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EFFECT OF PARTICLE SIZE ON THE DISSOLUTION CHARACTERISTICS OF CHLORTHALIDONE

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ABSTRACT

The particle size reduction of chlorthalidone by fluid energy milling, Alpine milling and Fitzpatrick milling were evaluated. The desired particle size was achieved by both the fluid energy milling and Alpine milling processes. Alpine milling, however, is a more complex process and is susceptible to product decomposition, whereas fluid energy milling is a simple and efficient process without any risk of product decomposition. The desired particle size cannot be achieved by Fitzmilling because of the low probability of impaction force on particles. The dissolution rate of the chlorthalidone from chlorthalidone/propranolol hydrochloride tablets (25/80 mg) prepared with fluid energy milled chlorthalidone was significantly better than the tablets prepared with Fitzpatrick-milled chlorthalidone. The minimum effective specific surface area of chlorthalidone needed for maximum dissolution in water was found to be around 3.5 m^2/g.

INTRODUCTION

The reduction of particle size in order to expose larger surface areas to the dissolution medium is the obvious choice for improving dissolution of poorly water-soluble drugs such as chlorthalidone. Such particle size reduction by micronization is used with many poorly water-soluble drugs (1-4). The greater surface area of finely subdivided drug in contact

with biological fluids brings about more rapid dissolution and more rapid gastrointestinal absorption (5-7). This fact has led many manufacturers to produce certain drugs in the forms of micronized powders (particle size 5 μ) to be incorporated into various dosage forms (8).
Particle size reduction can be achieved by both impaction and attrition. The aims of the present study are (a) to evaluate the various milling processes for the particle size reduction of chlorthalidone, and (b) to select the material with minimum specific surface area of chlorthalidone needed for maximum dissolution in water.

EXPERIMENTAL

Materials

The following ingredients were used:

Chlorthalidone USP
Propranolol hydrochloride USP
Lactose USP
Starch 1500
Microcrystalline cellulose NF
Magnesium stearate NF

Equipment

A 8" micronizer fluid energy mill, Alpine stud mill model Contraplex 250 CW, and Fitzpatrick mill model D with hammer forward and #00 screen were used for particle size reduction of chlorthalidone. The Alpine air-jet sieve model A-200 and Coulter counter model TA were used for particle size analysis of chlorthalidone. A Quantasorb surface analyzer model 05-10 was used for the determination of specific surface areas of chlorthalidone.

Preparation of Chlorthalidone/Propranolol Hydrochloride (25/80 mg) Tablets

The tablets were prepared by wet granulation technique using chlorthalidone with different specific surface areas. The physical parameters of these tablets such as weight, shape, thickness, hardness and disintegration time were the same. Replicate assays were conducted for chlorthalidone

content. Only those samples containing 100 ± 5% of the chlorthalidone content were used in the dissolution rate studies.

Dissolution Rate Studies

Dissolution was conducted on at least 6 tablets in a USPXX apparatus (Hanson Research) with paddle rotating at 75 rpm using 900 mL of purified water USP and sampling at 30, 60 and 90 minute intervals.

Samples were filtered through a 0.45 micron Millipore filter and analyzed by HPLC using a Whatman ODS-3 column. The mobile phase consisted of 0.01M 1-octanesulfonic acid sodium salt in 1% aqueous acetic acid: acetontrile:methanol (62:33:5). The UV 254 nm was used as a detector.

Results

The physicochemical parameters of chlorthalidone before size reduction are presented in Table 1. The process parameters and the evaluation of the resultant reduced sized chlorthalidone by air-jet milling, Alpine milling and Fitzpatrick milling processes are presented in Tables 2, 3 and 4, respectively. The dissolution rate profiles of chlorthalidone from chlorthalidone/propranolol hydrochloride (25/80 mg) tablets prepared with air-jet milled chlorthalidone versus Fitzpatrick-milled chlorthalidone are shown in Figure 1. The specific surface areas versus the dissolution rates in water at 60 minute intervals are shown in Figure 2.

Discussion of Results

The results as presented in Table 2 indicate that the desired particle size was achieved in the air-jet mill by varying the compressed air pressure. The grinding chamber was cold during milling due to the expansion of air. This cooling effect protects the product from decomposition during milling. The specific surface area of the micronized chlorthalidone was about 15 times greater than the original material (Table 1). The bulk density of micronized chlorthalidone was also greatly reduced, indicating a considerable particle size reduction.

TABLE 1

PHYSICOCHEMICAL PARAMETERS OF CHLORTHALIDONE BEFORE MILLING

True density	1.60 g/cm^3
Bulk density	0.74 g/cm^3
Tapped density	0.90 g/cm^3
Specific surface area BET	0.34 m^2/g
Average particle size (Alpine Sieve)	73 μ
Chemical assay by HPLC	99.8%

The chemical assay of the micronized material did not show any evidence of decomposition. The results of Table 3 indicate that the desired particle size can also be achieved by Alpine milling. However, considerable heat was generated between the stud disks during the Alpine milling of chlorthalidone. This has resulted in accumulation of yellowish material between the stud disks. The chemical analysis of the Alpine milled material indicated the presence of about 0.5% of the decomposition product which was identified as chlorthalidone carboxylic acid (CCA). The Alpine milling process has several problems such as tedious cleaning procedure, cross-contamination, and powder build-up between the studs. These problems were not encountered during the air-jet milling process.

The results in Table 4 indicate that the desired particle size cannot be achieved by Fitzpatrick milling. The results show that the lowest particle size achieved by this process is about 53 microns. This type of milling does not give sufficient impact to break the particle to the desired size. The distribution of particle size is also wide. It can also be seen that by feeding the mill in a single 2 kg charge, the reduction in average particle size is significantly less than that

TABLE 2

EVALUATION OF MICRONIZATION OF CHLORTHALIDONE BY AIR JET MILL

Parameter	A	B
Type of jet mill	8" micronizer with 6A7 nozzle	8" micronizer with 6A7 nozzle
Feeder type	Ereiz	Ereiz
Collection type	Sleeve	Sleeve
Pusher Air pressure	100 psi	70 psi
Manifold air pressure	100 psi	70 psi
Inlet temperature	20°C	20°C
Outlet temperature	20°C	20°C
Feed rate of chlorthalidone	358 g/min	358 g/min
Average Particle Size		
(a) by Alpine Sieve	8.4 μ	10.8 μ
(b) by Coulter Counter	6.3 μ	10.0 μ
Specific surface area (m^2/g) BET	5.4	3.5
Bulk density g/cm^3	0.298	0.384
Tapped density g/cm^3	0.408	0.572
Chemical assay by HPLC	99.7%	100.0%
	No evidence of decomposition	

TABLE 3

EVALUATION OF ALPINE MILLING OF CHLORTHALIDONE

Type of Mill Used	250 cw
Rotor Type	Stud
Impactor Number	240
RPM House	11,200
RPM Door	5,600
Main Motor Load Empty/Full	12/12.5
Door Load Empty/Full	7/7.5
Feeder Type	Shaker
Feeder setting	1
Feed Rate of Chlorthalidone	150 lbs/hr.
Quantity Processed	97 lbs.
Average Particle Size	
(a) by Alpine Sieve	11.0 μ
(b) by Coulter Counter	5.885 μ
Specific surface area (m^2/g) BET	5.3
Bulk density g/cm^3	0.267
Tapped density g/cm^3	0.460
Chemical Assay by HPLC	99.5
	Less than 0.5% was detected as CCA, a degradation product of CTD

TABLE 4

EVALUATION OF FITZPATRICK MILLING OF CHLORTHALIDONE

	#1	#2
Type of Fitzpatrick Mill Used	Model D	Model D
Hammer Speed	5,000 rpm	5,000 rpm
Screen	#00	#00
Feed Mode for Chlorthalidone	4 x 500	1 x 2,000
Average Particle Size (by Alpine Sieve)	53 μ	71 μ
Specific surface area (m^2/g) BET	0.38	0.35
Bulk Density	0.72	0.73
Tapped Density	1.01	0.982
Chemical Assay	99.7%	99.7%

achieved when the mill is fed in four 500 g charges. The results as presented in Figure 1 indicate that the chlorthalidone/propranolol hydrochloride (25/80 mg) tablets prepared with the micronized chlorthalidone showed a 54% increase in dissolution rate of chlorthalidone at 60 minutes over that prepared with the Fitzpatrick-milled chlorthalidone.

The results as presented in Figure 2 indicate that the minimum effective specific surface area needed for the maximum dissolution rate of chlorthalidone is about 3.5 m^2/g. There was no further increase in the dissolution rate above this specific surface area.

CONCLUSION

The desired particle size reduction of chlorthalidone can be achieved efficiently without decomposition by fluid energy milling. The minimum

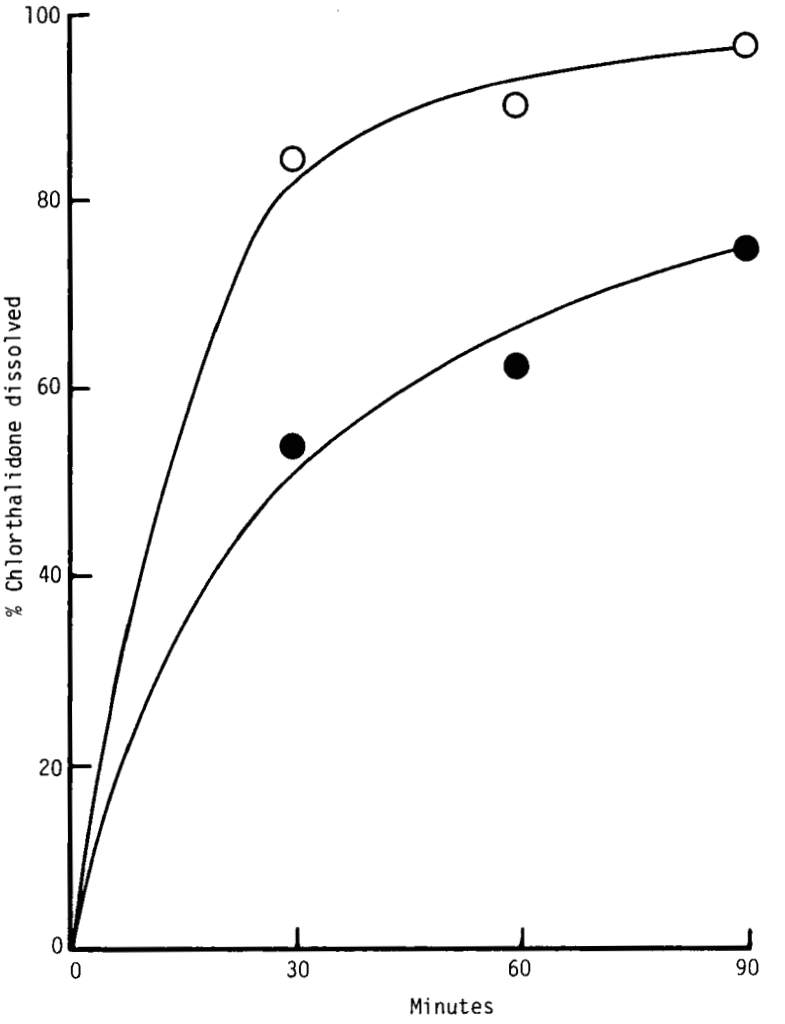

Figure 1: Dissolution profiles of chlorthalidone from chlorthalidone/propranolol hydrochloride tablets

Key: ○ micronized chlorthalidone
● Fitzmilled chlorthalidone

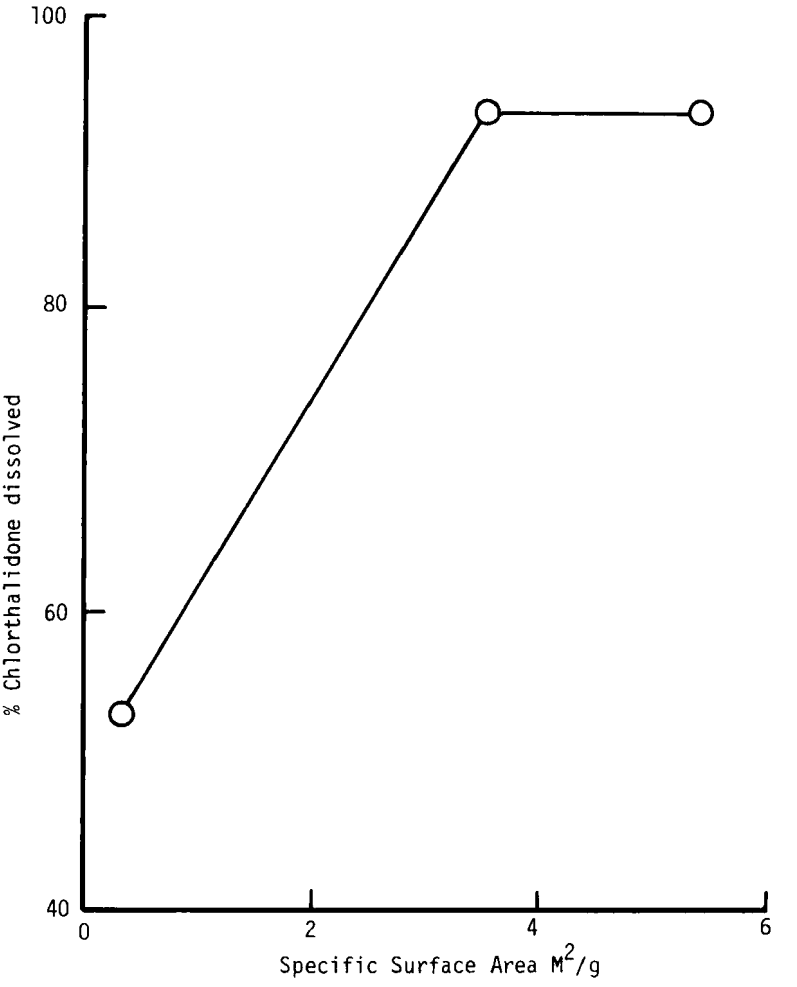

Figure 2: % chlorthalidone dissolved from chlorthalidone/ propranolol hydrochloride tablets at 60 minutes vs. specific surface area of chlorthalidone

effective specific surface area needed for the maximum dissolution rate of chlorthalidone is about 3.5 m^2/g. There is no need to increase the specific surface area beyond this value.

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