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CONTROLLED CRYSTALLIZATION OF CHLORPROPAMIDE FROM SURFACTANT AND POLYMER SOLUTIONS

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ABSTRACT

Chlorpropamide crystals were prepared by recrystallization technique from alcoholic solution of Polysorbate 80, Polyethylene Glycol and Polyvinyl- pyrrolidone. Marked enhancement in the dissolution rate of the formed crystals was observed.The enhancement was found to be a function of molecular weight of the polymer used Thus the percentage drug dissoluted after three hours at 10 % polymer concentration was found to be 37, 41 and 55 % for Polyvinylpyrrolidone K30 K64 and K90 respectively, and 27, 31, 32 % for Polyethylene Glycol 4000, 6000, and 20000 respectively.This may be due to possible solubilization effect of the surfactant and polymers.Also solution of the polymer may produce an ultrafine crystals of the drug, mainly due to the difficulty of growth of the crystals in highly viscous medium of the polymer. Infrared study revealed that no polymorphic change or complex formation had occurred.

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I N T R O D U C T I O N

Certain medicinal agents may be produced to exist in either a crystalline or an amorphous state. Since the amorphous form of a chemical is usually more soluble than the crystalline form, different extents of drug absorption may result with consequent differences in the degree of tharmacological activity obtained from each (1).The various polymorphic forms usually exhibit different X-ray diffraction patterns,infrared spectra, densities, melting point and solubilities (2) .

Many drugs may be prepared in a particular polymorphic form by appropriate choice of crystallization condition (solvent, temperature and crystallization rate), by melting and subsequent cooling at particular rates, by use of pressure or by the intentional addition of impurities (2).

Chiou et al (3) have described a unique method consisting of recrystallization of drug in aqueous surfactant solution . This method has been successfully used in the formulation of fast release dosage forms containing slightly water soluble drugs.

Numerous trials have been made to enhance the dissolution rate of poorly water soluble drugs done by Nagger et al (4) Solid formulations of phenylbutazone were prepared by recrystallization technique from polysorbate 80 solution. The presence of surfactant in the formulations caused an increase in dissolution rate.

The effect of crystallization of poorly water soluble sulfamethoxazole in aqueous surfactants solution on in vitro dissolution rate were investigated by Gadalla and Ebian (5). Marked enhancement was observed and infrared spectra studies indicated no polymorphic change.

Ismail et al (6) observed an enhancement in the dissolution rate of phenacetin as a result of recrystallization from different surfactants.

The aim of this work was to study the effect of crystallization of chlorpropamide from surfactant and polymers solutions on the dissolution rate of the drug. Furthermore the formed crystals were physically examined.

EXPERIMENTAL

MATERIALS

Chlorpropamide (CP) was supplied from El-Nile Co. Egypt, Polyethylene glycol (PEG) 4000 , 6000 , and

20000 (Union Carbide ,New York) Polyvinylpyrrolidone (PVP) K30 , K64, K90 (BASF W. Germany) Polysorbate 80 (Atlas Chemical, Wilmington, DE) and potassium bromide ; special grade for IR.

APPARATUS

Spectrophotometer (Shimadzu Recording UV, Kyoto, Japan) Infrared Spectrophotometer (Unicam Sp. 200 G) and Electrothermal Melting Point Apparatus (Seti ,Cairo , Egypt)

METHODOLOGY

Controlled Crystallization of Chlorpropamide:

Five gm of CP powder was initially dissolved in 10 ml alcohol or 10 ml alcoholic solution of either surfactant or polymers used in this investigation by aid of gentle heat. The drug crystallization was achieved by cooling spontaneously to room temperature, left for 24 hrs, then left in refrigerator at 5°C for another 24 hrs. The formed crystals were collected by filtration and dried in a desiccator over calcium chloride. The dried crystals were then screened to particle size of 315-400 um.

Effect of Crystals Washing:

Portion of the formed crystals was washed by pouring distilled water on the crystals while present on filter paper in a funnel for 2 hrs then dried in desiccator over Calcium chloride for 24 hrs.The dried crystals are subjected to dissolution study.

Dissolution studies:

The dissolution studies were conducted in 0.1 N HCl at 37° C. Fifty mg of the crystals was introduced into empty tea bag previously tested for any leaching in the medium, then tied firmly with a cotton thread and suspended in 100 ml of 0.1 N HCl in a beaker 150 ml capacity. The system was continuously stirred by magnetic stirrer rotating at 100 r.p.m. The temperature was kept constant at 37°C. ± 0.5 At specified time intervals, aliquot was withdrawn for analysis and replaced with fresh 0.1 N HCl previously warmed at 37°C. The drug content was determined spectrophotometrically at 232 nm after suitable dilution by 0.01 N HCl(7). The dissolution rate of non treated crystals was served as a basis for comparison.

Melting Point Determination:

MP of the samples was determined at a rate of heating of 2°C / min, until the temperature reached then the rate was lowered to 0.2° C./ min until complete melting occurred. The melting point recorded for each sample was the average of five readings.

Infrared Study:
The IR spectra of the powdered drug and the formed crystals was traced using IR spectrophotometer. The dried samples were inserted, each separately, in potassium bromide discs and tested for IR spectra at the low scanning speed to ensure for maximal resolution.

RESULTS AND DISCUSSION

The hypoglycemic medicaments, CP have certain limited solubility in water. This property has led some workers to suspect poor as well as variable bioavailability of some commercial brands of this drug (8). An increase in the dissolution rate of CP has been reported using the solid dispersion technique with PEGs and PVP (9).In this report a new method of crystallization differ from the precipitation method described by Chiou et al (3) and soaking or shaking methods described by Ebian et al (10). This method involved the preparation of the supersaturated solution of the drug in presence of the surfactant or the polymer by aid of gentle heat and then crystallization was achieved by cooling.

The results of dissolution rate were analyzed according to zero- first- and second-order kinetics as well as diffusion controlled mechanism. From Table 1 , it is clear that the CV % proving the prevalence of a semi-logarthmic straight-line relationship indicating that the dissolution of the crystals follow first order kinetics. On semi-logarithmic basis, the computer generated data are shown in table 2. The results of the dissolution studies, expressed in terms of % dissolved as a function of time are shown in Figs 1 to 3 .The results revealed that the dissolution rate of CP is enhanced. Untreated crystals of the drug exhibited slow and steady release , while crystals prepared in presence of different additives showed more quicker and progressive pattern of release , depending mainly on the nature of the additives and its concentration .

TABLE 1
Coefficient of Variation (Percent) as Criterion for Estimating the General Pattern of Dissolution Rate of Chlorpropamide Crystals Prepared in the Presence of Different Additives.

Additives	Percentage Released			Square Root of Time (min.)
	Cumulative Dissolution	Log Retained	Reciprocal of Retained	
Control	3.04	0.06	0.28	2.20
Tween 80	5.15	0.19	0.74	2.95
PEG 4000	5.43	0.15	0.64	5.00
PEG 6000	7.51	0.36	1.40	3.74
PEG 20000	13.01	0.70	2.75	8.72
PVP K30	3.84	0.33	1.26	1.98
PVP K64	3.01	0.37	1.33	1.57
PVP K90	9.47	0.72	2.61	5.99

The enhancement of the dissolution rate of CP from the treated crystals might be interpreted on the basis of the suggestion made by Chiou et al (11).They stated that some surfactant molecules, due to their surface activity, might be adsorbed onto the hydrophobic surface of the crystals. The adsorption would undoubtedly increase the wettability of the crystals and thereby increase their dissolution rate. The presence of the additives during crystallization process might also cause a defect in the crystal structure and crystal would become thermodynamically unstable and hence, they dissolve faster.The possibility of the formation of a solid solution of the water soluble surfactant in the drug crystal might also enhance the dissolution (11).

On dissolving the drug in alcohol, the particles will pass into the molecular dimension and are therefore dispersed in matrix of the soluble carrier in an extremely fine state of subdivision so the dissolution rate of the formed crystals were more rapid than that of the control. On increasing the proportion of the polymer,the viscosity of the crystallization medium is increased, thereby, the crystallization of the drug is retarded owing to the slow migration and difficulty in nucleation of the drug due to the extremely high viscosity of the medium (12,13) and even if the drug commences to nucleate, the particle size of the formed microcrystals will be very small .

TABLE 2
Mathematical and Statistical Data Pertinent to a Study the Effect of Different Additives on the Dissolution of Chlorpropamide Crystals Prepared in Presence of Different Additives.

Additives	1 %				2 %				3 %				5 %				10 %			
	Y Intercept (a)	Slope (b) -4×10	K -4×10	t 50% (hrs)	Y Intercept (a)	Slope (b) -4×10	K -4×10	t 50% (hrs)	Y Intercept (a)	Slope (b) -4×10	K -4×10	t 50% (hrs)	Y Intercept (a)	Slope (b) -4×10	K -4×10	t 50% (hrs)	Y Intercept (a)	Slope (b) -4×10	K -4×10	t 50% (hrs)
Control	1.9726	- 1	3	38.22																
Tween 80	1.9838	- 3	8	15.22	1.9950	- 5	12	9.83	1.9914	- 7	15	7.52	1.9447	- 8	18	6.47	1.9460	- 8	18	6.32
PEG 4000	1.9883	- 3	7	15.77	1.9933	- 4	8	14.32	1.9874	- 4	9	12.20	1.9882	- 9	20	5.82	1.9904	- 9	21	5.56
PEG 6000	1.9717	- 4	9	12.98	1.9615	- 6	13	9.08	1.9601	- 6	15	7.86	1.9532	- 9	22	5.28	1.9798	- 10	24	4.84
PEG 20000	1.9780	- 6	13	8.82	1.9704	- 6	14	8.42	1.9421	- 8	18	6.41	1.9436	- 9	20	5.83	1.9545	- 9	21	5.61
PVP K30	1.9625	- 3	7	16.22	1.8693	- 5	11	10.73	1.8639	- 6	13	8.58	1.8754	- 6	14	8.26	1.8911	- 8	17	6.62
PVP K6A	1.8366	- 5	12	9.37	1.8249	- 7	16	7.35	1.8549	- 7	16	7.02	1.8626	- 8	18	6.32	1.8879	- 8	19	6.02
PVP K90	1.9834	- 4	9	13.38	1.9614	- 5	11	10.82	1.9782	- 9	20	5.75	1.8530	- 16	38	3.06	1.8707	- 18	41	2.80

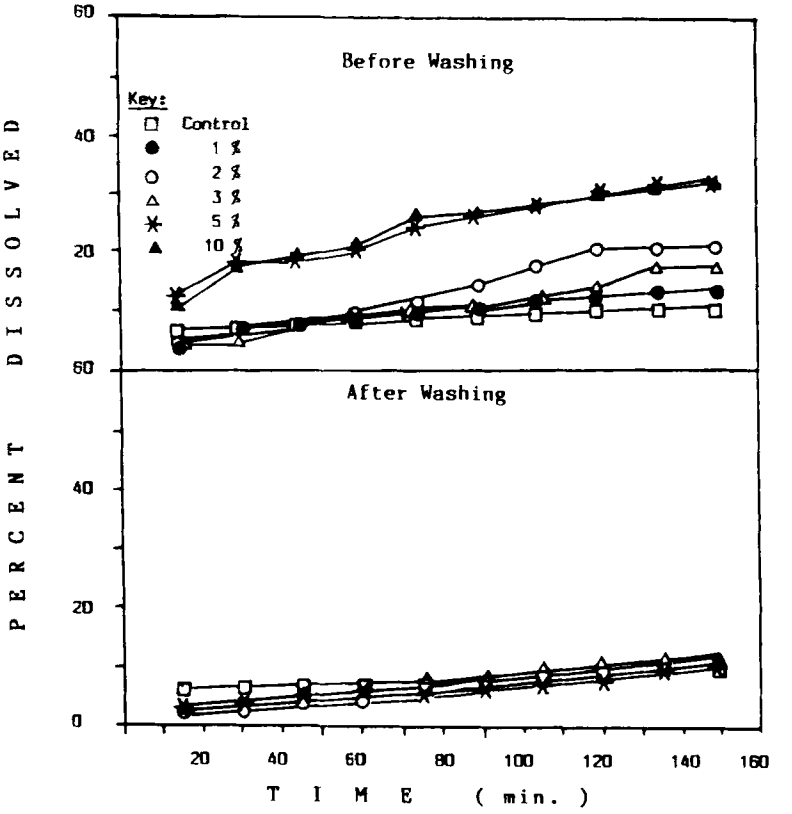

FIGURE 1
Dissolution Rate of Chlorpropamide Crystals Prepared in Presence of Different Concentrations of Tween 80

The faster dissolution rate of the crystals formed in PEGs and PVP solutions over the control probably reflect a significant reduction in the crystalline size of the drug following the crystallization from polymer solution. The decrease in the interfacial energy of the system, associated with an increase in the surface of the ultrafinely crystallized drug exposed to the dissolution medium, appears to be the major factor responsible of the observed potentiation. Solution of PEGs and PVP can also be expected to produce an ultrafine or colloidal crystals of the drug. This mainly due to the difficulty of growth of the crystals in highly viscous medium. Such condition was supported by a study of the ability of PVP to inhibit the crystal growth of sulfathiazole and methyl prednisolone in

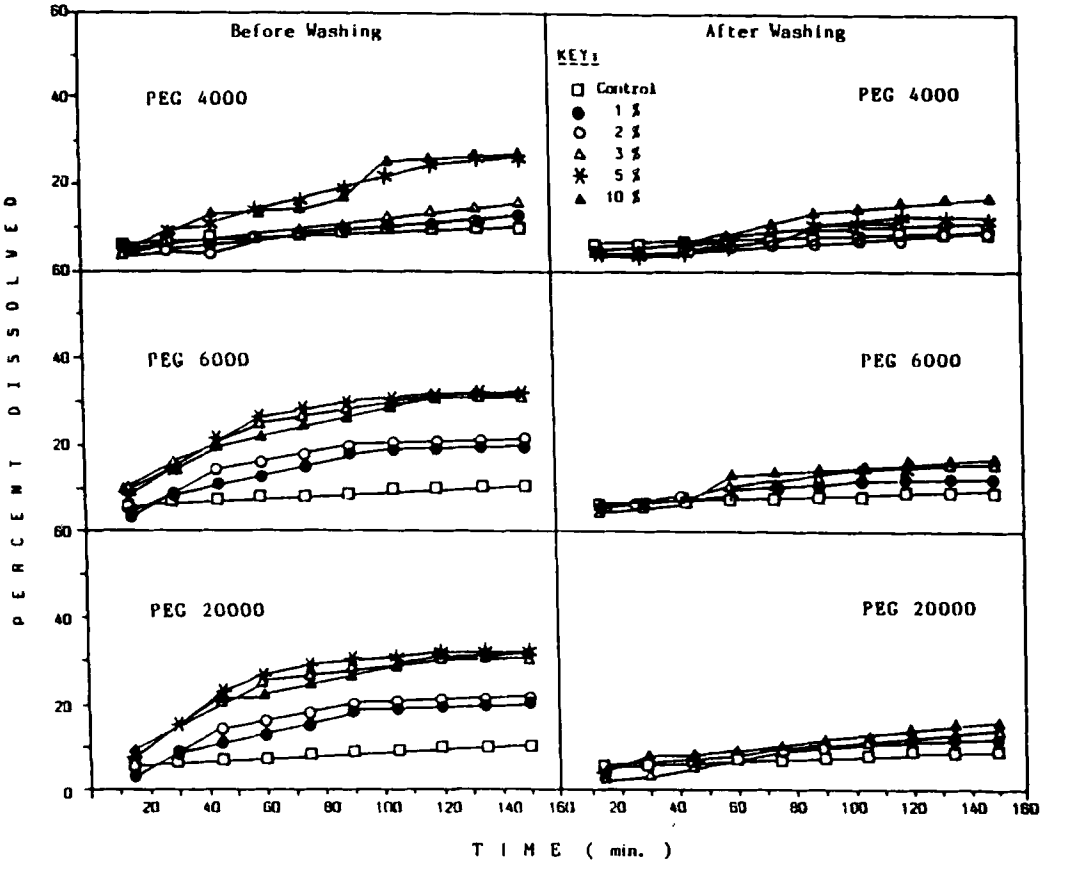

FIGURE 2
Dissolution Rate of Chlorpropamide Crystals Prepared in Presence of Different Grades of PEGs

water, even at a very low concentration (14). It seems logic to assume that PEG polymer may also act as protective colloid in retarding the coagulation, aggregation or coarsening of the fine crystals.

Another factor which might also contribute to the fast dissolution was possible solubilization effect of the surfactant and the polymers.

The increase in the dissolution rate on increasing the concentration of additives in the crystallization medium may be attributed to the fact that, as the amount of surfactant or polymer molecules increased, their amounts occluded and/or adsorbed will increase which in turn affect the dissolution rate. These results are in agreement

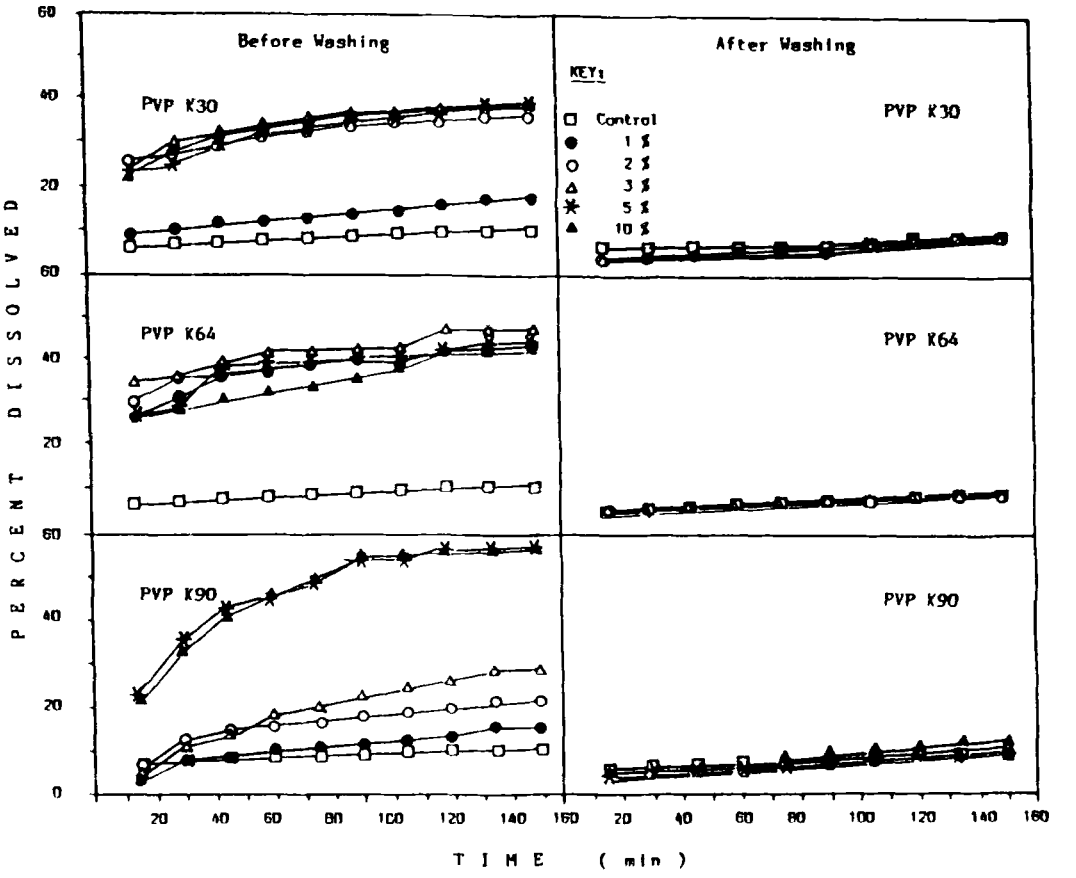

FIGURE 3
Dissolution Rate of Chlorpropamide Crystals Prepared in Presence of Different Grades of PVP

with those reported by Wurster and Pilli (15) who stated that the dissolution rate of acidic drugs was found to increase by the adsorbent.

The effect of molecular weight of the polymer used on the dissolution rate of CP was also investigated. The greater the molecular weight of the polymer, the more distinct and pronounced is the enhancement of the dissolution rate of the drug (Table 2 and Figs 1-3) This may be due to that on using the polymer of higher molecular weight, the viscosity of its solution was higher than the polymer of lower molecular weight, leading to more fine crystals which are of rapid dissolution. Also as the

molecular weight increases, needles to say the molecular size increases, the amount of the additives adsorbed on the surface of the formed crystals increases leading to increased wettability and hence rapid dissolution.

The IR sudy ruled out any interaction between the drug and any of the used polymers or surfactant. Figure 4 shows that there is no significant difference between the IR spectra of the prepared crystals and the parent drug. Meanwhile, the peaks in the spectra of the treated crystals are not as sharp as that of the pure CP which is due to the presence of the additives.Also this figure shows that no complexation occurs between CP and Polysorbate 80 , PEGs or PVP as all functional groups still show their bands with slight shift in some peaks and appearance of additional peaks due to the presence of these additives. The presence of surfactant or polymers during the crystallization process of CP did not result in a different polymorphic form.

The melting range results indicated the presence of surfactant or the polymers inside the crystals which was reflected by their effect in lowering the melting range of the treated crystals (Table 3).

TABLE 3
Melting Range of Chlorpropamide Crystals Prepared in the Presence of Different Concentrations of Surfactant and Polymers

Additives	Melting Range °C				
	1%	2%	3%	5%	10%
Tween 80	121-124	120-123	120-123	118-121	112-115
PEG 4000	118-120	119-123	119-123	114-116	114-118
PEG 6000	115-120	119-121	119-122	119-121	114-118
PEG 20000	115-120	120-122	120-125	116-120	114-117
PVP K30	115-121	116-121	117-122	116-120	112-116
PVP K64	120-125	119-123	116-120	112-117	113-117
PVP K90	123-125	120-124	120-123	118-120	114-118

Melting Range of Conrtol Crystals = 121-129°C

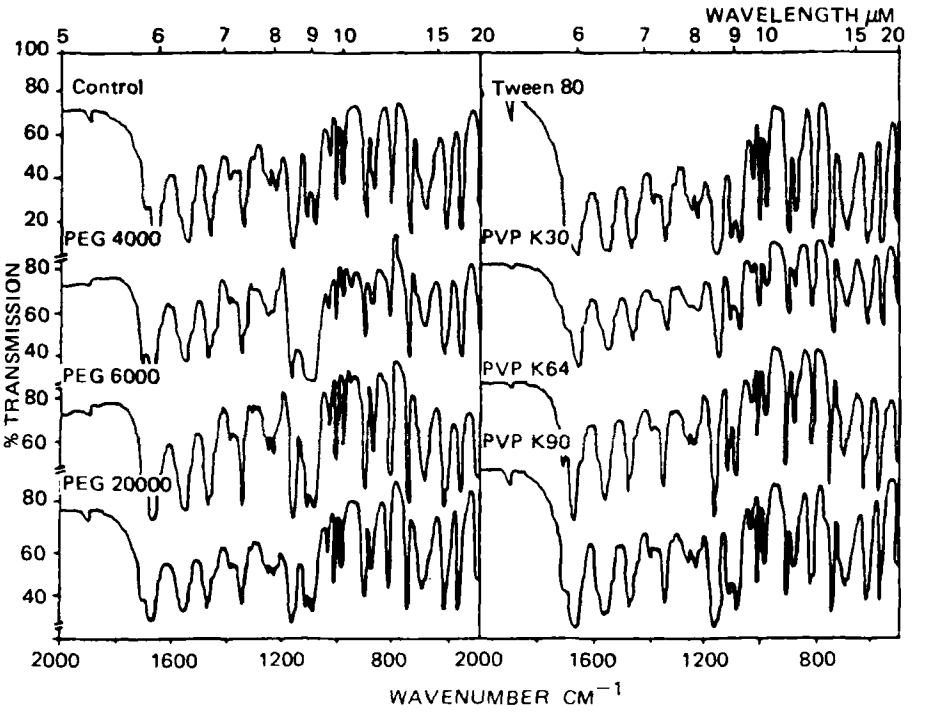

FIGURE 4
Infrared Spectrum of Chlorpropamide Crystals Prepared in Presence of Different Additives

Washing the crystals desorb and hence remove some of adsorbed surfactant or polymers , decrease its surface contact and hence decrease its dissolution rate (5).This also proved that there was no complex formation between the drug and surfactant or polymers and the process was only adsorption phenomena. The dissolution rate of the washed crystal is still faster than the control non treated crystals which indicates the presence of some of the surfactant or polymer inside the crystals (Figs 1-3)

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