

Amsorb

A New Carbon Dioxide Absorbent for Use in Anesthetic Breathing Systems

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Background: This article describes a carbon dioxide absorbent for use in anesthesia. The absorbent consists of calcium hydroxide with a compatible humectant, namely, calcium chloride. The absorbent mixture does not contain sodium or potassium hydroxide but includes two setting agents (calcium sulphate and polyvinylpyrrolidone) to improve hardness and porosity.

Methods: The resultant mixture was formulated and subjected to standardized tests for hardness, porosity, and carbon dioxide absorption. Additionally, the new absorbent was exposed *in vitro* to sevoflurane, desflurane, isoflurane, and enflurane to determine whether these anesthetics were degraded to either

compound A or carbon monoxide. The performance data and inertness of the absorbent were compared with two currently available brands of soda lime: Intersorb (Intersurgical Ltd., Berkshire, United Kingdom) and Dragorsorb (Drager, Lübeck, Germany).

Results: The new carbon dioxide absorbent conformed to United States Pharmacopeia specifications in terms of carbon dioxide absorption, granule hardness, and porosity. When the new material was exposed to sevoflurane (2%) in oxygen at a flow rate of 1 l/min, concentrations of compound A did not increase above those found in the parent drug (1.3–3.3 ppm). In the same experiment, mean \pm SD concentrations of compound A (32.5 ± 4.5 ppm) were observed when both traditional brands of soda lime were used. After dehydration of the traditional soda limes, immediate exposure to desflurane (6%), enflurane (2%), and isoflurane (2%) produced concentrations of carbon monoxide of 600.0 ± 10.0 ppm, 580.0 ± 9.8 ppm, and 620.0 ± 10.1 ppm, respectively. In contrast, concentrations of carbon monoxide were negligible (1–3 ppm) when the anhydrous new absorbent was exposed to the same anesthetics.

Conclusions: The new material is an effective carbon dioxide absorbent and is chemically unreactive with sevoflurane, enflurane, isoflurane, and desflurane. (Key words: Toxicity; volatile.)

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DESPITE an interval of 80 yr, soda lime still remains an effective—and the most widely used—method of removing carbon dioxide from closed and semiclosed anesthetic breathing systems. However, it is far from ideal. Two aspects of the use of carbon dioxide absorbents in anesthesia are causing increasing concern: (1) sevoflurane undergoes degradation in the presence of soda lime to an olefin ($\text{CF}_2 = \text{C}(\text{CF}_3)\text{OCH}_2\text{F}$; compound A), which has been the subject of intense debate because of possible nephrotoxicity^{1–3}; and (2) the generation of carbon monoxide, which may occur when desflurane, enflurane, and isoflurane are passed through the currently available dehydrated carbon dioxide absorbents.^{4,5}

Each of these problems is directly related to the presence of monovalent hydroxide bases contained within the present commercially available absorbents. To address these concerns, we developed a novel carbon

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dioxide absorbent that does not contain sodium or potassium hydroxide.

We previously reported our initial experiments designed to optimize granule formulation and hardness.⁶ Our aims in these studies were as follows: (1) to evaluate the carbon dioxide absorption characteristics of a calcium hydroxide-containing compound that did not contain strong alkali; (2) to show that the operating temperature, hardness, and porosity profiles of the new absorbent conformed to United States Pharmacopeia (USP XXII); (3) to show that compound A was not produced when sevoflurane was exposed to this new absorbent; and (4) to measure the carbon monoxide concentrations generated when the new absorbent was dehydrated and exposed to desflurane, isoflurane, and enflurane.

Methods

Calcium hydroxide (CaOH₂; 70%) (RMC Ltd., Essex, United Kingdom) and calcium chloride (CaCl₂; 0.7%; Molecular Products Ltd., Thaxted, Essex, United Kingdom), together with the setting agents calcium sulphate (CaSO₄; 0.7%; British Gypsum, Slough, Berkshire, United Kingdom) and polyvinylpyrrolidone (0.7%; BASF, Frankfurt, Germany), were weighed and mixed using a small Z blade mixer for 5 min. Water (28% w/w) was added in aliquots, and the resultant wet mass was passed through a 3.35-mm sieve and tray dried at 70°C for 60–120 min. The resultant dry material was then rewetted with water to constant moisture of 14.5% by weight. This material has been patented and named Amsorb (Armstrong Medical Ltd., Coleraine, Northern Ireland; Armstrong Medical Ltd. holds the worldwide intellectual property and trademark rights of this material).

Granular Size Distribution (Mesh Analysis) and Hardness

This test was performed by agitating a 100-g sample of each absorbent in a steel pan (roller mill machine) together with 15 ball bearings of 1-cm diameter. This was shaken for 30 min, after which the granules were passed through a series of sieves with mesh diameters of 8 mm, 4.75 mm, 2.36 mm, and 0.425 mm, respectively. The amount of absorbent that passed through the respective sieve sizes was recorded as a percentage of the whole. Any material that passed through the 0.425-mm sieve was classified as dust (see Appendix for USP specifications).

Using only the material retained on the 4.75- and 2.36-mm sieves, 200-g samples of the new absorbent and each of the named brands of soda lime together with 15 ball bearings of 1-cm diameter were agitated in a roller mill testing machine with a steel pan for 30 min. The ground material was then placed on the 2.36-mm sieve and reagitated on the steel pan. Retention of at least 80% of the original sample weight was required for acceptability. Minimum desirable hardness, as determined by USP, should be at least 80 on a scale of 100 (see Appendix for USP specifications).

Pore size distribution and total pore volume data were obtained using mercury porosimetry (ERBA porosimeter 200 series; Carlo Erba, Milan, Italy). This technique involves an apparatus that contains mercury within a calibrated volume, vacuum chamber. A sample within the vacuum chamber will cause a detectable pressure change when the system is pressurized to 1 atmosphere. This change in pressure reflects the skeletal density (*i.e.*, pore volume) of the material in question.

Carbon Dioxide Absorption

One kilogram of the new material and the two other brands of soda lime ($n = 3$) was placed in a standard soda lime canister (height, 11 cm; internal diameter, 10 cm; radius, 5 cm; Datex-Ohmeda Ltd., Hatfield, England) and attached to the common gas outlet of an anesthesia machine (Ohmeda Modulus II, Datex-Ohmeda Ltd.). Oxygen and carbon dioxide were mixed to give an end-tidal carbon dioxide concentration of 45 mmHg before insertion of the absorbent-filled canister. Indwelling probes gave a continuous recording of the temperature of the absorbent. A Datex Capnomac (Datex Ltd., Helsinki, Finland) gas analyzer was connected at the exit port of the canister, and at time zero, the gas mixture was allowed to pass through the canister. Serial recordings were made of carbon dioxide concentrations and stored in a portable computer (fig. 1). When the concentration of the effluent carbon dioxide reached 5 mmHg, the time was noted, and the time per unit weight of the absorbent was recorded. The volume of carbon dioxide absorbed per kilogram of each absorbent was calculated.

Production and Measurement of Compound A

Two currently available brands of soda lime and the new material were each tested on three occasions in this experiment. One hundred grams of each absorbent (fresh) was placed in a similar canister to that used in the first experiment. A 50:50 gas mixture of oxygen/nitrous oxide with 2% sevoflurane was passed through the can-

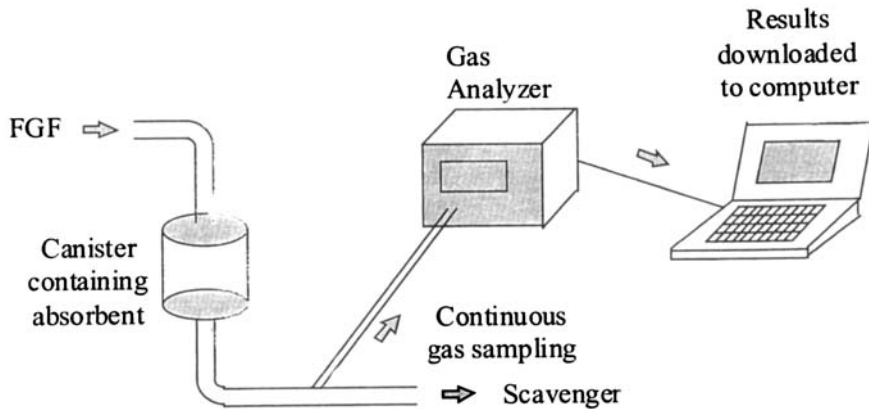


Fig. 1. Diagram showing the apparatus used to evaluate the carbon dioxide absorber profiles of the new material and traditional soda limes. (Fresh gas flow [FGF] = 4.5% carbon dioxide in 500 ml oxygen and 500 ml nitrous oxide, delivered from a standard anesthesia machine).

ister at a flow rate of 1 l/min. Gas samples (5 ml) for estimation of compound A concentrations were removed from an exhaust port distal to the canister into gas-tight syringes at 30-min intervals for a period of 150 min. A gas chromatographic method using a coated-carbon packing material and flame ionization detection was used to measure the amount of compound A in vapor-phase samples of sevoflurane. A dilute gaseous preparation of sevoflurane was used as a surrogate standard because it is commonly available in very high purity. As an internal standard, *n*-butyl chloride was chosen for its availability, volatility, and retention characteristics. The concentrations in each sample were measured using a Perkin Elmer 1B analyzer and a Perkin Elmer 1B gas chromatography system (Perkin Elmer, Pomona, CA) equipped with a flame ionization detector and electronic processing. The gas chromatograph column was 6 m long, with a 3.5-mm internal diameter; it had a liquid phase of Altech AT-100 on a 60/80 Graphpac GB packing material. The injection port temperature was 133°C, the initial oven temperature was 130°C, and the flame ionization detector temperature was 225°C. The carrier gas was nitrogen, with a carrier gas flow rate of 30 ml/min.

The relative response factor of compound A to sevoflurane was determined to be 0.864 on a volume/volume basis. Calibration curves from gaseous preparations of compound A were linear, in the range of 0.2–8 ppm (vol/vol), which corresponds to 1.5–59 ppm in an undiluted sample. An additional sample dilution brings higher-level samples (up to 430 ppm compound A) into the linear range of the method.

Generation and Measurement of Carbon Monoxide

Three samples (300 g) each of the two types of soda lime and of the new material were dehydrated in an oven at 250°F for 8 h. The samples were then reweighed, and

a 15% loss of weight after drying was used to indicate complete dehydration of the absorbents. A 100-g sample of each dry material was then placed in a canister similar to that used in the previous experiments, then oxygen/nitrous oxide in a 50:50 mix at a flow rate of 1 l/min and carbon dioxide at a flow rate of 40 ml/min was passed through the canister. Each absorbent was then exposed to desflurane (6%), enflurane (2%), and isoflurane (2%). After 1 min, a sample of the gas was collected and analyzed for carbon monoxide content using a recently calibrated carbon monoxide meter (CO-Tester; F.I.M., Villeurbanne, France). This device is an electrochemical meter with a response time of 30 s and a measurement range of 0–1,500 ppm. It has an annual drift of 2% and its linearity from 0 to 1,000 ppm is $\pm 4\%$.

To mimic more closely the drying conditions that occur in clinical practice, three 100-g samples of each of the three absorbents were weighed and then exposed to a continuous flow of oxygen at 6 l/min for a period of 48 h. After this drying technique was performed, the absorbents were reweighed, and the carbon monoxide experiment was repeated as before. Gas flow drying succeeded in dehydrating the absorbents to a value of 70% of the original-weight.

All data are presented as mean \pm SD and were analyzed using unpaired Student *t* tests. A *P* value < 0.05 was considered statistically significant.

Results

The results for hardness, moisture content, operating temperature, porosity, and mesh analysis are shown in tables 1 and 2. The new absorbent showed a hardness value of 94.2%, with a moisture content of 14.1% and a mean \pm SD operating temperature of $36.1 \pm 2.3^\circ\text{C}$.

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Table 1. Physical Properties of Amsorb, Intersorb, and Dragorsorb

Test	Hardness USP XXII >75% (% retained)	Moisture Content USP XXII 12–19% (% loss at 140°C)	Operating Temperature after 1 h (°C) [mean (SD)]	Porosity (total pore volume; cm ³ /g) [mean (SD)]
Amsorb (n = 3)	94.2	14.1	36.1 (2.3)	0.30 (0.01)
Intersorb (n = 3)	90.0	15.3	39.1 (1.5)	0.29 (0.01)
Dragorsorb (n = 3)	94.0	16.1	38.0 (2.6)	0.28 (0.01)

USP = United States Pharmacopeia.

Mesh analysis of the new absorbent showed that 0.5%, 85.6%, and 13.5% were retained by sieves with mesh diameters of 4.75 mm, 2.36 mm, and 0.425 mm, respectively. The percentage of the material that passed through a 0.425-mm sieve (*i.e.*, classified as dust) was 0.4%.

The carbon dioxide absorption characteristics of 1 kg of the absorbents are shown in table 3. The mean \pm SD duration of carbon dioxide absorption to the measured breakthrough point of 5 mmHg was 252 ± 5.6 min, 300 ± 7.6 min, and 260 ± 2.0 min for the new material, Intersorb (Intersurgical Ltd., Berkshire, United Kingdom), and Dragorsorb (Dräger, Lübeck, Germany), respectively. The mean \pm SD amount of carbon dioxide absorbed for each material was 102 ± 1.5 l/kg, 120 ± 1.0 l/kg, and 115 ± 1.5 l/kg, respectively.

Analysis of the gas samples taken from the test circuit when the new absorbent was exposed to sevoflurane 2% showed that compound A concentrations remained less than 3.3 ppm throughout the study period. Compound A is normally present as a contaminant of sevoflurane at

Table 2. Mesh Analysis of Amsorb, Intersorb, and Dragorsorb

Mesh Size (mm)	Amsorb (n = 3) (% Retained)	Intersorb (n = 3) (% Retained)	Dragorsorb (n = 3) (% Retained)
4.75	0.5 (<7.0%)*	0.9	0.1
2.36	85.6 (balance)*	86.5	84.3
0.425	13.5 (<15%)*	11.9	15.1
% of material classified as dust <0.425 (classified as dust)	0.4 (<2.0%)	0.7	0.5

* United States Pharmacopeia XXII specification in parentheses.

Table 3. Carbon Dioxide Absorption Characteristics of 1 kg Amsorb, Intersorb, and Dragorsorb When Exposed to a Flow of 400 ml/min CO₂

Test	Duration to 5 mmHg Breakthrough (min) (USP XXII 210 min)	CO ₂ Absorption (L/kg) (USP XXII 80 L/kg)
Amsorb (n = 3)	252 (5.6)	102 (1.5)
Intersorb (n = 3)	300 (7.6)	120 (1.0)
Dragorsorb (n = 3)	260 (2.0)	115 (1.5)

Data are mean (SD). USP-NF XXII requirements are given in parentheses. USP = United States Pharmacopeia.

these concentrations. In contrast, when the standard soda limes were used, the mean \pm SD concentrations of compound A increased steadily from a baseline of 2.5 ± 2.2 ppm to 32.3 ± 4.5 ppm at the end of the experiment (fig. 2).

The oven-dehydrated soda limes produced high concentrations of carbon monoxide compared with Amsorb (table 4). The soda lime brands that were dried using a continuous flow of oxygen for 48 h produced mean \pm SD carbon monoxide concentrations of 223 ± 9.7 ppm, 201 ± 4.1 ppm, and 190 ± 5.8 ppm, respectively, when exposed to desflurane, enflurane, and isoflurane. Again, minimal amounts of carbon monoxide were generated when the new material was gas dried and exposed to the same anesthetics (table 4).

Discussion

The results of this study demonstrate that it is possible to formulate an efficient carbon dioxide absorbent without the use of strong alkali. The new material conforms to and exceeds USP specifications for medical-grade carbon dioxide absorbents. The material has an efficient carbon dioxide absorption profile and compares favorably with other commercial soda lime-based absorbents. In addition, we have shown that sevoflurane, desflurane, enflurane, and isoflurane are not degraded when exposed to this material during *in vitro* testing.

The present formulation of soda lime comprises 95% CaOH₂ and either NaOH or KOH with some water present (2–18%). Barium hydroxide lime (Baralyme; Allied Health Care, St. Louis, MO) comprises 80% CaOH₂ and 20% BaOH₂·8H₂O. The eight waters of crystallization present in BaOH₂ serve to fuse the mixture so that it will hold its shape under various conditions of heat and moisture. The presence of water is essential to the efficient absorption of carbon dioxide by the specific absorbent. (The reaction of absorption and neutralization of

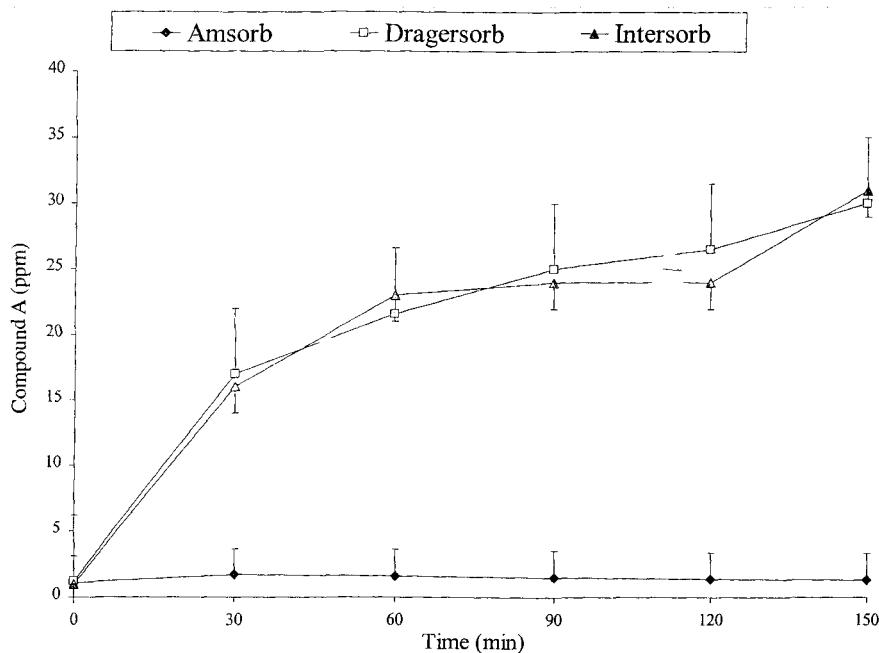


Fig. 2. Concentrations of compound A (ppm) when Amsorb ($n = 3$), Intersorb ($n = 3$), and Dragorsorb ($n = 3$) were exposed to sevoflurane (2%) in oxygen (1 l/min). Data are mean \pm SD.

carbon dioxide with soda lime initially depends on water to produce carbonic acid, which then reacts with sodium or potassium hydroxide to form the respective carbonates. Calcium hydroxide then combines with the carbonates to form calcium carbonate and regenerate sodium and potassium hydroxide.)

The carbon dioxide absorbent properties of the new absorbent depend on a stable, intrinsic moisture content. The incorporation of calcium chloride as a humectant allows the calcium hydroxide to remain damp at all times without resorting to the hygroscopic properties

Table 4. Carbon Monoxide Concentrations (ppm) Produced from Oven-dried and Gas Flow-dried Soda Lime and Amsorb (250°C for 8 h, 6 l/min O₂ for 48 h) When Exposed for 1 min to a Gas Mixture Containing O₂/N₂O in 50:50 Mix and Desflurane (6%), Enflurane (2%), and Isoflurane (2%) at a Flow Rate of 1 l/min, with CO₂ at 40 ml/min

Volatile Agent	Soda Lime (100 g)	Amsorb (100 g)
Oven-dried		
Desflurane ($n = 3$)	600 (10.0)*	1.7 (1.1)
Enflurane ($n = 3$)	580 (9.8)*	1.5 (1.2)
Isoflurane ($n = 3$)	620 (10.1)*	1.4 (1.1)
Gas flow-dried		
Desflurane ($n = 3$)	223 (9.7)*	1.2 (1.0)
Enflurane ($n = 3$)	201 (4.1)*	2.3 (1.6)
Isoflurane ($n = 3$)	190 (5.8)*	1.5 (1.1)

Data are mean \pm SD.

* $P < 0.05$.

conferred by sodium or potassium hydroxide in standard soda limes.

It has been known for many years that materials used for carbon dioxide absorption can cause the degradation of volatile anesthetics. In the presence of soda lime, halothane is converted to 2-bromo-2-chloro-1,1-difluoroethylene. This compound has been detected after exposure of patients to halothane in closed and semiclosed breathing systems when soda lime is used as a carbon dioxide absorbent.⁷

However, of more clinical relevance is the formation of compound A. Compound A is a vinyl ether and is also produced when sevoflurane is heated in the presence of soda lime, as are low concentrations of several other degradation products, termed compounds B, C, D, and E. Compound A is formed as a result of an elimination reaction initiated by proton abstraction. The presence of sodium or potassium hydroxide is fundamental to this reaction.⁸

During clinical anesthesia, nonenzymatic degradation of sevoflurane by the carbon dioxide absorbent (soda lime or barium hydroxide lime) results in concentrations of compound A that may reach peaks of approximately 30 ppm and 40 ppm, respectively.⁹ Studies in both animals and humans have not fully allayed the concerns regarding the possible toxicity of compound A.^{3,10-15} In view of these various findings, there is continuing concern that compound A might cause renal injury in hu-

mans who undergo low-flow anesthesia with sevoflurane. We have shown that if NaOH or KOH are removed from the carbon dioxide absorbent, then compound A is not produced by normally hydrated Amsorb. This suggests that the presence of strong bases, such as sodium hydroxide and potassium hydroxide, may be a factor in the dehalogenation of sevoflurane to compound A.

Another concern with the use of soda lime as a carbon dioxide absorbent is the generation of carbon monoxide within low-flow breathing systems. A recent case report identified carboxyhemoglobin concentrations of more than 30% during inhalation anesthesia.¹⁶ Again, these observations are supported by data from both animal and human investigations.¹⁷⁻¹⁹ Signs and symptoms of carbon monoxide toxicity may be masked during anesthesia.²⁰ Carbon monoxide is neurotoxic and cardiotoxic, and the ill patient is especially vulnerable.²¹ A recent study predicted that severely anemic patients may have carboxyhemoglobin concentrations in the lethal range after 30 min of exposure to carbon monoxide from desflurane breakdown.²² Patients with advanced coronary artery disease and angina pectoris experience a significant decrease in exercise tolerance after exposure to low concentrations of carbon monoxide sufficient to increase their carboxyhemoglobin saturation to 5%.²³ Indeed, it has been suggested that there is no concentration of carbon monoxide that does not exert a significant stress on patients with advanced cardiovascular disease.²⁴

The mechanism by which carbon monoxide formation from volatile anesthetics occurs remains unclear. However, in a series of experiments, Baxter *et al.*⁴ postulated that base-catalyzed difluoromethoxy proton abstraction is an initial step in carbon monoxide formation. Their results also confirm that this base-catalyzed reaction was greater with potassium than with sodium hydroxide. To deal with this problem, we removed NaOH and KOH from the absorbent. This offers a more logical approach than that advocated by Baxter *et al.*, who suggest designing a safer anesthetic that does not undergo carbon dioxide absorbent-catalyzed degradation to carbon monoxide.⁴ We have shown that carbon monoxide was not produced when either oven or gas dried absorbent without the presence of strong base was exposed to desflurane, enflurane, and isoflurane. Thus, CaOH₂ alone is not capable of initiating the reaction responsible for carbon monoxide production, and it is the presence of NaOH and/or KOH within the current carbon dioxide absorbents that mediates the degradation of volatile anesthetics to carbon monoxide.

Amsorb as tested under the conditions of this study does not produce clinically significant amounts of carbon monoxide in the first minute of reaction. Levels of carbon monoxide far in excess of 600 ppm have been observed in previous studies.^{4,5,16,18} The important issue in the present study is the complete absence of carbon monoxide generation observed at the specific measurement interval when Amsorb was exposed to desflurane, isoflurane, and enflurane.

In conclusion, our *in vitro* data show that Amsorb is an effective carbon dioxide absorbent. It seems to be chemically unreactive with modern volatile anesthetics because of the absence of strong alkali within the granule matrix.

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Appendix: United States Pharmacopeia XXII: National Formulary Requirements

Carbon Dioxide Absorbents

The efficient absorption of carbon dioxide is of critical importance in operating apparatus used for administering anesthetic gases and oxygen and for determining the metabolic rate through measurement of the respiratory exchanges. For this reason, the United States Pharmacopeia National Formulary standards are provided in this section for soda lime carbon dioxide absorbent

Soda Lime

Soda lime is a mixture of calcium hydroxide and sodium or potassium hydroxide, or both. It may contain an indicator that is inert

toward anesthetic gases such as ether, cyclopropane, and nitrous oxide and that changes color when the soda lime no longer can absorb carbon dioxide.

Identification. A. Place a granule of soda lime on a piece of moistened red litmus paper: the paper turns blue immediately. B. A solution of soda lime in acetic acid responds to tests for calcium. It also imparts a yellow color to a luminous flame, which, when viewed through cobalt glass, may show a violet color.

Size of Granules. Screen 100 gm soda lime for 5 min as directed under *Powder Fineness: Method for Determining Uniformity of Fineness* using a mechanical shaker. It passes completely through a no. 2 standard mesh sieve, and not more than 2.0% passes through a no. 40 standard mesh sieve. Not more than 7.0% is retained on the coarse-mesh sieve, and not more than 15% passes through the fine-mesh sieve designated on the label.

Loss on Drying. In a tared weighing bottle, weigh accurately approximately 10 gm soda lime, and dry it at 105°C for 2 h. It loses not less than 12.0% and not more than 19.0% of its weight.

Moisture Absorption. Place approximately 10 gm soda lime in a tared weighing bottle with a diameter of 50 mm and a height of 30 mm, and weigh it. Then place the bottle, with cover removed, for 24 h in a closed container in which the atmosphere is maintained at 85% relative humidity by being in equilibrium with sulfuric acid with a specific gravity of 1.16, then weigh again. The increase in the weight is not more than 7.5%.

Hardness. Screen 200 gm soda lime on a mechanical sieve shaker, with a frequency of oscillation of 285 ± 3 cycles per minute, for 3 min to remove granules both coarser and finer than the labeled particle size. Weigh 50 gm of the granules retained on the screen and place them in a hardness pan with a diameter of 200 mm, a concave brass bottom 7.9 mm thick at the circumference and 3.2 mm thick at the center, and an inside spherical radius of curvature of 109 cm. Add 15 steel balls of 7.9 mm diameter and shake on a mechanical sieve shaker for 30 min. Remove the steel balls, brush the contents of the hardness pan onto a fine-mesh sieve, shake for 3 min on the mechanical sieve shaker, and weigh. The percentage of soda lime retained on the screen is not less than 75%, and represents the hardness.

Carbon Dioxide. The test apparatus consists of a temperature-controlled cavity that is uniformly packed with a weighed, uniform particle size sample of soda lime absorbent. A constant flow of 4% carbon dioxide is passed through the cavity. When the effluent carbon dioxide reaches 0.5%, the test is ended, and the time per unit weight of the absorbent is recorded. This should exceed 210 min/kg of absorbent.

Packaging and Storage. Preserve in tight containers. Do not expose packaging to harsh environmental conditions.

Labeling. If an indicator has been added, the name and color change are stated on the container label. The container label also indicates the mesh size in terms of standard-mesh sieve sizes.