Microcrystallization Methods for Aspirin, Mebutamate, and Quinine Sulfate

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Abstract □ A technique to obtain microcrystals of some drugs was investigated. As high as 80–90% of the crystals obtained by this method had dimensions below 10 μ. The process is only applicable to drugs that are more soluble in glycerin than in water. It consists of diluting, with ice water, a hot saturated solution of the drug in glycerin while stirring at high speed and applying external cooling. Yields and economics of the process are also mentioned. The microcrystalline drugs (aspirin, mebutamate, and quinine sulfate) were found to possess increased solubilities which seemed to be due to the particle size rather than polymorphism or any other change. When administered orally to experimental animals, microcrystalline aspirin attained quicker and higher serum levels than did the raw form.

Keyphrases □ Microcrystallization methods—aspirin, mebutamate, quinine sulfate □ Microcrystalline drugs—method of preparing aspirin, mebutamate, quinine sulfate, effect of particle size □ Aspirin—preparation of microcrystalline form, effect on serum levels □ Mebutamate—preparation of microcrystalline form □ Quinine sulfate—preparation of microcrystalline form

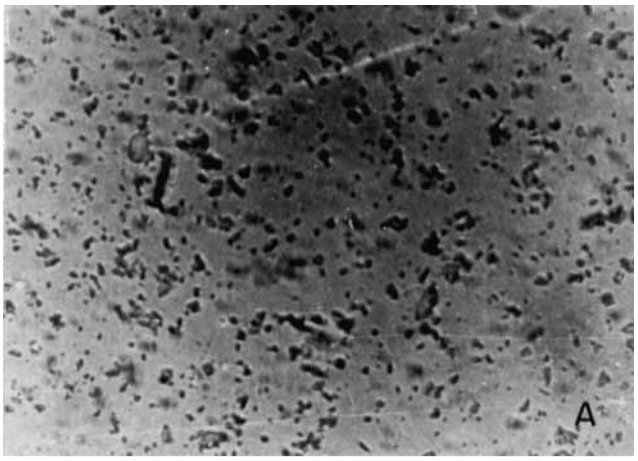
Microcrystallization of sparingly soluble drugs was tried by previous researchers (1–5). The purpose of this study was to examine whether the crystallization of some drugs that are more soluble in glycerin than in water could be controlled by dilution with ice water, external cooling, and high speed stirring. Although these factors which influence crystallization are well known, study of the glycerin–water system proved to be ideal because glycerin is cheap and comparatively innocuous and the whole process can be adapted for largescale production. The problem of cooling large quantities of liquid is not significant, because the saturated solution of drug in glycerin at 80° is diluted with ice water at 3° and the external cooling needed has only to bring the resulting temperature of 40° to about 5°.

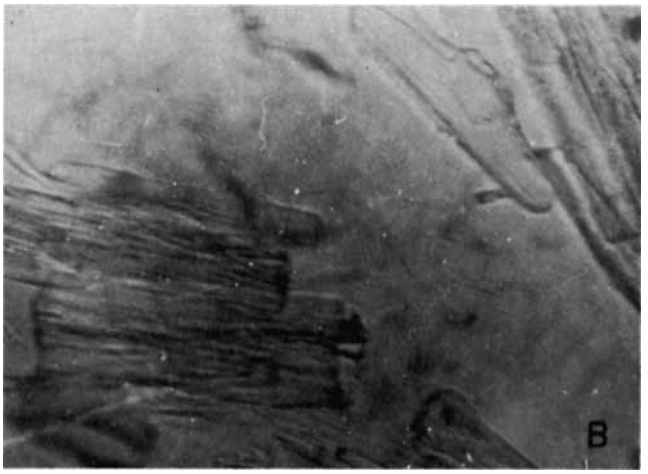
The drugs chosen for the study included aspirin, mebutamate, and quinine sulfate. The microcrystalline products obtained had interesting properties such as higher solubility in water while the melting points corresponded to chemically pure forms. They did not seem to be polymorphs or to have undergone any other change in the process. When microcrystalline aspirin, for example, was given orally to rabbits, the serum level concentration rose quicker and higher than with the raw drugs. Another point of interest is that the glycerin could be reused for subsequent batches without affecting the efficiency of the process.

Figure 1—*Setup for microcrystallization.*

Table I—Yield, Percentage Occurrence, and Solubility of Microcrystalline Aspirin

	Weight Taken, g.	Weight Obtained, g.	Yield, %	Particle Size, μ	Occurrence, %	Solubility in Water at 29°, % w/v	
						Of Raw Aspirin	Of Microcrystalline Aspirin
Processed with fresh glycerin	50	41.3	82.6	1–4	99–100	0.359	0.571
Processed with recovered glycerin containing 8.7 g. of aspirin	50, including weight in glycerin	41.2	82.4	1.5–4	99–100		0.569





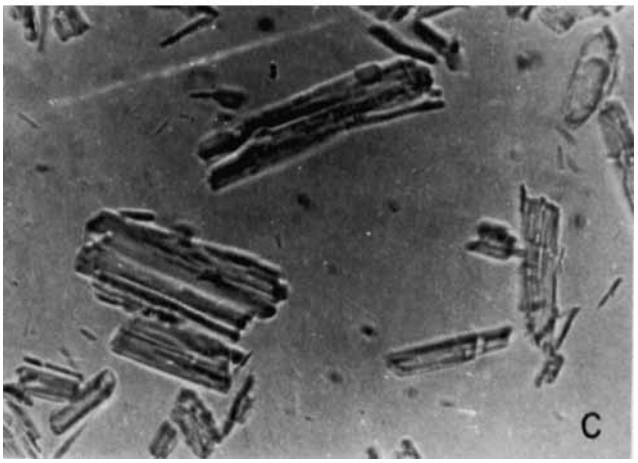


Figure 2—*(A) Microcrystallized aspirin seen in a random field (× 450). (B) Raw form of aspirin. (C) Commercial sample of micronized aspirin seen in a random field (×450).*

EXPERIMENTAL

Materials—Commercial aspirin (average crystal size 1–2 mm.), mebutamate (average crystal size 150 μ), and quinine sulfate (average crystal size 130 μ), conforming to pharmacopeial standards, were used for this study. Pharmacopeial grade glycerin was used for the process.

Apparatus—The experimental setup consisted of a stainless steel jacketed vessel (2 l.) fitted with a high speed stirrer (5000 r.p.m.). Figure 1 shows the arrangement for adding ice water at a fast rate.

Methods—The following methods were arrived at after studying the effects on particle size with various amounts of each drug, various amounts of glycerin, various amounts of ice water, and various temperatures. Only the conditions giving the best results are reported.

1. Aspirin (50 g.) was dissolved in 1125 ml. of glycerin at 80° to obtain a saturated solution. The clear solution was transferred to the stainless steel vessel. Stirring and external cooling were started immediately. This procedure was followed by the quick addition of ice water at 3°. Stirring was continued until the temperature dropped to 5° (7–10 min.).

The slurry of microcrystals was filtered under vacuum through grade 44 filter paper. The filtration was slow but could be accelerated by the addition of ice water at 3°. The product was washed with ice water, suction filtered, and dried in an air circulation drier.

The filtrate (2 l.) contained 8.7 g. of aspirin; it was vacuum distilled to remove about 96% (maximum) of the added water. It could then be reused for fresh batches.

2. Mebutamate (52.5 g.) was dissolved in 1125 ml. of glycerin at 80° to obtain a clear saturated solution. The process was repeated as described for aspirin. The filtrate (2 l.) contained 7.9 g. of mebutamate.

3. Quinine sulfate (63 g.) was dissolved in 1125 ml. of glycerin at 80° to obtain a clear saturated solution. The process was followed as described for aspirin. The filtrate (2 l.) contained 8 g. of quinine sulfate.

RESULTS

Tables I–III show the results of particle-size occurrence, solubility, and yields for aspirin, mebutamate, and quinine sulfate,

Table II—Yield, Percentage Occurrence, and Solubility of Microcrystalline Mebutamate

	Weight taken, g.	Weight Obtained, g.	Yield, %	Particle Size, μ	Occurrence, %	Solubility in Water at 29°, % w/v	
						Of Raw Mebutamate	Of Microcrystalline Mebutamate
Processed with fresh glycerin	52.5	44.6	84.9	1.5–6	99–100	0.549	0.675
Processed with recovered glycerin containing 7.9 g. of mebutamate	52.48, including weight in glycerin	44.58	84.96	1.5–7	99–100		0.669

Table III—Yield, Percentage Occurrence, and Solubility of Microcrystalline Quinine Sulfate

	Weight taken, g.	Weight Obtained, g.	Yield, %	Particle Size, μ	Occurrence, %	Solubility in Water at 29°, % w/v: Of Raw Quinine Sulfate	Solubility in Water at 29°, % w/v: Of Microcrystalline Quinine Sulfate
Processed with fresh glycerin	63	55	87.3	1–10	88	0.258	0.543
Processed with recovered glycerin containing 8 g. of quinine sulfate	62.8, including weight in glycerin	54.8	87.2	1–10	80		0.540

respectively. Table IV shows the solubility and percent w/v of the drugs in 75:25 glycerin–water mixtures, these mixtures being the ones from which the microcrystals were obtained. Table V shows the melting points and optical rotations of microcrystalline drugs and of corresponding chemically pure forms. Figure 1 shows the setup for obtaining the microcrystals. Figure 2 shows photomicrographs of microcrystals of aspirin, its raw form, and a commercial sample of micronized aspirin. Figure 3 shows the salicylate serum levels of rabbits receiving orally microcrystalline aspirin and its raw form.

DISCUSSION

From Tables I–III, it can be seen that the microcrystallization process described is quite successful from both yield and quality viewpoints. As high as 80–90% of the crystals had dimensions below 10 μ. Any mechanical process of micronization could hardly be expected to give such values in one operation. Figure 2 illustrates the fact that a commercial brand of micronized aspirin does contain a large percentage of coarse crystals. The microcrystals obtained have increased solubilities, and it can be said that blood serum levels are higher than those obtained after the administration of raw forms. The process could be adapted for largescale production of microcrystals of drugs that are more soluble in glycerin than in water.

Table IV—Solubility of Drugs in 75:25 Glycerin–Water Mixtures at Two Temperatures

Drug	Solubility at 29°	Percent w/v at 3°
Aspirin	0.459	0.238
Mebutamate	0.804	0.421
Quinine sulfate	0.465	0.229

Table V—Melting Points and Optical Rotations of Raw and Microcrystallized Drugs

Drug	Melting Point: Raw Form	Melting Point: Microcrystalline Form	Optical Rotation
Aspirin	136°	138°	—
Mebutamate	77°	78°	—
Quinine sulfate	—	—	$[\alpha]_D^{25}$ −220° for both forms

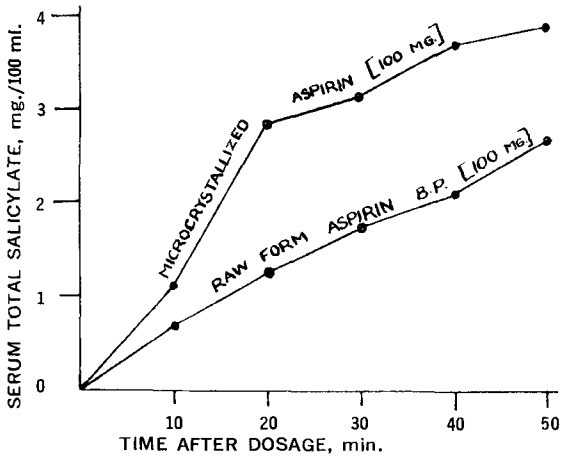


Figure 3—*Salicylate serum level in rabbits receiving both forms of aspirin orally.*

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