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Evaluation Of Quick Disintegrating Calcium Carbonate Tablets

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ABSTRACT The purpose of this investigation was to develop a rapidly disintegrating calcium carbonate (CC) tablet by direct compression and compare it with commercially available calcium tablets. CC tablets were formulated on a Carver press using 3 different forms of CC direct compressed granules (Cal-Carb 4450®, Cal-Carb 4457®, and Cal-Carb 4462®). The breaking strength was measured using a Stokes-Monsanto hardness tester. The disintegration and dissolution properties of the tablets were studied using USP methodology. The calcium concentration was determined by an atomic absorption spectrophotometer. Scanning electron microscopy was used to evaluate the surface topography of the granules and tablets. Breaking strength of Cal-Carb 4450®, Cal-Carb 4457®, and Cal-Carb 4462® tablets was in the range of 7.2 to 7.7 kg, as compared with a hardness of 6.2 kg and 10 kg for the commercially available calcium tablets Citracal® and Tums®, respectively. The disintegration time for the tablets presented in the order earlier was 4.1, 2.1, 1.9, 2.9, and 9.7 minutes, respectively. The dissolution studies showed that all formulations released 100% of the elemental calcium in simulated gastric fluid in less than 20 minutes. In summary, this study clearly demonstrated that quick disintegrating CC tablets can be formulated without expensive effervescence technology.

KEYWORDS: Calcium Carbonate Tablets, Quick Disintegrating, Effervescence

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INTRODUCTION

Dietary calcium requirements increase as one ages [1]. Adequate calcium is generally derived from either food or supplements. Dairy foods are the best source of calcium, and approximately 31% of calcium is generally absorbed orally from whole milk [2]. However, for those unable or unwilling to consume adequate amounts of dairy products, calcium carbonate (CC) has been the most widely used and least expensive dietary supplement for calcium [3]. CC has been extensively used as an antacid, in the treatment of osteoporosis [4,5], and also in the management of hyperphosphatemia in renal failure [6,7].

Despite their wide use, recent studies on CC tablets marketed in the United States and Canada indicate that many products exhibit poor oral bioavailability [8,9]. Studies have also suggested that the disintegration time of CC tablets may be a more valid indicator of calcium bioavailability than the USP dissolution test [10]. To achieve better availability, quick disintegrating calcium formulations utilizing effervescence technology have been developed. One such formulation available commercially is Citracal®. A consumer vinegar test has also been developed that can quickly determine the disintegration time of commercially available calcium tablets. This test has been shown to agree with USP disintegration tests in 87% to 93% of cases [11]. The bioavailability of tablet formulations is affected by various factors, including its disintegration, dissolution, hardness, and moisture content [12-14]. Use of various starches as disintegrating agents in calcium tablet formulation has also been reported [15-17].

The objective of this investigation was to develop quick

disintegrating CC tablets by direct compression without utilizing an expensive effervescence technology. Disintegration time, dissolution characteristics, and hardness of these tablets were compared with commercially available calcium tablets. . Scanning electron microscopy (SEM) was also used to evaluate the surface characteristics of the granules before and after compression.

MATERIALS AND METHODS

Materials

Two commercially available calcium tablets, Tums® (CC with sugar, SKB Consumer Healthcare, Pittsburgh, PA) and Citracal® (effervescent calcium citrate, Mission Pharmacal, San Antonio, TX), were used in conjunction with three formulated CC tablets in this study. CC granules (Cal-Carb 4450®, Cal-Carb 4457®, and Cal-Carb 4462®) were obtained from Chr. Hansen Ingredient Technology, Mahwah, NJ.

Tablet Formulation

The three tablet formulations developed contained approximately 36% (wt/wt) of elemental calcium. Weighed amounts of granules containing 500 mg of elemental calcium were compressed with a Carver press. The compression pressure used was 900 psi with a dwell time of 10 seconds. Flat-faced circular punches and die (16 mm, i.d.) were used in this study. Formulated CC tablets did not contain any other inactive materials. The average weights of Cal-Carb 4450®, Cal-Carb 4457®, and Cal-Carb 4462® tablets were 1379 ± 0.9, 1386 ± 0.7, and 1415 ± 1.0 mg, respectively.

Disintegration Time

Two disintegration media were used in this investigation: simulated gastric fluid USP without enzymes and regular white vinegar. Simulated gastric fluid (pH of 1.2) was prepared by dissolving 1 g of NaCl in 500 mL of deionized water, adding 7 mL of concentrated HCl, and adjusting the volume to 1000 mL with water. A USP disintegration apparatus (Vankel Ind., Edison, NJ) and 900 mL of either simulated gastric fluid or vinegar at 37°C was used in this investigation. The effect of moisture on the disintegration time of CC tablets was also evaluated by exposing tablets to various humidity conditions prior to the disintegration studies.

Determination of the Breaking Strength of the Tablets

The breaking strength (in kg) of each tablet was tested using a Stokes-Monsanto hardness tester (DT Stokes, Bristol, PA). The formulated as well as the commercial tablets were circular and flat. After the dial on the tester was set to zero, a tablet was placed between the two jaws. The breaking point was determined by gradually increasing the force on the tester. Breaking strength is the force applied (in kg) to break the tablet radially into two halves. Hardness testing was also performed on the tablets that were exposed to various relative humidity conditions.

Moisture Uptake Studies

All three formulated CC tablets and Tums® Regular Strength (containing 400 mg elemental calcium) were exposed to three different humidity conditions at 23°C. Controlled humidity chambers (31%, 45%, and 79.3% relative humidity [RH]) were constructed using various saturated salt solutions in desiccators. The 31% RH desiccator contained a saturated solution of CC, the 45% RH contained potassium nitrate, and the 79.3% RH contained ammonium chloride. Tablets were subjected to these humidities for approximately 60 days.

Dissolution Properties of CC Tablets

Dissolution characteristics of the formulated CC tablets and Citracal® were determined using a USP Dissolution Apparatus 2. Simulated gastric fluid (900 mL at 37°C), without enzymes, was used as the dissolution medium. At predetermined time intervals (0, 2, 5, 10, 15, 30, 45, 60, 90, and 120 minutes), 4 mL of the release medium was collected through a filter assembly and replaced with the same volume of fresh buffer. The calcium content in the sample was determined by atomic absorption spectrophotometry.

Assay of Calcium Carbonate

The calcium content of each sample (collected during dissolution studies) was assayed by a Varian Atomic Absorption Spectrophotometer (model-AA200, Varian, Sugar Land, TX). To increase the testing procedure sensitivity, lanthanum chloride (24.67 mg/mL) was added as a releasing agent to both the standard and unknown samples. The unknown samples were diluted appropriately when necessary. The unknown concentration was determined from a calibration curve.

Scanning Electron Microscopy

The microstructure and surface topography of the granules before and after compression were evaluated by a Philips XL20 Scanning Electron Microscope. in which the voltage was set at 1 kV. No coatings were applied to the samples. The scanning electron (SE) mode was selected to examine the overall surface morphology, and the through lens detection (TLD) mode was used to view the detailed structure.

RESULTS AND DISCUSSION

The chemical compositions and several physical properties of the CC granules used in this investigation are listed in **Table 1.** The active ingredient in Cal-Carb 4450® and Cal-Carb 4457® was identical (calcium carbonate USP), but Cal-Carb 4462® contained precipitated CC. The calcium content of all granules was identical (36% wt/wt). Maltodextrin was used as an inactive material in Cal-Carb 4450® granules, but the other granules contained pregelatinized starch as an inactive ingredient. Even though there were no significant differences in the particle size of the granules, the bulk density of the Cal-Carb 4462® granules was slightly lower than that of the other granules.

Table 1. General Properties of Calcium Carbonate (CC) Granules Used in This Study

Type of CC Granules Used	Active Ingre-dient	Inactive Ingre-dient	Calcium Content, % (w/w)	Bulk Density (g/cc) Loose	Tap	Particle size
4450	CC USP	Maltodextrin	36.2	1–1.3	1.15–1.45	5% on US #20 and 25% through US # 200 sieve
4457	CC USP	Pregelatinized Starch NF	36.1	1–1.3	1.15–1.45	5% on US #20 and 25% through US # 200 sieve
4462	Precipitated CC USP	Pregelatinized Starch NF	36.2	0.95	1.05	5% on US #20 and 20% through US # 200 sieve

Disintegration times of all 5 calcium tablets studied fell within USP specifications, which may, in part, be due to the hardness characteristics of the individual formulations and the type of the excipient present in the formulation. Breaking strengths of all 5 formulations are depicted in **Table 2.**

Table 2: Hardness of the Tablet Formulations

Breaking Strength in kg				
TumsÒ	CitracalÒ	Cal-Carb 4450®	Cal-Carb 4457®	Cal-Carb 4462®
10.0 ± 0.5*	6.2 ± 1.04*	7.17 ± 0.29*	7.17 ± 0.76*	7.67 ± 0.29*

*Mean ± SD, *n* = 3.

The hardness values for the tablets prepared using Cal-Carb granules 4450, 4457, and 4462 were 7.17, 7.17, and 7.67 kg, respectively. The corresponding disintegration times observed were 4.7, 2.05, and 1.93 minutes, respectively. These results clearly suggest that the disintegration times of these tablets are more a function of the type of excipient than the hardness of the tablets. Hardness of the three tablets formulated in this laboratory (Cal-Carb 4450®, Cal-Carb 4457®, Cal-Carb 4462®) fell between the hardness of the two commercial products (Citracal® and Tums®). The study further revealed that the compression pressure used for making the CC tablets produced tablets with acceptable strength.

The disintegration time of various calcium tablets in simulated gastric fluid is shown in **Figure 1.**

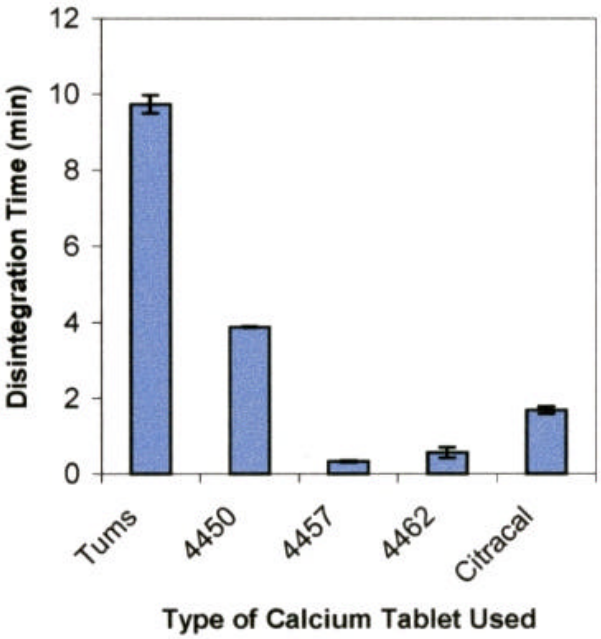


Figure 1. Disintegration time of various calcium carbonate tablets in simulated gastric fluid without enzyme.

The disintegration time of Tums® in simulated gastric fluid was about 10 minutes, while Citracal® the effervescent formulation, had a disintegration time of approximately two minutes. The formulated tablets, with the exception of Cal-Carb 4450®, disintegrated faster than the commercial products. The disintegration time of calcium tablets in vinegar is shown in **Figure 2.**

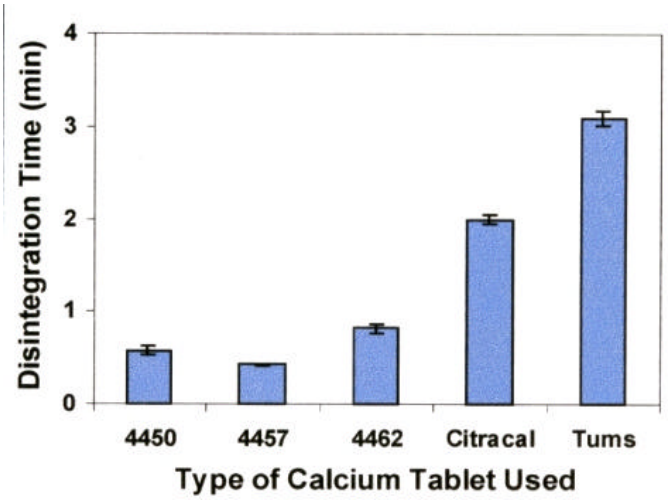


Figure 2. Disintegration time of various calcium carbonate tablets in white vinegar (consumer vinegar test).

Although Cal-Carb 4450® took slightly more time than Citracal® to disintegrate in simulated gastric fluid (**Figure 1**), its disintegration was considerably faster than Citracal® during the consumer vinegar test. The differences in the disintegration times of Cal-Carb 4450® tablets may be attributable to the interactions between the maltodextrins used in these tablets and the two different disintegration media. A single factor analysis of variance (ANOVA) was used to determine the significant differences, among the mean disintegration times of the 4 quick disintegrating CC tablet formulations (Cal-Carb 4450®, 4457®, and 4462® and Citracal®). Results of this analysis revealed significant differences in the mean disintegration time ($p < 0.001$). Post-hoc Tukey. s HSD test further demonstrated that the 4 disintegration times for the tablet formulations were significantly different.

The effect of moisture upon the hardness and disintegration of the CC tablets was also studied. The average equilibrium moisture uptake by Cal-Carb 4450® tablets at 31%, 45%, and 79.3% RH was 0.7, 0.8, and 1.7% respectively. Under similar conditions Cal-Carb 4457® adsorbs 0.7%, 0.9%, and 1.4% moisture. However, the moisture uptake by Cal-Carb 4462® tablets at three different humidity conditions was 0.6%, 1.1%, and 1.6%, respectively. No significant differences in the moisture uptake were found for the three formulated tablets at each RH value. The moisture content of the granules prior to compression was in the range of 0.4% to 0.7 %. **Figure 3** represents the effect of moisture on the hardness of each tablet formulation.

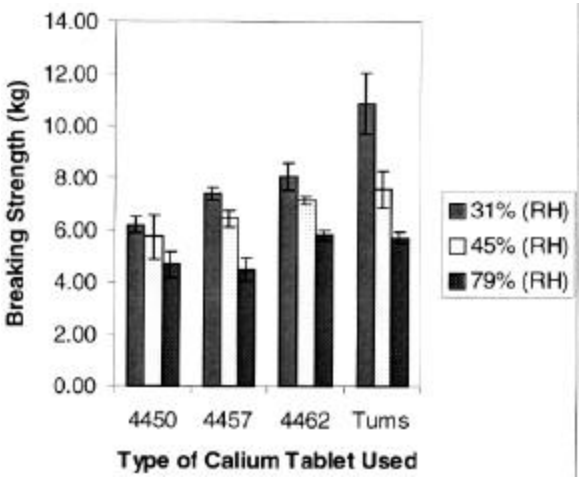


Figure 3. Effect of moisture on the hardness of various calcium carbonate tablets.

As expected, the hardness of each tablet was found to be inversely proportional to the percentage relative humidity. Interestingly, RH had the greatest effect on the hardness of Tums® tablets. The effect of RH on the disintegration time of the CC tablets in simulated gastric fluid is shown in **Figure 4.** The three RH conditions studied did not affect the disintegration time of the formulated CC tablets. **Figure 5** shows the dissolution characteristics of the 4 quick disintegrating calcium tablets.

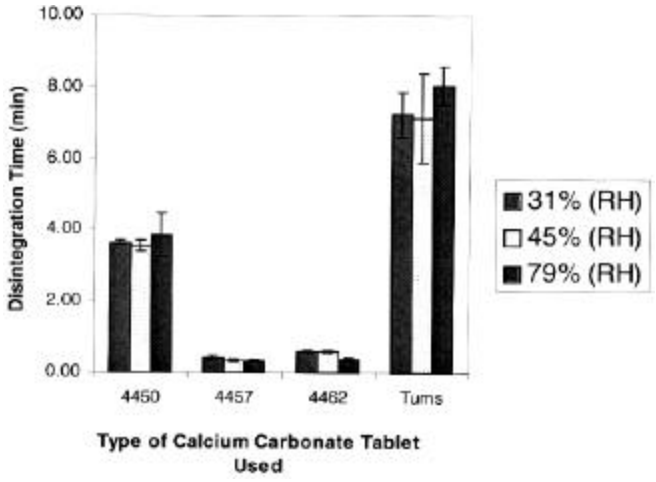


Figure 4. Effect of moisture on the disintegration time of various calcium carbonate tablets. Disintegration was determined by a USP Disintegration Apparatus using simulated gastric fluid, without enzyme, as the disintegrating medium.

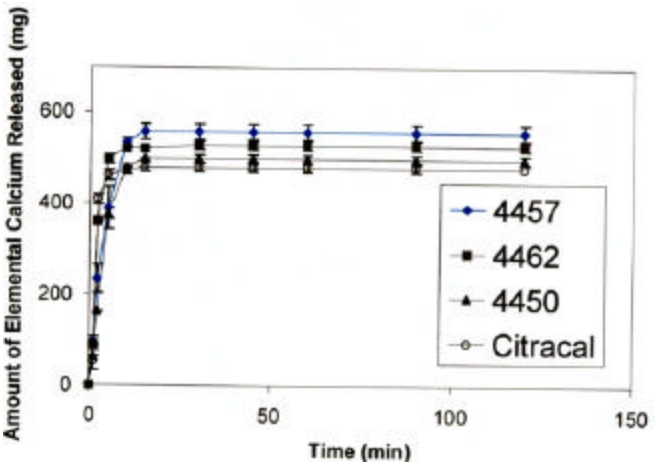


Figure 5. Dissolution profiles of various quick-release calcium carbonate tablets.

All 4 formulations tested released 100% of elemental calcium into the simulated gastric fluid in less than 20 minutes. The results of this study clearly indicate that calcium quickly dissolves into the dissolution medium in all 4 formulations investigated.

Our laboratory was interested in understanding why the three different CC granules had variable disintegration properties after compression. Cal-Carb 4450® contained maltodextrin as the inactive material while the other granules contain pregelatinized starch. We believe that the pregelatinized starch contributed to the quick disintegration of tablets formulated from these granules. The work of Chowhan [15] and Makino et al. [19] also supports this hypothesis. Starch functions as a disintegrant by drawing water into the tablet causing it to swell and break into fragments. According to Mollan and Celik, disintegration properties of maltodextrin are not controlled by the porosity or bonding within the tablets, as is the case with starch. The disintegration of tablets with maltodextrin is generally controlled by a rate-limiting gel layer that forms around the tablet upon immersion into water [20].

SEM was used to determine differencesin the overall surface morphology of granules before and after compression. SEmicrographs of all granules before compression were obtained at two magnifications (X840 and X1680). The micrographs of Cal-Carb 4457® are shown in **Figure 6.**

Surface morphologies of the other granules were identical to that of Cal-Carb 4457®. Surface characteristics of all three granules were evaluated after compression. Tablets made from Cal-Carb 4457® clearly have greater grain boundaries (**Figure 7**, sample c (I) and (II)) than the other samples (**Figure 7 (a) and (b)**). These differences in grain boundaries could contribute to differences in the surface area, thereby causing better interaction with the disintegrating medium and quick disintegration.

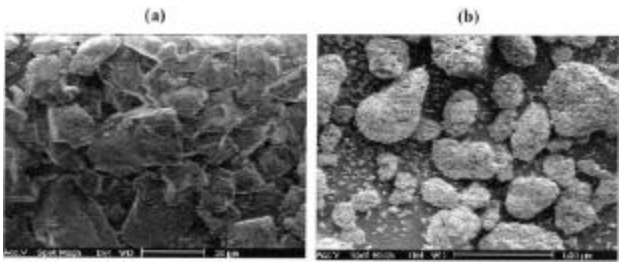


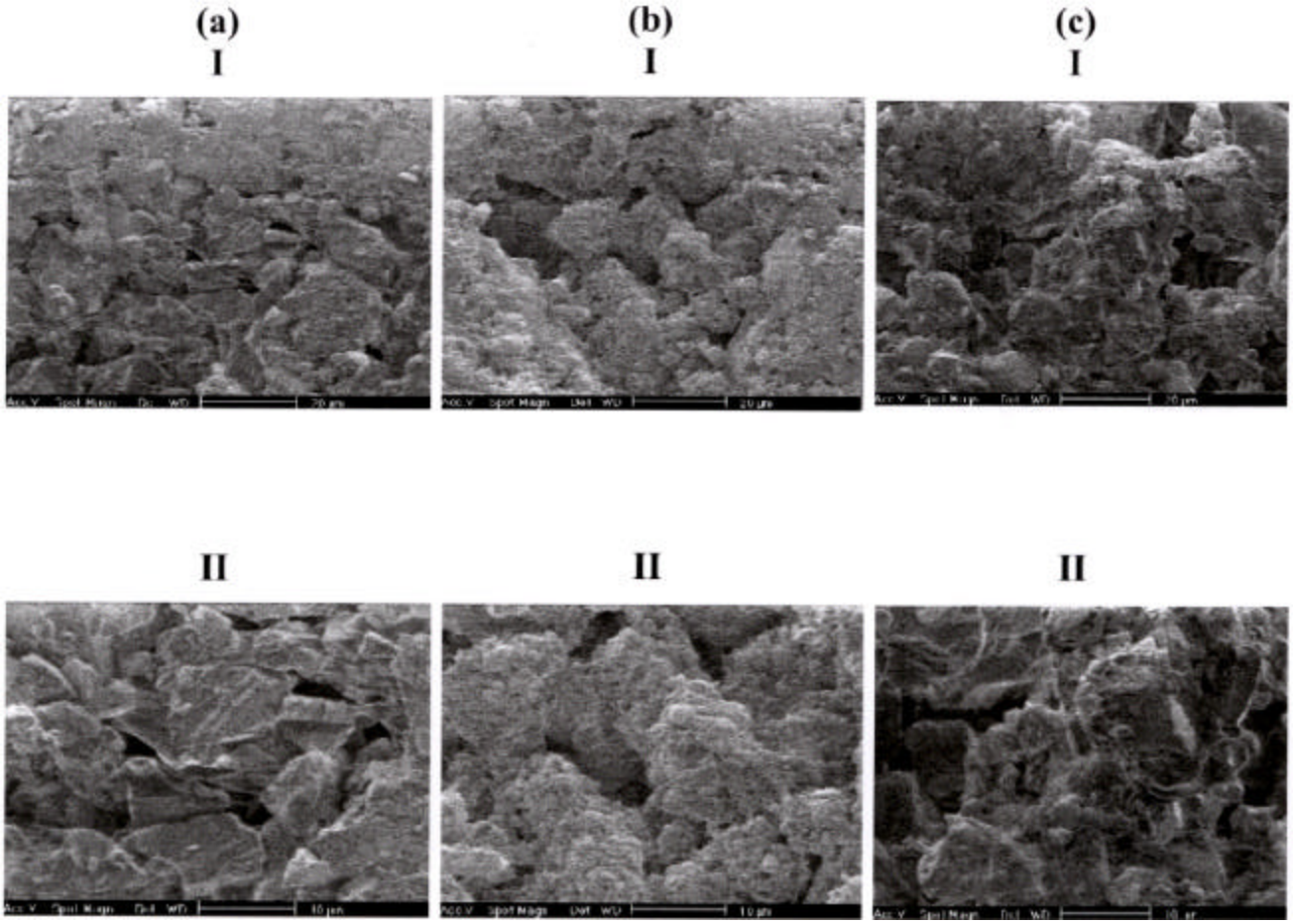
Figure 6. Scanning electron micrographs of Cal-Carb 4457® granules (a) before compression at 840 magnification and (b) at 1680 magnification.

CONCLUSIONS

Moisture and hardness are inversely related in commercially available and formulated CC tablets, but moisture has little effect on disintegration time. Two formulated CC tablets (Cal-Carb 4457® and Cal-Carb 4462®) disintegrated more quickly in simulated gastric fluid than both Citracal® and Tums®. All formulated tablets disintegrated more rapidly than Citracal® in vinegar. The presence of pregelatinized starch in the granule was thought to be responsible for the quick disintegration and dissolution characteristics of the formulated tablets. These findings are similar to the characteristics of Citracal®. All the elemental calcium was released into the simulated gastric fluid in less than 20 minutes. SEM studies revealed that differences in the grain boundary are partly responsible for the quick disintegration of these tablets.

In summary, this study clearly demonstrated that one could develop a quick disintegrating calcium tablet by using a direct compression method. Such a method avoids the expensive effervescence technique and produces tablets that can disintegrate even faster than the effervescent calcium formulation.

Figure 7. Scanning electron micrographs of various calcium carbonate granules after compression: (a-I) Cal-Carb 4450® at 840 magnification, (a-II) Cal-Carb 4450® at 1680 magnification, (b-I) Cal-Carb 4462® granules at 840 magnification, (b-II) Cal-Carb 4462® granules at 1680 magnification, (c-I) Cal-Carb 4457® granules at 840 magnification, and (C-II) Cal-Carb 4457® granules at 1680 magnification



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