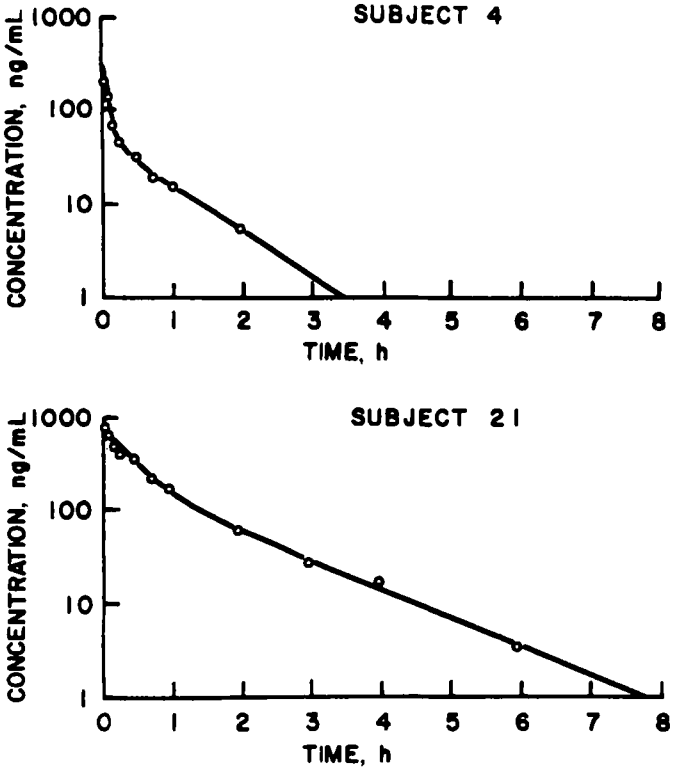

Figure 1—*Plasma concentration of milrinone in human volunteers after intravenous administration. Data points are plasma concentrations observed in two subjects with widely divergent clearance rates and concentrations predicted by the open two-compartment model (solid line).*

oral administration of 75 mg to volunteers, the mean terminal elimination half-life of amrinone was 4.33 h (1).

The mean half-life of amrinone in patients with congestive heart failure was 8.3 h (11), which is more than twice that seen in volunteers with normal cardiac function. We anticipate a similar increase in the terminal elimination half-life of milrinone in patients with congestive heart failure. The decrease in renal and hepatic blood flow in patients with severe cardiac impairment may be responsible for this increase in the duration of the drug in plasma. We are currently studying the pharmacokinetics of milrinone in patients with congestive heart failure as part of clinical efficacy trials. Attempts will be made to correlate the effects of dose on the terminal elimination half-life of milrinone.

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Crystallinity and Dissolution Rate of Tolbutamide Solid Dispersions Prepared by the Melt Method

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Received October 24, 1983, from the **Drug Dynamics Institute, College of Pharmacy and* ‡*Department of Chemical Engineering, University of Texas at Austin, Austin, TX 78712.* Accepted for publication December 21, 1983.

Abstract □ The influence of cooling rate of solid dispersions prepared by the melt method was studied by X-ray diffraction and scanning electron microscopy. Tolbutamide was the model drug investigated, and the carriers included urea and polyethylene glycol 6000. Slow-cooled urea dispersions of tolbutamide demonstrated a complete lack of crystallinity suggesting the formation of an amorphous material. The rapidly cooled dispersion showed peaks for urea and an absence of drug in the X-ray pattern, suggesting that a true molecular dispersion was formed. The X-ray patterns of rapid- and slow-cooled dispersions of tolbutamide and polyethylene glycol 6000 demonstrated that a physical mixture of drug and carrier resulted from both methods of dispersion preparation.

Keyphrases □ Solid dispersions—melt method of preparation, cooling rates and physicochemical properties □ Tolbutamide—solid dispersions with urea and polyethylene glycol 6000 □ X-ray diffraction—tolbutamide, solid dispersions, carriers □ Scanning electron microscopy—solid dispersions □ Dissolution rates—tolbutamide, solid dispersions

The rate-determining step in the absorption process for drugs of low solubility is generally the dissolution rate of such drugs in the GI fluids rather than the rapidity of their diffusion across the gut wall. The formation of solid dispersions of the drug with a water-soluble carrier is one of several techniques that can be used to improve the dissolution properties of poorly soluble or hydrophobic drugs. In 1961, Sekiguchi and Obi (1) became the first researchers to propose the use of solid dis-

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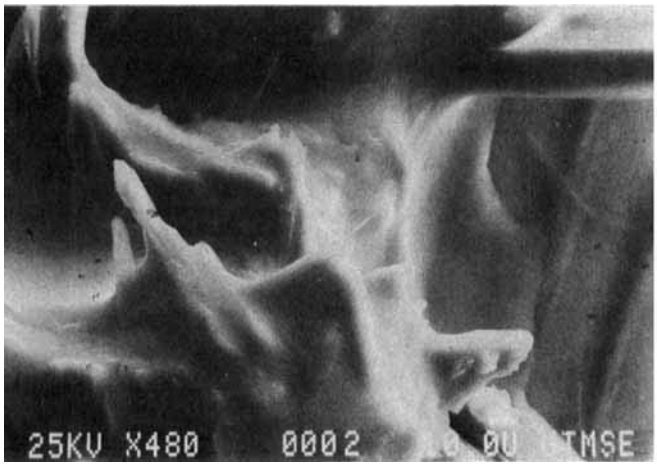

Figure 1—*Scanning electron micrograph of a urea–tolbutamide (2:1) dispersion prepared by process B and aged for 1 d at 25°C.*

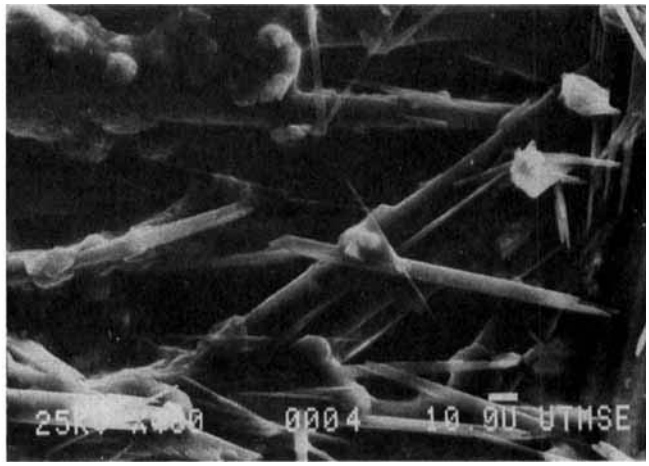

Figure 3—*Scanning electron micrograph of a urea–tolbutamide (2:1) dispersion prepared by process B and aged for 5 months at 25°C.*

persions to increase the dissolution rate and oral absorption of drugs. In recent reports, (2–6), the great variety of drug molecules and water-soluble carriers used to prepare solid dispersions have been reviewed.

Although in previous reports the technology of solid dispersions has been extensively examined, systems in which this technique is utilized have been fraught with problems; thus, few systems have been marketed (3). Since solid dispersions are dynamic systems, further research into the physicochemical properties of these systems is certainly warranted. In recent studies, it has been shown that soluble complexes between drug and carrier may form (7). Kaur and co-workers (5) have studied the phase equilibrium phenomena of solid dispersion systems, whereas Ravis and Chen (4) have compared, by X-ray analysis, the difference in crystallinity between solid dispersions and physical mixtures of drug and carrier. Significant contributions have been made by Ford and Rubinstein (8), who have studied the effect of aging on the dissolution properties of an indomethacin–polyethylene glycol 6000 solid dispersion.

One aspect of solid dispersion technology that has received little attention has been the method of sample preparation. A brief survey of the literature has indicated that there is no uniform method presently used to prepare solid dispersions by the melt method. In several cases, the temperatures to which the carrier and drug were subjected were not reported. Dispersions have been solidified by cooling the melt to room temperature (9, 10). Kaur and co-workers (5, 6) cooled their samples to 4°C, Chiou and Niazi poured the melts onto a stainless steel plate (11), whereas Allen and co-workers (12) rapidly solidified their samples by pouring the melt into an aluminum dish that was placed in a block of dry ice. Other investigators have employed metal pans (2), ice baths (7), and dry ice–acetone baths (13).

The objective of this study was to investigate the influence of cooling conditions on the physicochemical properties of solid dispersions prepared by the melt method. Urea and polyethylene glycol 6000 were the carriers studied, and tolbutamide (1-butyl-3-(*p*-tolylsulfonyl)urea) was the model drug investigated. Some preliminary results were also obtained with salicylic acid and sulfathiazole.

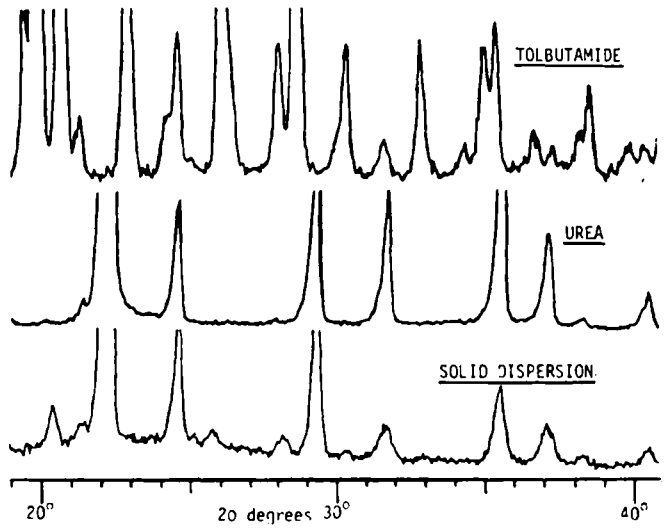

Figure 2—*X-ray patterns of drug, carrier, and rapid-cooled dispersion.*

EXPERIMENTAL SECTION

Materials—Urea[1] (mp 139.7°C), polyethylene glycol 6000[2] (mp 56°C), tolbutamide[3] (mp 125.5°C), salicylic acid[4] (mp 158°C), and sulfathiazole[2] (mp 202°C) were used.

Methods—X-ray diffraction patterns were obtained with an X-ray diffractometer[5] with $CuK_{\alpha 1}$ radiation (0.15405 nm) over a 2θ range of 6–50°. The scanning electron micrographs were recorded on a microscope[6]. Dissolution profiles of drug from dispersion samples were determined with the USP paddle apparatus. For the tolbutamide samples, 900 mL of pH 6.0 buffer were stirred at 50 rpm and maintained at 37°C. The melts were prepared by first heating the carrier in an aluminum dish over an oil bath to 5°C above the melting point of the carrier. The drug was then dissolved into the molten carrier and stirred for 2 min to ensure a homogeneous dispersion. Two methods of cooling were employed. Process A involved the flash cooling of the dispersion by immersion of the aluminum dish containing the molten dispersion in a bath of dry ice and acetone. The preparation of the dispersion by Process B involved the gradual cooling of the oil bath under ambient conditions over a period of several hours. Dispersions from both processes were then passed through a 20-mesh screen, and the 20- to 40-mesh fraction was retained for the dissolution study. Ground samples of the dispersion were employed for the scanning electron microscopic evaluation of the surface crystalline properties. Dispersions in the 60–100 mesh range were used for X-ray analysis. Ratios of carrier to drug, 2:1 w/w, were used for all samples with the exception of the polyethylene glycol 6000–sulfathiazole system, in which a 4:1 ratio was employed. For all these systems, full solution dispersions were obtained prior to the cooling step.

[1] Matheson, Coleman and Bell, Norwood, Ohio.
[2] City Chemical Corp., New York, N.Y.
[3] The Upjohn Co., Kalamazoo, Mich.
[4] Fisher Scientific Co., Fair Lawn, N.J.
[5] Philips.
[6] JEOL JSM35.

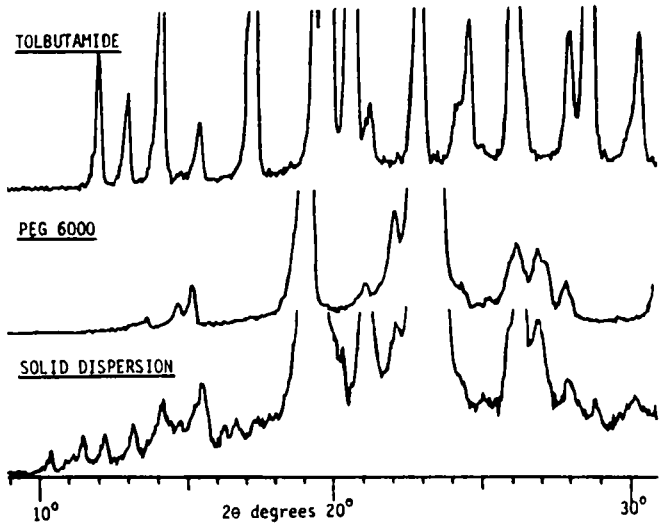

Figure 4—*X-ray patterns of drug, carrier, and rapid-cooled dispersion.*

RESULTS AND DISCUSSION

Powder X-ray diffraction patterns of tolbutamide, urea, and polyethylene glycol 6000 were taken of samples that were both slow and flash cooled. For each material alone, the rate of cooling did not influence the crystallinity since the peak widths of the diffraction profiles remained constant. No additional new diffraction lines were detected, indicating that no degradation or new compound formation had occurred. Minor changes in the intensity of some peaks were seen with samples prepared by either process. However, this was probably due to changes in preferred orientation rather than any alteration in the physicochemical properties of the material. The multitude of peaks obtained with urea and tolbutamide verified the crystalline properties of these solids. The two most intense peaks in the X-ray pattern for polyethylene glycol 6000 were found at 19.2 and 23.4°.

A study of the physical mixture of tolbutamide–urea produced a pattern which was due to the combination of the drug and carrier. Markedly different results were evident with the urea–tolbutamide dispersions prepared by the rapid- and slow-cooled methods. The X-ray patterns for the slow-cooled dispersions demonstrated a complete lack of crystallinity, suggesting the formation of an amorphous material. A scanning electron micrograph of this dispersion is shown in Fig. 1. The X-ray patterns shown in Fig. 2 are those of tolbutamide, urea, and the dispersion prepared by process A (rapid cooled). The complete absence of peaks for the tolbutamide in the dispersion is readily evident. All peaks present from the dispersion sample are those of the carrier. This phenomenon could be due to the formation of a true molecular dispersion of the tolbutamide within the urea matrix, or alternatively, it could mean that tolbutamide is present on the surface of the urea crystals as an amorphous coating.

A similar phenomenon has been reported by Chiou (14) with the griseofulvin–polyethylene glycol 6000 system. Since the peaks for the drug were absent in the X-ray diffraction pattern, Chiou has proposed that an amorphous form of griseofulvin was present in the melt after cooling. However, when X-ray diffraction studies were repeated several days later, major diffraction peaks of griseofulvin were present, indicating crystal formation in the dispersion. This result was obtained for all samples studied with the exception of the 5% drug sample. An examination of the tolbutamide–urea dispersion prepared by process A after storage at 25°C for 45 d indicated that no tolbutamide peaks were present in the X-ray diffraction pattern. These preliminary stability data suggest that some form of molecular interaction may be present between tolbutamide and urea to maintain the drug in the amorphous state. Storage of the slow-cooled dispersion (Fig. 1) at 25°C for 5 months resulted in crystal growth (Fig. 3). The X-ray pattern of this sample was identical to that of the solid dispersion (Fig. 2), indicating that the crystals consisted of urea rather than tolbutamide. X-ray examination of physical mixtures of tolbutamide–urea verified that samples containing as little as 2% drug yield peaks for tolbutamide.

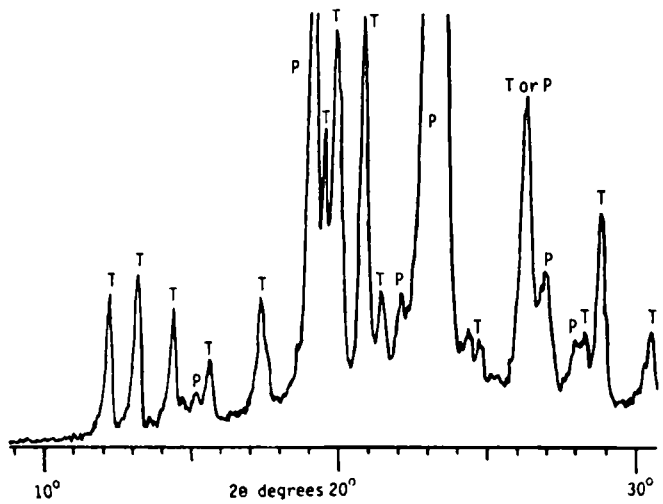

Figure 5—*X-ray pattern of polyethylene glycol 6000–tolbutamide dispersion prepared by process B.*

Table I—Dissolution Characteristics of Polyethylene Glycol 6000–Tolbutamide (2:1) Dispersions [a]

Time, min	Percent Drug Released [b]		
	Rapid Cooled (Process A)	Slow Cooled (Process B)	Physical Mixture
6	36.9 ± 5.3	29.7 ± 2.6	27.8 ± 4.0
10	60.4 ± 3.5	45.8 ± 3.5	44.4 ± 4.2
15	72.3 ± 4.4	57.9 ± 3.5	60.1 ± 1.9
20	78.3 ± 5.4	64.4 ± 1.6	64.2 ± 2.5
25	86.7 ± 4.7	71.5 ± 2.9	70.8 ± 3.4
40	91.0 ± 4.3	75.6 ± 3.5	80.0 ± 2.4
60	96.3 ± 3.0	84.6 ± 1.9	82.8 ± 1.5
100	100.6 ± 1.2	90.5 ± 1.0	87.5 ± 1.8

[a] In 900 mL of pH 6.0 buffer maintained at 37°C and agitated at 50 rpm by the USP paddle method. [b] Mean ± *SD*.

The X-ray patterns of tolbutamide, polyethylene glycol 6000, and the solid dispersion prepared by process A are shown in Fig. 4. Comparison of these patterns indicates that the dispersion is present as a physical mixture of the drug and carrier. The slow-cooled dispersion shown in Fig. 5 had a very similar pattern to the dispersion shown in Fig. 4. The higher intensity of peaks shown in Fig. 5 suggested a greater degree of crystallinity from the slow-cooled samples. This phenomenon was verified by scanning electron microscopy.

The dissolution properties of tolbutamide–polyethylene glycol 6000 dispersions prepared by process A and process B were compared with the dissolution properties of tolbutamide from the physical mixture of the drug and polyethylene glycol 6000 (Table I). Insignificant differences were seen in the dissolution properties of drug from the slow-cooled dispersion and the physical mixture. However, ~15% more drug passed into solution at most time intervals for the dispersion prepared by process A. This phenomenon was probably due to a particle size effect since a smaller drug particle was expected from the flash-cooled dispersion. The lower degree of crystallinity for this dispersion was verified by the X-ray diffraction patterns (Figs. 4 and 5). The greater dissolution rate of dispersions prepared by process A may also be attributed to a greater energy of the drug particles in these dispersions. Less crystalline or more amorphous forms generally possess greater thermodynamic activities than more crystalline forms of the same substance (15).

The peaks for sulfathiazole in the X-ray diffraction patterns of sulfathiazole–urea dispersions were absent for both the slow- and flash-cooled dispersions. This result was similar to that for the tolbutamide–urea dispersions prepared by process A. A physical mixture of both drug and carrier was found with the sulfathiazole–polyethylene glycol 6000 samples. Salicylic acid in urea dispersions produced new peaks in the X-ray diffraction patterns, suggesting that either an interaction occurred or a polymorphic change in either the drug or carrier took place to form a new phase.

In summary, the applications of X-ray diffraction to study the physicochemical properties of solid dispersions have been demonstrated. The rate of cooling of melt dispersions will, in many cases, influence the physical state of both drug and carrier. Other techniques are presently being evaluated for use in conjunction with X-ray diffraction to differentiate and identify polymorphic transitions, degradation product or complex formation, molecular dispersion formation, physical mixtures, and the determination of degrees of crystallinity in the melt dispersions. Future studies will also employ X-ray diffraction to examine changes in the microcrystalline properties of these dispersions as a function of time and temperature.

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A High-Performance Liquid Chromatographic Method for The Simultaneous Determination of Nicardipine and Its Pyridine Metabolite II in Plasma

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Received September 29, 1983, from the *Department of Analytical and Metabolic Chemistry, Syntex Research, Palo Alto, CA 94304.* Accepted for publication December 5, 1983.

Abstract □ A rapid and specific method in which reverse-phase high-performance liquid chromatography (HPLC) with UV detection was used for the simultaneous determination of nicardipine and its pyridine metabolite II in human plasma is described. Nicardipine, its pyridine metabolite II, and the internal standard were extracted from plasma and partially purified by acid–base partitioning. Final purification and quantitation were achieved by HPLC by using a reverse-phase column and a UV detector (254 nm). The extraction efficiencies for nicardipine and its pyridine metabolite II from 1 mL of plasma were 77.4 and 81.1%, respectively. The sensitivity of the assay was 5 ng/mL for both nicardipine and its pyridine metabolite II, and the linear concentration range of the assay was 5–150 ng/mL for both compounds. The low coefficients of variation (≤5%) for samples spiked with nicardipine and its pyridine metabolite II in this concentration range demonstrate good reliability and reproducibility of the assay. The HPLC procedure has been validated by comparison with a GC–electron-capture detection (ECD) procedure, which gives the combined concentration of nicardipine–its pyridine metabolite II (total) and with an HPLC/GC–ECD procedure, which gives the concentration of its pyridine metabolite II. All three methods, which were developed in our laboratory, were used to analyze nicardipine and its pyridine metabolite II in specimens of plasma from subjects treated with nicardipine hydrochloride. Good correlations were found for concentrations of nicardipine, its pyridine metabolite II, and nicardipine plus the metabolite determined by these three procedures. The HPLC procedure is suitable for use in pharmacokinetic studies following administration of nicardipine hydrochloride to humans.

Keyphrases □ Nicardipine—simultaneous determination with its pyridine metabolite II, reverse-phase HPLC □ HPLC—reverse-phase simultaneous determination of nicardipine and its pyridine metabolite II in human plasma

Nicardipine hydrochloride, 2-(*N*-benzyl-*N*-methylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride (I), is a new calcium entry-blocking agent with potent oral vasodilating activity. The therapeutic efficacy of this compound for the treatment of angina, hypertension, and cerebrovascular disease is under investigation.

Nicardipine hydrochloride, which is effective at relatively low doses, undergoes extensive first-pass metabolism to produce several metabolites (1). Therefore, a sensitive and specific method is required for its determination in human plasma. Various methods have been reported for the determination of nicardipine in plasma. These include gas chromatography (GC) with either electron-capture detection (GC–ECD) (2) or with mass spectrometric detection (GC–MS) (3). However, these methods are relatively nonspecific because they require oxidation of nicardipine prior to GC analysis. Since the product of this oxidation is the pyridine metabolite II of nicardipine, these methods measure the combined concentration of nicardipine plus its pyridine metabolite II (total). Pharmacokinetic analyses of data generated by these methods can be misleading in view of the fact that the vasodilative activity of the pyridine metabolite II is only $^1/_{300}$ that of the parent drug (4). The individual concentrations of nicardipine and its metabolite in human plasma have been investigated recently using a TLC–GC–MS method (5), in which nicardipine was separated from its pyridine metabolite II by TLC prior to analysis by GC–MS. These investigators have found that in healthy volunteers and hypertensive patients, the concentration of nicardipine relative to that of the combined concentrations of nicardipine plus its pyridine metabolite II ranged from 74% to 99% (5). Recently, we developed a method using high-performance liquid chromatography (HPLC) in conjunction with GC–ECD which allowed the individual concentrations of nicardipine and its pyridine metabolite II to be determined[1]. In this HPLC/GC–ECD method, which was developed prior to the availability in our laboratory of a high-sensitivity HPLC detector, HPLC was used to separate nicardipine from the pyridine metabolite II prior to analysis of the latter by GC–ECD. The concentration of nicardipine in a sample of plasma was obtained by subtracting the concentration of the pyridine metabolite II as determined by the HPLC/GC–ECD assay from the combined concentration of nicardipine plus the pyridine metabolite II as determined by the GC–ECD method

[1] Unpublished results (a brief description of this method is given in the text).

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