DRUG DEVELOPMENT COMMUNICATIONS, 1(6), 553-566 (1974-1975)

FORMULATION OF GRISEOFULVIN TABLETS

K. A. Khan
Beechams Pharmaceuticals
Worthing, England

C. T. Rhodes
Department of Pharmacy
University of Rhode Island
Kingston, Rhode Island 02881

ABSTRACT

Difficulties in the formulation of griseofulvin tablets are reviewed. A number of griseofulvin direct compression, pre-compression and polyvinylpyrrolidone granulated tablet formulation have been successfully produced and evaluated, in all cases a mixture of dicalcium phosphate dihydrate and calcium phosphato-carbonate complex was used as tablet matrix. Attempts to use other direct compression tablet matrices proved unsuccessful. The tablets produced have been compared with two commercially available products and the data obtained indicated that the formulations developed in this study have potential for further exploitation.

INTRODUCTION

Griseofulvin is a most useful drug for the treatment of a variety of fungal infections, it is widely used, and daily dosage may be as high as 1 G per day. Tablets usually contain 125, 250 or 500 mg of drug. In order to improve dissolution, the micronized material (1) is widely used. The combination of high dosage, fine particle size, and the hydrophobic nature of the molecular structure present difficult problems to the pharmaceutical formulator.

Harwood and Pilpel (2) reported that griseofulvin tablets are generally made from granules. They proposed bowl granulation of griseofulvin using polyvinylpyrrolidone as a granulating agent.

In the present paper, the authors describe investigation of a number of formulations designed for use as direct compression griseofulvin tablet matrices. The products obtained are compared with two commercially available griseofulvin tablets.

The authors have previously published a number of studies dealing with the utility of dicalcium phosphate dihydrate as a direct compression matrix (3) and in this investigation attempts have been made to exploit this material for the formulation of direct compres-

sion griseofulvin tablets. Pharmaceutically the most widely used form of calcium phosphate dihydrate is 'Emcompress' supplied by Edward Mendell Inc.

EXPERIMENTAL

Materials - Griseofulvin[1], mean particle size estimated by use of Fisher sub sieve sizer 3/6 m, bulk density 0.265g cm^{-3}, tap density (20 taps). 0.412g cm^{-3}. Cation exchange resin[2], dicalcium phosphate dihydrate[3], calcium phosphato-carbonate complex[4], magnesium stearate[5], colloidal silica[6], tale B. P.[7], polyvinyl-pyrrolidone[8], spray dried lactose[9], modified starch[10], microcrystalline cellulose[11].

---

[1]B. P. Fine, I.C.I., Macclesfield, England.

[2]'Amberlite' IR8 88 Lennig, London, England.

[3]Albright and Wilson, Oldbury, England.

[4]'Calfos' 50 mesh Calfos, London, England.

[5]British Drug Houses, Poole, England.

[6]'Serosil', Bush Beach and Segner Bagley, Cheshire, England.

[7]Evans Medical, Speke, England.

[8]'Kollidone 25', Victor Blagdon, London, England.

[9]McKesson and Robins, Ramsgate, England.

[10]'Sta-Rx' 1500, Staley, London, England.

[11]'Avice pH', Honeywell and Stein, London, England.

Methods - Tablets were prepared using a Mannesty F3 single punch press. Simple direct compression, precompression, and granulation techniques were all evaluated.

A number of precompression techniques were tested, the most satisfactory was found to be as follows. Drug and diluent were blended and cation exchange resin added both internally and externally. The mixture was precompressed, the slugs were broken and forced through a number 16 hand screen, blended with the rest of the formula and compressed using 11.11 mm, 7/16" normal concave punches.

The most satisfactory results were obtained with the following formula griseofulvin 125 mg. calcium phosphato-carbonate complex 20 mg. calcium phosphate dihydrate 380 mg. magnesium stearate 5 mg for the precompression, adding calcium phosphato-carbonate complex 5 mg. calcium phosphate dihydrate 95 mg. cation exchange resin 13 mg. magnesium stearate 9 mg. and colloidal silica 3 mg before the final compression.

Another technique used involved pretreatment of the griseofulvin powder by granulating the drug in an electric mixer using 4% w/w/ polyvinylpyrrolidone dissolved in distilled water as a granulating liquid. The objective of this exercise was to increase the particle size of griseofulvin by granulation and then incorporating these granules into the dicalcium phosphate dihydrate, calcium phosphato-carbonate mixture. The following formula was used: griseofulvin 100 mg. polyvinylpyrrolidone 4 mg. distilled water 0.04 cm^3. The wet mass prepared by using the solution of polyvinylpyrrolidone as granulating agent (which was added in small increments) was in the form of granules. The granules were then passed through a number 8 hand screen. The product was dried at 60°C for 18 hours and the dried granules finally forced through a number 16 mesh hand screen. The particle size distribution of the granules was estimated by use of an Alpine air jet sieve. It was found that the average particle size was 500 mm. The granules were blended with the other components of the formulation and the resultant mixture compressed into tablets.

In order to compare the properties of the tablets prepared in this study with presently available commercial products lots of tablets produced for the British market by Manufacturers I and II were included in the evaluating study, results are shown in Tables I and II.

Table I

Variations in weight and hardness of commercial griseofulvin tablets (manufactured by I and II) as compared with those directly compressed in this study

	Manufacturer I	Manufacturer II	Directly compressed*
Mean weight, mg.	145.7	143.6	725.6
Relative standard deviation % (weight)	1.2	0.87	1.4
Mean hardness (Erweka)	2.5	2.5	6.2
Relative standard deviation % (hardness)	35.2	32.0	33.8

*Formula G Griseofulvin 125 mg. calcium phosphato-carbonate complex 30 mg. colloidal silica 4 mg. magnesium stearate 11 mg. cation exchange resin 15 mg. dicalcium phosphate dihydrate 570 mg.

Griseofulvin was also directly compressed using formulas similar to those developed by Reier[A](4) and Manudhane[B](5). The composition of the two products was as follows:

A	Griseofulvin	125 mg
	Spray dried lactose	100 mg
	Microcrystalline cellulose	400 mg
	Magnesium stearate	10 mg
B	Griseofulvin	125 mg
	Modified starch	250 mg
	Microcrystalline cellulose	250 mg
	Magnesium stearate	10 mg

Tablets were evaluated as described previously (3, 6, 7).

Table II

Variations in the idsintegration times of commercially available and directly compressed griseofulvin tablets prepared in this study

		Manufacturer I minutes	Manufacturer II seconds	Directly compressed, this study - seconds
	1	90	181.6	69.5
	2	65	188.6	58.6
	3	24	190.2	53.5
Disintegration	4	20	181.7	55.2
	5	35	183.8	75.7
e of ten	6	43	209.5	61.3
	7	120 (taken as	182.3	59.3
ets		120 minutes)		
	8	30	178.3	55.8
ted	9	25	185.0	61.2
	10	47	173.0	70.3
dividually				
ean disintegration ime		50 minutes	185.4seconds	62.0 seconds
Standard deviation		30.9	9.2	7.5
Relative standard deviation (%)		61.9	4.9	12.0

RESULTS AND DISCUSSION

As previously indicated, it was expected that formulation of this drug would present unique problems and the data obtained in this study confirmed this; mean particle size 3.6 μm, a bulk density value of only 0.265 g cm^{-3} and very poor flow and compression properties. Although, the authors have gained considerable exper-

ience in compressing drugs in a hydraulic press, using such techniques as painting the inside of the punches and dies with stearic acid in order to assist ejection, absolutely no success was achieved with this drug on the hydraulic press despite the fact that many other "difficult" drugs have been so compressed in our laboratories.

A number of direct compression formulas were tested (Table III); results are shown in Table IV. Both formulations A and B were directly compressible, however, their flow properties were poor (Bulk density A 0.229 g cm^{-3}, B 0.345 g cm^{-3}; tap density, 20 taps, A 0.476 g cm^{-3}, B 0.562 g cm^{-3}), thus even at maximum die fill settings, tablets of the required weight could not be produced. Formulation C showed some signs of lamination. It is suspected that this problem is due to the difference in particle size of the drug and the dicalcium phosphate dihydrate; vibration in the hopper tending to cause separation. This problem is also reflected in the rather high weight variation shown in Table IV for this formulation. The appearance of the tablets was satisfactory but not as shiny as most formulators would consider desirable. The use of stearic acid and talc had little affect on the tablet. However, increasing the amount of colloidal silica and magnesium stearate (D and E) or reduction in the drug:excipient ratio (F) resulted in significant improvement,

Table III

Composition, in mg.
direct compression tablet formulations of griseofulvin
using dicalcium phosphate dihydrate

Formula	Griseofulvin	Calcium phosphate-carbonate	Dicalcium phosphate dihydrate	Cation exchange resin	Magnesium stearate	Colloidal silica
C	125	19	356	10	8	2.5
D[1]	125	19	356	10	8	3.0
E	125	25	475	12	9	3.0
F[2]	75	19	356	9	7	2.0

[1] Addition of 2% talc had no significant effect.

[2] Reduction of griseofulvin content to 50 mg had no significant effect.

Table IV

Properties of direct compression tablet formulations of griseofulvin using dicalcium phosphate dihydrate

Formula	Mean tablet weight, mg	Relative standard deviation of weight %	Hardness, Erweka	Disintegration Time mins.	Lubrication	Appearance
C	524	6.6	8.0	0.25	F*	F
D	529	4.6	6.0	0.25	F	F
E	595	1.9	8.5	0.20	G**	G
F	468	2.9	8.0	0.33	G	G

* Fair

** Good

weight variation, lubrication and appearance. In all cases, the disintegration times are very satisfactory; it is, of course, appreciated that the biological availability of these tablets can only be fully appraised by in vivo studies. It is felt, however, that these pilot scale formulations merit further investigation for large scale production.

Results of the precompression and granulation techniques are shown in Table V; reproducibility of the granulation procedure is indicated by the data in Table VI.

Tables I and II show some rather discouraging data regarding the properties of commercial griseofulvin tablets available on the British market. Since only one lot of each manufacturer was tested, no general conclusions may be induced but it is a matter of concern that any griseofulvin tablets produced by a major manufacturer should be available with a mean disintegration time of 50 minutes. It is very doubtful if the tablets produced by manufacturer I, tested in this study would give anything like adequate clinical performance. By comparison, the direct compression formula produced in this study and the tablets of manufacturer II seem to give reliable and rapid disintegration.

Table V

Properties of precompressed and polyvinylpyrrolidone granulated griseofulvin tablets

Formulation technique	Mean weight mg.	Relative standard deviation, %	Hardness, Erweka	Disintegration time, mins.	Lubrication	Appearance
Precompression **	634	1.7	6.8	0.66	G	G
Granulation with polyvinlypyrrolidone	535	0.8	10.5	0.25	VG*	VG

*Very good

**Griseofulvin pretreated (16 mesh granules) 130 mg (griseofulvin 125 mg), calcium phosphato carbonate complex 19 mg, dicalcium phosphate dihydrate 356 mg, cation exchange resin 10 mg. magnesium stearate 7.5 mg., colloidal silica 2.5 mg.

Table VI

Griseofulvin tablets granulated with polyvinylpyrrolidone, batch to batch variation

	Batch number		
	1	2	3
Mean weight, mg.	543.2	535.8	548.2
Relative standard	0.88	0.83	0.76
Mean hardness, Erweka	9.6	10.5	11.0
Mean disintegration time, mins.	0.33	0.25	0.33

The major advantage of the precompression technique lies in the excellent compaction properties of the selected formula; the slugging was easily achieved. The data obtained in this study indicates that dicalcium phosphate dihydrate is readily reworkable.

The tablets produced by granulation with polyvinylpyrrolidone were outstanding in appearance (Table V). This method of tablet preparation represents a deviation from the concept of simple direct compression but on a large scale, the pretreated granules could, of course, be stored and used when required.

All the tablets formulated in this work had friability values of less than 0.5%.

It is suggested that the data presented in this work indicates that the direct compression technique, simple or modified, using dicalcium phosphate dihydrate offers great potential for griseofulvin.

References

(1) B. A. Matthews and C. T. Rhodes, J. Pharm. Sci., 56, 838 (1967).

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

(3) K. A. Khan, and C. T. Rhodes, J. Pharm. Sci. 64, 166 (1975).

(4) G. E. Reier, Ph. D. Thesis, University of Maryland, (1964).

(5) K. S. Manudhane, Ph. D. Thesis, University of Maryland (1967).

(6) K. A. Khan and C. T. Rhodes, Pharm. Acta. Helv. 47, 41 (1972).

(7) K. A. Khan, Ph. D. Thesis, C.N.A.A. Portsmouth (1973).