

-continued

Time (min)	Sporanox™ 98P0800E	Test Example 1
pH 6.0 media, 100 rpm, paddles		
0	0	0
5	1.1	4
10	1.2	20.2
30	2.2	58.5
45	2.8	69.7
60	3.2	76.4
120	3.7	77.6
180		82.3
240		81.1

EXAMPLE 2

To produce the solid dispersion, a solution was prepared by dispersing HP-50 (420 g) in methylene chloride (8400 g) and then adding itraconazole (280 g) and stirring to form a pale brown solution. This solution was then spray dried to form a powder.

A portion (292 g) of this spray dried powder was then blended with sodium starch glycolate (93.6 g) and colloidal silicon dioxide (Aerosil 200) (5.6 g) in a Collette mixer at high speed for 5 minutes. Magnesium stearate (8.8 g) was added to the blend from the Collette mixer and the mixture tumble blended until uniform.

This powder blend was then filled into size 0 gelatin capsules by hand. Each capsule was filled with 345 to 359 mg of powder, containing nominally 98 to 102 mg of itraconazole.

These test capsules were utilised in a pharmacokinetic study. 8 male volunteers were dosed with one 100 mg capsule after an overnight (10 hour) fast. The capsules were dosed with 240 ml water. At appropriate time intervals blood samples were taken from the subjects and the concentration of itraconazole in the plasma determined. The study was performed in a randomised 2 way crossover fashion with subjects receiving 100 mg itraconazole as a marketed capsule (Sporanox™) or as the test formulation described in example 2 above. The alternate dose was taken after a 2 week washout period.

A plot of the mean blood levels measured is as follows:

The data was analysed and the following standard mean pharmacokinetic parameters were obtained.

Parameter	Example capsule	Sporanox™ capsule (Lot 98P0800E)	Ratio
C _{max} (ng/ml)	182.6	56.0	326%
T _{max} (h)	2.94	3.44	85.5%
AUC (ng.h/ml)	1776	622	285%
AUC _{inf} (ng.h/ml)	1875	664	282%

It can be seen from these results that significantly higher plasma itraconazole levels are obtained from the formulation described in the example than the marketed capsule form under these conditions.

Indeed, it was expected that the itraconazole formulation of this invention would have a later T_{max} (time to maximum blood concentration of active) than SporanoX™, due to the use of an enteric polymer, which should not have solubilised until after passing through the stomach. This is in compari-

son to the water-soluble polymers used in SporanoX™ that would solubilise in the stomach.

However, it can be seen from the above data that the T_{max} of the formulation of the present invention is at least similar to the T_{max} of SporanoX™, if not shorter than it. Together with the greatly increased C_{max}, this result was surprising.

EXAMPLE 3

Test capsules from Example 2 containing 100 mg of itraconazole were also utilised in a pharmacokinetic study under fed conditions, primarily for comparison with the pharmacokinetic results of Example 2 to determine whether there was any food effect.

The study was again conducted as a single dose, crossover study in 8 health male adult subjects, but under fed conditions. The subjects commenced eating a standard high fat breakfast 20 minutes prior to dose administration, having fasted for at least 10 hours prior to that.

A two week washout period between administration of the dose for each of the two treatments was again used, and the comparative product was again two 100 mg itraconazole capsules marketed as SporanoX™.

At appropriate time intervals blood samples were taken from the subjects and the concentration of itraconazole in the plasma determined.

A plot of the mean blood levels from the fasted study of example 2 (Fasted Study CM4799) and the fed study of Example 3 (Fed Study CM6000) is as shown in FIG. 2.

The data from the fed study of Example 3 was analysed and the following mean standard pharmacokinetic parameters were obtained:

Parameter	Example 3 Capsule (Fed)	Example 2 Capsule (Fasted)
C _{max} (ng/ml)	148.20	182.6
T _{max} (h)	10.25	2.94
AUC (ng.h/ml)	1806	1776
AUC _{inf} (ng.h/ml)	1997	1875

It can be seen from these results that the example formulation produces plasma profiles considered bioequivalent in terms of AUC under fasting and fed conditions, due to the AUC under fed conditions being about 102% of the AUC under fasted conditions, which is well within the range of 80 to 120%. This is an indication that the total amount of drug absorbed over time is essentially equivalent under fed and fasted conditions.

Finally, it will be appreciated that there may be other variations and modifications to the compositions described herein that are also within the scope of the present invention.

What is claimed is:

1. A pharmaceutical composition consisting essentially of about 100 mg of an azole antifungal drug and optionally at least one polymer having acidic functional groups wherein in vivo the composition provides a mean C_{MAX} of at least 100 ng/ml, after administration in the fasted state.

2. A pharmaceutical composition according to claim 1, wherein said at least one polymer having acidic functional groups is present.

3. A pharmaceutical composition according to claim 1, wherein in vivo the composition provides a mean C_{MAX} of at least 150 to 250 ng/ml, after administration of the azole antifungal drug in the fasted state.

4. A pharmaceutical composition according to claim 1, wherein the azole antifungal drug is itraconazole.