, R.K. Nayak, J. Plostnieks and W.A. Cressman, Drug Devel. Indust. Pharm., 5(1), 17 (1979).

2) R. Atkinson, C. Bedford, K.J. Child and E.G. Tomich, Nature, 193, 588 (1962).

3) M. Kraml, J. Dubuc and R. Guadry, Antibiot. Chemotherapy, 12, 232 (1962).

4) K. Sekiguchi, K. Ito, E. Owado and K. Ueno, Chem. Pharm. Bull., 12 1192 (1964).

5) J.R. Mavel, D.A. Schlichting, C. Danton, E.J. Levy and M.M. Cahn, J. Invest. Dermatol., 42, 197 (1964).

6) M. Mayersohn and M. Gibaldi, J. Pharm. Sci., 55, 1323 (1966).

7) W.L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1376 (1971).

8) D.C. Monkhouse and J.L. Lach, J. Pharm. Sci., 61, 1430 (1972).

9) J.W. McGinity and M.R. Harris, Drug Devel. Indust. Pharm., in press.

10) R.G. Croumse, J. Invest. Derm., 37, 529 (1961).

11) K.A. Khan and C.T. Rhodes, Drug Devel. Comm., 1(6), 553 (1975).

12) C.F. Harwood and N. Pilpel, J. Pharm. Sci., 57, 478 (1968).

13) K.A. Khan and C.T. Rhodes, Drug Devel. Comm., 2(1), 77 (1976).

14. J.W. McGinity and M.R. Harris, unpublished data.