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Increasing Dissolution Rates of Griseofulvin by Adsorption to a Silicon Dioxide(การเพิ่มอัตราการละลายของ Griseofulvin โดยการดูดซับบน Silicon Dioxide)

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ORIGINAL ARTICLE

Increasing Dissolution Rates of Griseofulvin by Adsorption to a Silicon Dioxide

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Abstract :

Griseofulvin-silicon dioxide adsorbates of various ratios ranged from 1 : 0 to 1 : 9 were prepared by solvent deposition methods using three organic solvents, acetone, chloroform and methylene chloride. Dissolution profiles clearly showed that absorption to silicon dioxide increased the dissolution rates of griseofulvin. In addition, the dissolution increased with the increasing amount of silicon dioxide. The dissolution rates obtained from drug-silicon dioxide triturations, prepared by simple mixing method, also showed an increase as the amount of silicon dioxide increased up to drug : silicon dioxide 1 : 3 ratio. Further increase in the amount of silicon dioxide did not improve the dissolution. The preparation methods caused a markedly difference in the dissolution profiles. Of all the drug-silicon dioxide 1 : 1 ratios, adsorbates prepared by acetone deposition method exhibited the greatest dissolution rate, followed by simple mixing triturations, adsorbates prepared by chloroform deposition, and methylene chloride deposition methods. Griseofulvin tablets containing 1 : 1 adsorbates

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prepared by acetone deposition method or micronized powder were then prepared by wet granulation method. Dissolution comparison of these tablets confirmed that absorption to silicon dioxide could be used to improve the dissolution rate of griseofulvin tablets.

Introduction

Preparations of solid oral dosage forms containing poorly soluble drugs always have problems in solubilization of these drugs in the gastrointestinal tract. The rates of absorption of the drugs from the stomach of intestine are limited. Thus, the bioavailabilities are incomplete. Several methods have been approached to overcome these problems [1, 2]. Increasing the dissolution of poorly soluble drug by the use of adsorbent was initially suggested by Monkhouse and Lach [3, 4]. It is based on the concept of increasing the surface available for dissolution. By this method, the drug is dispersed on the surface of an insoluble microparticulate adsorbent carrier and then released in an unbound absorbable form upon contact with dissolution medium.

Griseofulvin, an antifungal agent, is very slightly soluble in water. Its aqueous solubility is 15 μg/ml at 37°C [5]. This drug has been selected for many studies aimed at improving its dissolution rate and absorption [3,4,6-11].

Silicon dioxides are extensively used in the production of a large number of pharmaceutical dosage forms [12]. They have been proposed as adsorbents for enhancing the dissolution rates of poorly soluble drugs [3,4,8,11,13].

The purpose of this investigation is to evaluate the potential of a silicon dioxide, Syloid 244, and the effect of preparation methods on the dissolution rate of griseofulvin. The samples will be prepared by two dispersion methods, simple mixing and solvent deposition using three organic solvents. Various ratios of the triturations and adsorbates thus prepared will be studied for their dissolution rates using modified beaker method [14]. Selected sample will be compressed to tablets. The dissolution will again be investigated using the USP dissolution Type I method [15] and compared to tablets containing micronized griseofulvin.

Experimental

A. Chemicals – The following were obtained from commercial sources: Syloid 244[1], micronized griseofulvin[2], acetone[1], chloroform[3], methylene chloride[4], polysorbate 80[1], lactose[1], Tapioca starch[1], polyvinyl pyrrolidone 30 k[1], sodium lauryl sulfate[1], magnesium stearate[1], absolute ethanol[5], sodium hydroxide[6], and monobasic sodium phosphate[1].

[1] Pharmaceutical Sciences Ltd., Part., Bangkok, Thailand.
[2] Winco Pharma, Bangkok, Thailand.
[3] Mitsubishi Chemical, Tokyo, Japan.
[4] Mallinckrodt, Inc., Paris, Kentuckey 40381, U.S.A.
[5] Riedel-DeHaen AG Scelze-Hannover, Germany.
[6] Farmitalia, Carlo Erba, Milan, Italy.

B. Equipment – The following were used : the USP XIX dissolution apparatus[1], a spectrophotometer[2], a blender[3], US Standard sieves # 12 30 and 80 mesh[4], a pH meter[5], an oven[6], Stoke's Single Punch Tablet Machine[7], and a magnetic stirrer with heater[8],

C. Preparation of griseofulvin–silicon dioxide samples

Griseofulvin–silicon dioxide ratios 1 : 0, 1 : 1, 1 : 3, 1 : 5, 1 : 7 and 1 : 9 were prepared utilizing the following methods.

1. Simple Mixing

Griseofulvin 1.0 gm and the exact amount of Syloid 244, each passed through an 80–mesh sieve, were mixed in a blender for 5 minutes. The mixture was rescreened through an 80–mesh sieve and tumbled in a bottle for another 5 minutes to ensure homogeneity.

2. Solvent Deposition

The drug, 1.0 gm, was dissolved in 200 ml of various organic solvents, acetone, chloroform, and methylene chloride. Exact amount of Syloid 244 was dispersed in the drug solution. The mixture was stirred with magnetic stirrer while the solvent was evaporated at room temperature. The residue was dried at 40°C for 24 hours and passed through an 80–mesh sieve. The sieved material was then bottle–blended for 5 minutes.

D. Preparation of Griseofulvin Tablets

1. Formulation

Drug (micronized powder or drug in 1 : 1 adsorbate)	125 mg
Lactose	50 mg
Tapioca starch	12.5 mg
Polyvinylpyrrolidone 30 K	20 mg
Sodium lauryl sulfate	1.5 mg
Magnesium stearate	2.87 mg

2. Granulation

Adsorbate or pure drug, lactose, tapioca starch, polyvinyl pyrrolidone, and sodium lauryl sulfate were passed individually through a 20–mesh sieve. The ingredients were then bottle–blended for 3 minutes. The mixture was granulated with absolute alcohol as solvent. The damp mass was then passed through a 12–mesh

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[1] Hanson Research Corp., Northridge, Calif., U.S.A.

[2] Spectronic 2000, Bausch & Lomb Inc., New York, U.S.A.

[3] Model BL 100 G. Tokyo Toshiba Electric Co., Japan.

[4] Endecotts Ltd., London, England.

[5] Pye Model 292 pH meter, Pye Unicam Ltd., Cambridge. England.

[6] Lytzen oven, Copenhagen, Lyngby, Denmark.

[7] F.J. Stokes Machine Company, Pensylvania, U.S.A.

[8] Thermolyne, Dubuque, Iowa, U.S.A.

sieve and dried at 40°C. The dried granule was rescreened through a 30-mesh sieve. Magnesium stearate was added and the mixture was bottle-blended for 3 minutes.

3. Compression

The mixture was compressed to tablets by Stoke's Single Punch Tableting Machine using 3/8 inch, concave punches. The pressure was controlled to give tablet hardness of 4-6 KSI.

E. Dissolution Study

1. Adsorbates or triturations

The dissolution tests of the adsorbates or triturations were conducted by modified beaker method. The apparatus consists of a 1000-ml beaker, a magnetic stirrer with heater, and a thermometer. The adsorbate or trituration containing 25 mg griseofulvin was added to the beaker containing 500 ml of 0.02% polysorbate 80 in purified water as dissolution medium. It was reported that this dissolution medium had the same surface tension as gastrointestinal fluid and the surfactant would prevent clumping and floating of hydrophobic drugs [15]. The speed of stirrer was adjusted to 100 rpm and the temperature of dissolution medium was 37°C. A 5-ml sample was withdrawn at various time intervals and equal volume of fresh dissolution medium was added to maintain constant volume. A duplication was conducted in each experiment.

2. Tablets

The dissolution tests of griseofulvin tablets were conducted by USP dissolution type I method. A 900-ml of simulated intestinal fluid without enzyme was used as dissolution medium. The temperature of dissolution medium was maintained at 37°C. The baskets, each containing one tablet, were rotated at a speed of 100 rpm. Samples were withdrawn as in the dissolution study of adsorbates. Duplicate experiments were conducted.

3. Determination of Griseofulvin Concentration

Each sample was assayed for drug content by UV spectroscopy at the maximum wavelength of 292.7 nm. The percentage of drug dissolved was then calculated from standard curves.

Results

Percentages of griseofulvin dissolved from triturations and adsorbates at various time intervals are given in Table 1. Dissolution profiles of griseofulvin from triturations by simple mixing method, adsorbates by acetone deposition, chloroform deposition and methylene chloride deposition methods compared with pure drug are shown in Figures 1 to 4, respectively. Dissolution data indicated that silicon dioxide increased the dissolution of griscofulvin ranged from 8 to 40 percents after 30 minutes

Table 1 Percentage of griseofulvin dissolved* from drug : silicon dioxide samples by various dispersion methods in purified water containing 0.02% polysorbate 80

Dispersion Method	Ratio	Time (min)					
		5	10	15	20	25	30
Physical Mixing	1:0	28.65±0.30	29.35±0	29.35±0.30	31.02±0.15	35.35±0.30	40.02±0.15
	1:1	38.69±0.45	40.35±0.15	41.02±0.60	41.02±0.60	43.03±0.89	48.36±0.22
	1:3	54.03±0.07	54.36±0.15	54.36±0.37	55.03±0	55.03±0	55.03±0.22
	1:5	54.03±0.07	54.03±0.15	53.69±0.35	54.69±0.15	55.69±0.15	56.03±0.30
	1:7	51.36±0.30	51.69±0.45	50.36±0.45	51.69±0.15	52.03±0	53.36±0.15
	1:9	52.03±0.07	52.69±0	53.03±0	52.69±0.15	53.69±0.74	53.69±0.82
Acetone deposition	1:0	22.01±1.20	25.01±0.45	29.35±0.30	32.01±0.37	35.35±0.07	56.64±0.15
	1:1	51.69±0.07	54.69±0.22	56.03±0.22	57.36±0,15	58.69±0.22	58.70±0.07
	1:3	53.36±0.15	60.03±0.67	64.03±0.15	67.37±0.07	70.03±0.07	70.03±0.30
	1:5	55.03±0	60.03±0.30	65.37±0.07	66.37±0.07	68.37±0.15	70.70±0.30
	1:7	49.69±0.07	53.03±0	57.03±0.15	60.36±0.52	63.69±0.22	65.70±0.15
	1:9	57.36±0.07	66.37±0.30	67.37±0.07	71.70±0.07	74.04±0.07	76.71±0.07
chloroform deposition	1:0	35.02±0.15	35.02±0.07	34.68±0.30	34.02±0.30	34.68±0.07	35.02±0
	1:1	41.35±0.15	41.35±0.30	42.35±0.67	42.25±0.15	42.69±0.37	43.02±0.07
	1:3	49.36±0.15	51.36±0.30	53.03±0.15	53.69±0.07	54.03±0.30	54.69±0.15
	1:5	49.69±0.07	51.69±0.37	53.03±0.67	53.03±0.07	53.36±0.07	53.69±0.22
	1:7	56.03±0.15	59.03±0.15	59.36±0.45	59.03±0.15	59.36±0.45	60.36±0.07
	1:9	56.69±0.52	60.36±0.15	60.23±0.60	61.03±0.15	63.03±0.07	63.36±0.22
methylene chloride deposition	1:0	40.35±0.07	41.02±0.60	40.35±0.07	41.35±0.37	40.35±0	40.35±0
	1:1	43.02±0.07	42.02±0	43.02±0.15	42.69±0.45	42.69±0.15	42.69±0
	1:3	46.02±0.30	48.02±0.30	49.36±0.45	49.69±0.60	49.69±0.15	50.69±0
	1:5	44.02±0.30	47.36±0.15	50.03±0.15	50.69±0.07	51.69±0.15	52.69±0.22
	1:7	50.69±0.15	51.36±0.30	52.36±0.37	52.36±0.45	52.36±0.37	52.36±0.30
	1:9	56.03±0.07	57.36±0.30	57.69±0.45	57.69±0.60	58.70±0.15	58.70±0

* The numbers shown are mean ± S.D. from duplicate experiments

in dissolution medium. The preparation methods indeed had an effect on the dissolution of the drug. With solvent deposition method, the dissolution seemed to increase as the amount of silicon dioxide increased. The acetone deposition method gave the highest dissolution rate, followed by chloroform deposition method and methylene chloride deposition method respectively. The drug dissolved from adsorbates by acetone deposition method eventually increased as the time increased. The drug dissolved from adsorbates by other solvent deposition method, was slightly increased after 5 minutes in dissolution medium. With physical mixing method, the dissolution of the drug was increased with the amount of silicon dioxide to a certain rate. The triturations with the amount of silicon dioxide greater than 1 : 3 ratio exhibited the same dissolution rate.

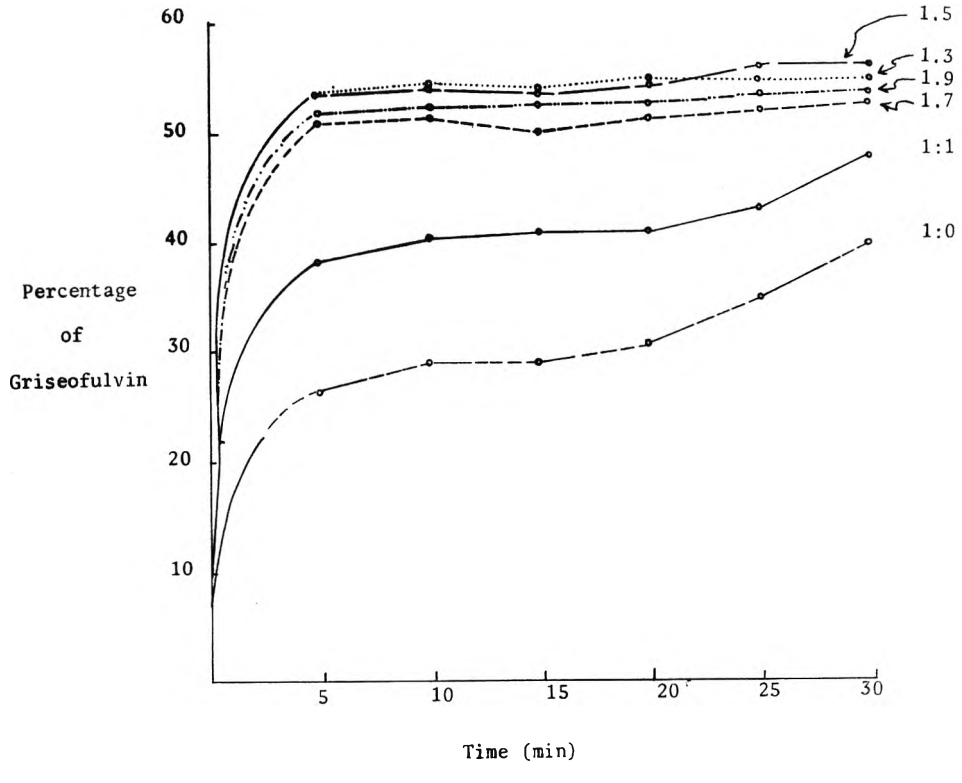

Figure 1 Dissolution profiles of various ratios of griseofulvin-silicon dioxide adsorbates by physical mixing method

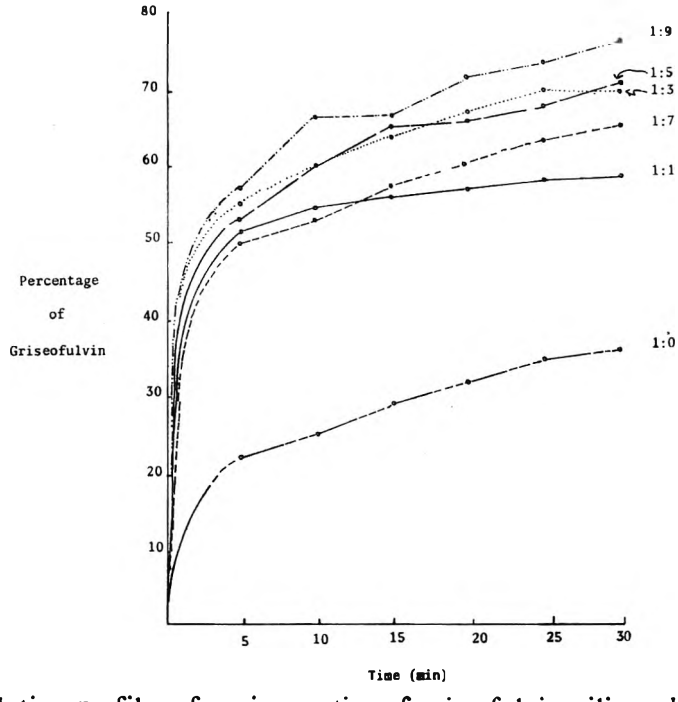

Figure 2 Dissolution profiles of various ratios of griseofulvin–silicon dioxide adsorbates by acetate deposition method

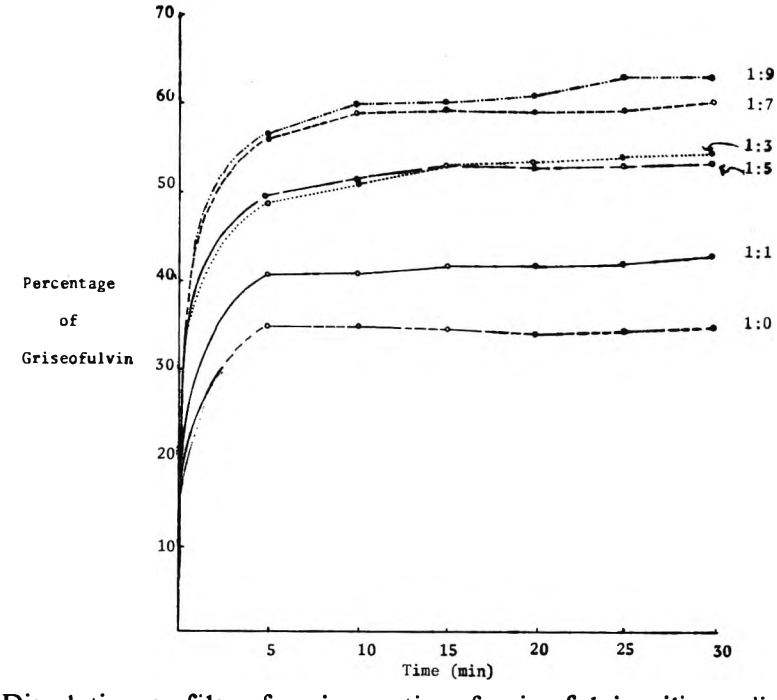

Figure 3 Dissolution profiles of various ratios of griseofulvin–silicon dioxide adsorbate by chloroform deposition method

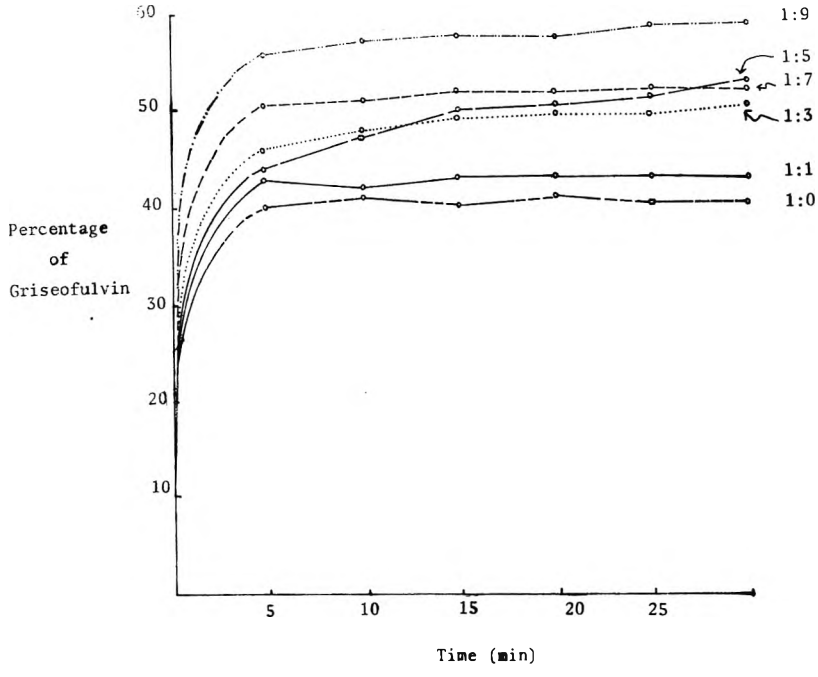

Figure 4 Dissolution profiles of various ratios griseofulvin-silicon dioxide adsorbates methylene chloride deposition method

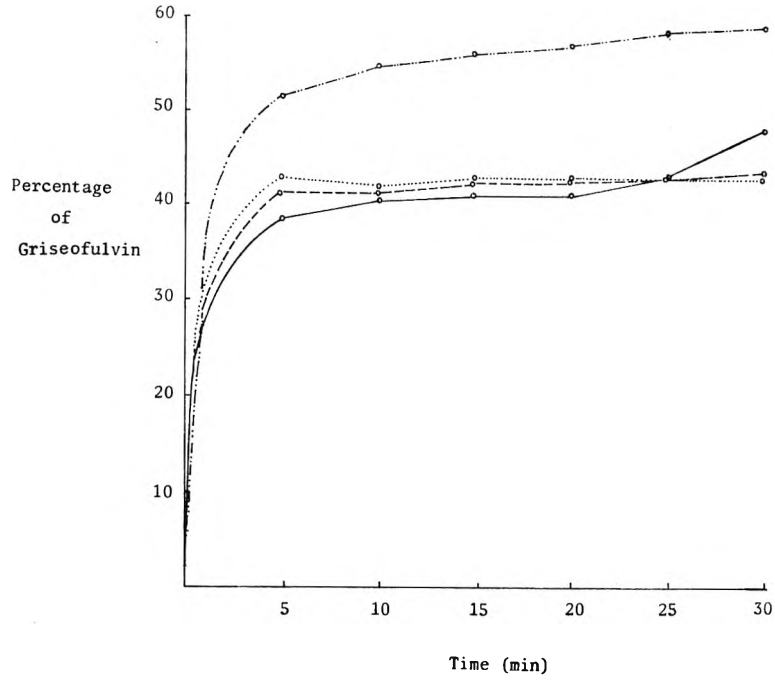

Figure 5 Influence of dispersion methods on dissolution profiles of griseofulvin-silicon dioxide 1 : 1 adsorbates

Comparison of the percent drug dissolved by various method of drug : silicon dioxide 1 : 1 ratio was shown in Figure 5. The acetone deposition method gave the highest dissolution and the percent drug dissolved was 10 to 16 percent higher than that obtained from other methods after 30 minutes. The chloroform and methylene chloride deposition methods showed the same dissolution rate at every time interval. The dissolution rate obtained from physical mixing method was slightly higher after 20 minutes than those obtained from adsorbates by chloroform and methylene chloride deposition methods.

Table 2 Percentage of griseofulvin dissolved* from tablets in simulated intestinal fluid

	Time (min)					
	5	10	15	20	25	30
Tablet containg micronized drug	46.02 ±0.37	46.69 ±0.15	48.36 ±0.30	47.36 ±0.15	48.02 ±0.30	51.36 ±0.52
Tablet containing drug: silicon dioxide 1:1 adsorbate by acetone deposition method	50.36 ±0.30	50.36 ±0.30	56.69 ±0.45	57.36 ±0.45	60.03 ±0.07	60.36 ±0.15

* The numbers shown are mean ± S.D. from duplicate experiments

Table 2 shows the percentages of drug dissolved from griseofulvin tablets containing 1 : 1 drug : silicon dioxide adsorbates by acetone deposition method or pure drug. The dissolution profiles in simulated intestinal fluid are demonstrated in Figure 6. The dissolution profile showed that tablets containing 1 : 1 adsorbates by acetone deposition method gave better dissolution than tablets containing pure drug. At every time interval, the percentage of drug dissolved from tablets containing adsorbates was higher than that containing pure drug.

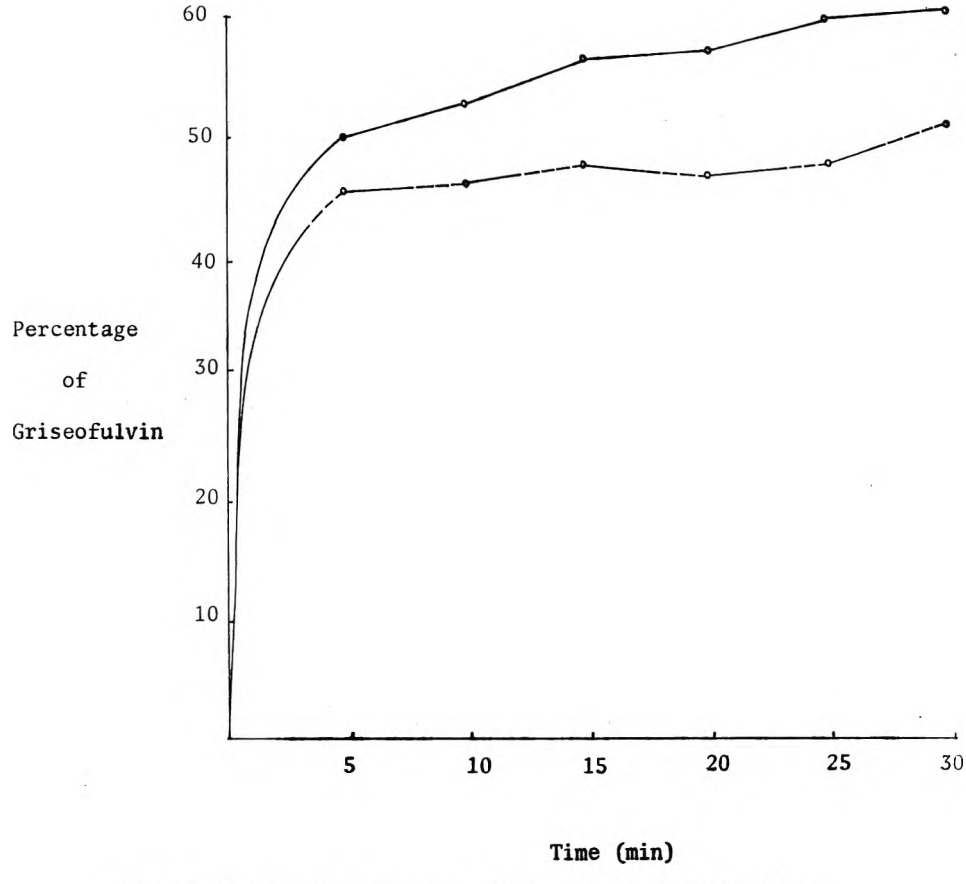

Figure 6 Dissolution comparision of griseofulvin tablets

Discussion and Conclusion

Griseofulvin showed a poor dissolution rate in distilled water containing 0.02% polysorbate 80. The percentage of the drug dissolved after 30 minutes was only 40%. This is due to its hydrophobicity and clumping together of the micronized powder [17]. When pure drug was treated with solvent, its dissolution was changed. The percentage of griseofulvin dissolved from acetone-treated drug was slightly decreased while the dissolution of chloroform-treated drug was markedly increased, especially the initial rate. This is possibly due to the change in particle size or physical character of the drug. After recrystalllization of a drug from different solvents, the drug may have different crystal sizes or forms [18], which in turn would the dissolution of the drug. The drug pretreated with acetone possibly had larger particle size than original crystals while the drug pretreated with chloroform or methylene chloride had smaller size. Chloroform and methylene chloride have similar chemical structure which is different from acetone. These two solvents would show the similar effect on the particle size of the drug.

Adsorption of griseofulvin to a silicon dioxide by solvent deposition method, markedly increased the dissolution rate. It can be reasoned that the drug in a microparticulate form molecularly dispersed on the extensive surface of the silica. This resulted in a decrease in particle size and the concomitant increase in surface area which increased the thermodynamic activity of the drug and hence, greatly enhanced the dissolution rate [4]. The increasing amount of silicon dioxide increased the dissolution rate especially in solvent deposition method. It is due to an increase in surface area of the silicon dioxide for the drug particle to be adsorbed on. This is in agreement with the previous reports [8, 11]. Simple mixing of a silicon dioxide to griseofulvin improved the dissolution of the drug because the particle was deaggregated. However, increasing the amount of silicon dioxide increased the dissolution to a certain rate. Amount of silicon dioxide greater than 1:3 ratio did not further increase the dissolution. It was suggested that silicon dioxide could have suppressed the dissolution through viscosity effects. Dissolution of griseofulvin was reported to be diffusion controlled and hence, susceptible to viscosity effects [11]. Increasing the amount of silicon dioxide increases the viscosity of the medium, thus decreases the dissolution.

Comparison of various dispersion method revealed that adsorbates with acetone deposition method exhibited the highest dissolution eventhough pure drug treated with this solvent showed the lowest. It would thus appear that acetone may influence the strength of the bonding of the drug to the surface of the silicon dioxide or may influence the orientation of the drug particle on the silica surface [9]. With the drug : silicon dioxide 1 : 1 ratio, adsorbate with acetone deposition method, impressively exhibited higher dissolution rate than adsorbate with simple mixing

method followed by other solvent deposition methods. This was contrary to the previous report [11] recommending simple blending as a means of promoting dissolution rate of the drug. Chloroform and methylene chloride deposition adsorbates did not show any difference in the dissolution rates. This suggested that these two solvent exhibited the same effect on the strength of the bonding of the drug to the surface of the silica or gave the same orientation of the drug particle on the silica surface.

Due to its higher dissolution rate and an optimal tablet weight, 1 : 1 adsorbate with acetone deposition method was the candidate to study the dissolution rate of the tablet compared to tablet containing micronized griseofulvin. Dissolution profile confirmed the dissolution - increasing effect of silicon dioxide. Tablet containing 1 : 1 adsorbate with acetone deposition method exhibited a higher dissolution rate than tablet containing micronized powder.

In conclusion it has been shown that surface adsorption of griseofulvin to a silicon dioxide can markedly increase the dissolution rate of this poorly soluble drug. Of various dispersion methods, adsorbates with acetone deposition method exhibited highest dissolution rate. Tablets containing 1 : 1 griseofulvin-silicon dioxide with acetone deposition method clearly showed an improvement in dissolution rate.

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การเพิ่มอัตราการละลายของ Griseofulvin โดยการดูดซับบน Silicon Dioxide

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บทคัดย่อ

การเตรียมสารถูกดูดซับ griseofulvin–silicon dioxide อัตราส่วนต่าง ๆ กัน ตั้งแต่ 1 : 0 ถึง 1 : 9 โดยวิธีเอาตัวทำละลายออกโดยใช้ตัวทำละลายอินทรีย์สามชนิด คือ acetone, chloroform และ methylene chloride เส้นร่างการละลายแสดงให้เห็นอย่างชัดเจนว่า การดูดซับบน silicon dioxide เพิ่มอัตราการละลายของ griseofulvin นอกจากนี้อัตราการละลายเพิ่มตามจำนวนของ silicon dioxide ที่เพิ่มขึ้น อัตราการละลายที่ได้จากสารบดเคล้าซึ่งเตรียมโดยวิธีผสมธรรมดาแสดงการเพิ่มเช่นกันตามจำนวนของ silicon dioxide ที่เพิ่มจนถึงอัตราส่วนตัวยา silicon dioxide 1 : 3 การเพิ่มจำนวน silicon dioxide มากกว่านี้มิได้ช่วยการละลาย วิธีเตรียมทำให้เกิดความแตกต่างในเส้นร่างการละลายอย่างเด่นชัด สารถูกดูดซับที่เตรียมโดยวิธีเอา acetone ออกให้อัตราการละลายที่ดีที่สุด ตามด้วยสารบดเคล้าที่เตรียมโดยวิธีผสมธรรมดา สารถูกดูดซับที่เตรียมโดยวิธีเอา chloroform ออก และวิธีเอา methylene chloride ออก ในการเตรียมยาเม็ด griseofulvin ที่ประกอบด้วยสารถูกดูดซับ 1 : 1 โดยวิธีเอา acetone ออกหรือผงยาชนิด micronized ด้วยวิธีแกรนูลเปียก การเปรียบเทียบการละลายของยาเม็ดยืนยันว่า การดูดซับบน silicon dioxide สามารถใช้ในการเพิ่มอัตราการละลายของยาเม็ด griseofulvin ได้

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