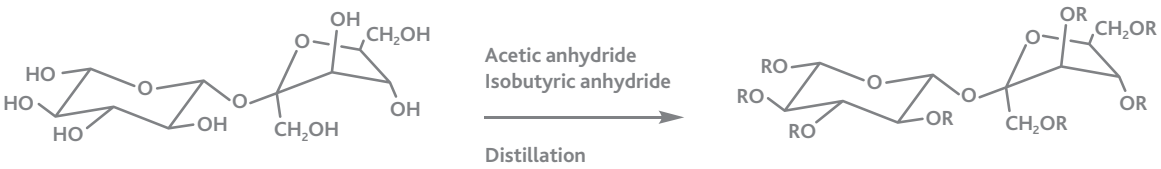
EASTMAN

Eastman BioSustane™ SAIB NF

for the development of abuse-deterrent formulations of opioid drugs

Eastman BioSustane™ SAIB NF is manufactured by Eastman in a dedicated Current Good Manufacturing Practices (cGMP) plant through the controlled esterification of sucrose with a mixture of acetic and isobutyric anhydrides and is highly purified by distillation. The chemical structure of BioSustane is shown in Figure 1.

Figure 1. Chemical structure of BioSustane



Sucrose
CAS 57-50-1

Sucrose acetate isobutyrate
CAS 126-13-6, 27216-37-1, or 137204-24-1

R = acetyl, isobutyl, or H
acetyl:isobutyl = 2:6 approx.

Note: Product is isomeric mixture.

Table 1. Typical physical and chemical properties of BioSustane[a]

Property	BioSustane SAIB NF
Molar mass, g/mol	832–856
Density @ 25°C, g/mL	1.15
Flash point, Cleveland open cup, °C (°F)	260 (500)
Solubility in water, wt%	0.1
Refractive index, nD20	1.454
Hydrolysis stability (refluxed in water for 96 hours), % wt loss	0.3
Vapor pressure, mm Hg @ 20°C	40
Brookfield viscosity, cP @ 30°C @ 100°C	 100,000 105

[a] *Properties reported here are typical of average lots. Eastman makes no representation that the material in any particular shipment will conform exactly to the listed properties.*

Viscosity behavior of BioSustane is shown in Figure 2 and Figure 3.

Figure 2. Viscosity behavior of BioSustane @ 50°C

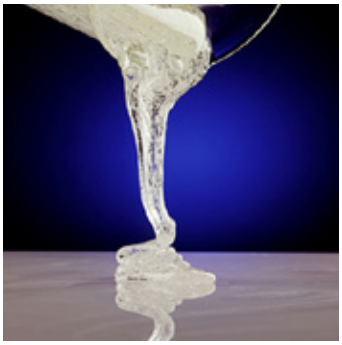
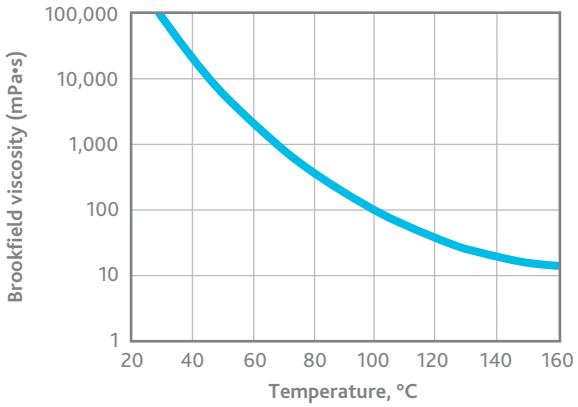


Figure 3. Viscosity/temperature behavior



Eastman BioSustane™ SAIB NF has numerous attributes that make it useful for drug delivery applications:

- High-viscosity liquid depot for extended drug delivery in enteral, parenteral, and topical applications
- Very good drug carrier and solvent for hydrophobic active ingredients
- Does not crystallize, so it remains amorphous at ambient temperature or when injected into tissue; this greatly facilitates a constant rate of drug delivery.
- Nonpolymeric, so it will not coagulate or precipitate when in contact with aqueous body fluids
- Soluble in many organic solvents and compatible with a wide range of materials
- The room-temperature viscosity of SAIB is significantly lowered by small amounts of organic solvent.
- Dispersible in water with the aid of organic solvents (alcohols, ketones, or esters) and surfactant, which makes it useful for making creams, ointments, and suspensions
- Bioadhesive properties; useful in transdermal, sublingual, and buccal patch applications

The use of BioSustane SAIB NF is being explored for its utility in opioid abuse drug formulations. In a model study conducted by researchers at Texas A&M's Irma Lerma Rangel College of Pharmacy, the feasibility of using BioSustane SAIB NF in opioid deterrent formulations was investigated. The scope and results of this study are presented in the following section.

Experimental design

Opioid abuse is an epidemic problem in the U.S. and can be gauged by consumption level. The U.S. constitutes 5% of the world's population but consumes 80% of global opioids. The U.S. Food and Drug Administration (FDA) has taken a lead among other federal agencies in combating prescription abuse by promoting abuse-deterrent formulations (ADFs). The agency has approved 10 ADF products. Seven products are based on a physical/chemical barrier approach, while three products are based on an agonist/antagonist combination design. Most ADFs are based on Polyox™, hypromellose, or both.

Model drug: Pseudoephedrine hydrochloride was used as a model based on the similarity of its physicochemical properties with those of opioid drugs (oxycodone, oxymorphone, hydrocodone, hydromorphone, morphine, etc.).

Experimental matrix

Table 2. Formulations

Ingredients	Formulation									
	F1-Control	F5-Control	F1	F2	F3	F4	F5	F6	F7	F8
Pseudoephedrine HCl	30	30	30	30	30	30	30	30	30	30
BioSustane	—	—	16.78	25.17	33.56	41.95	50.34	16.78	25.17	33.56
Polyethylene oxide	151.0	117.5	151.0	142.63	134.24	125.85	117.46	—	—	—
Hydroxypropyl methylcellulose K 100 M	—	—	—	—	—	—	—	151.02	142.63	134.24
Tocopherol acetate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Microcrystalline cellulose	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Colloidal silicon dioxide	6	6	6	6	6	6	6	6	6	6
Total (mg)	**219**	**186**	**236**	**236**	**236**	**236**	**236**	**236**	**236**	**236**

Drug: 12.7%
Sucrose acetate isobutyrate level: 7.1%–21.3%
Polymer level (polyethylene oxide and/or hydroxypropyl methylcellulose): 49.8%–64.0%
Microcrystalline cellulose: 12.7%
Tocopherol acetate: 0.085%
Magnesium stearate: 0.85%
Colloidal silicon dioxide: 2.5%

Method of addition of BioSustane SAIB NF

Method 1—Polymer (polyethylene oxide and/or hydroxypropyl methylcellulose) and tocopherol acetate are granulated with alcoholic solution of BioSustane. Formulations are uncured as well as heat cured (90°C for 30 minutes).

Method 2—Pseudoephedrine HCl, polymer (polyethylene oxide and/or hydroxypropyl methylcellulose), and tocopherol acetate are granulated with alcoholic solution of BioSustane. Formulations are uncured as well as heat cured (90°C for 30 minutes).

Abuse deterrence evaluation

Those choosing to abuse opioid medications for nontherapeutic or recreational reasons often chew the pill to release the drug quickly, or more commonly, crush it for inhalation or solubilize it for injection. The goal of most abuse deterrent formulations is to impose mechanical barriers that make crushing or chewing the pill difficult.

Tablet hardness/mechanical strength

Biting force of a human is approximately 50 kg or 490 N. The hardness of SAIB formulations is >490 N after heat curing. Therefore, BioSustane does not interfere with crush-resistant properties of Polyox™ polymer. Crush-resistant formulations are difficult to manipulate, and abusers must make great effort to manipulate these formulations.

Table 3. Tablet hardness measurements

Formulation	Method of manufacturing	Uncured	Cured
Uncured		Hardness (force to fracture, N)	
F1(1)	Method 1	58.3 ± 1.2	>490
F2(1)		36.4 ± 3.3	>490
F3(1)		31.2 ± 1.0	>490
F4(1)		17.0 ± 0.9	>490
F5(1)		22.0 ± 3.5	>490
F1(2)	Method 2	45.4 ± 4.0	>490
F2(2)		31.4 ± 3.6	>490
F3(2)		29.1 ± 3.0	>490
F4(2)		25.8 ± 1.8	>490
F5(2)		18.5 ± 1.6	>490
F1-Control		41.5 ± 0.4	>490
F5-Control		53.5 ± 12.5	>490

Nasal abuse assessment

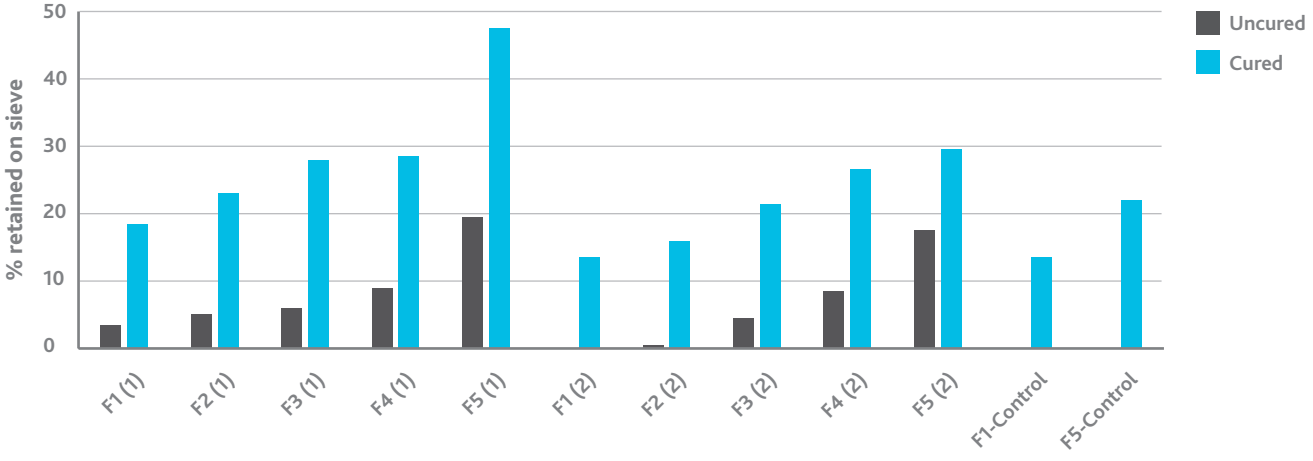
Formulations have nasal abuse potential if they can be powdered to particles of <500 µm. Each formulation was ground in a standard coffee grinder for one minute and three minutes and then the particle size distributions were determined.

Table 4. Particle size distribution after grinding

Formulation	Method of manufacturing	Grinding time (min)	% retained on sieve #18	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)
Uncured						
F1(1)	Method 1	1	3.8	2.6 ± 1.4	21.6 ± 10.8	58.4 ± 9.5
F2(1)			5.2	9.1 ± 0.5	98.8 ± 9.9	291.2 ± 11.6
F3(1)			6.1	4.8 ± 1.2	93.2 ± 10.3	339.6 ± 17.5
F4(1)			9.2	15.9 ± 7.1	129.9 ± 20.6	320.4 ± 35.3
F5(1)			19.5	25.0 ± 6.8	148.1 ± 7.5	346.4 ± 12.6
F1(2)	Method 2		0.0	7.1 ± 3.5	90.0 ± 4.0	268.9 ± 6.2
F2(2)			0.5	8.6 ± 0.3	95.4 ± 2.2	291.1 ± 6.5
F3(2)			4.6	14.6 ± 8.3	100.1 ± 3.9	357.4 ± 48.8
F4(2)			9.0	17.4 ± 0.5	139.9 ± 6.5	327.5 ± 31.9
F5(2)			17.5	28.7 ± 7.1	148.0 ± 9.5	319.5 ± 18.5
F1-Control			0.0	0.7 ± 0.9	33.2 ± 14.0	241.7 ± 11.0
F5-Control			0.0	1.4 ± 1.0	64.2 ± 8.9	266.4 ± 7.6
Cured						
F1(1)	Method 1	3	18.7	2.3 ± 0.6	75.3 ± 4.7	372.7 ± 6.1
F2(1)			22.8	2.5 ± 1.9	82.3 ± 7.0	395.7 ± 14.4
F3(1)			27.7	4.7 ± 0.1	94.1 ± 3.3	388.8 ± 27.5
F4(1)			28.2	11.6 ± 0.7	144.8 ± 9.9	387.2 ± 12.0
F5(1)			47.9	41.6 ± 6.9	216.0 ± 18.0	421.3 ± 32.5
F1(2)	Method 2		13.8	4.4 ± 0.2	70.2 ± 3.0	349.3 ± 6.5
F2(2)			16.0	3.9 ± 0.1	77.7 ± 2.4	369.6 ± 0.9
F3(2)			21.3	5.3 ± 0.2	123.4 ± 8.7	381.5 ± 8.0
F4(2)			26.7	11.1 ± 1.3	126.4 ± 4.1	374.5 ± 25.4
F5(2)			29.6	16.8 ± 0.4	144.5 ± 7.4	367.4 ± 14.5
F1-Control	NA		13.8	1.5 ± 0.0	13.3 ± 2.3	338 ± 6.4
F5-Control	NA		22.0	1.1 ± 0.0	7.3 ± 1.7	284.6 ± 9.4

Addition of SAIB increases the particle size, and up to 47% of the ground powder is >1 mm. See Figure 4.

Figure 4. Percentage tablet powder retained on sieve after grinding



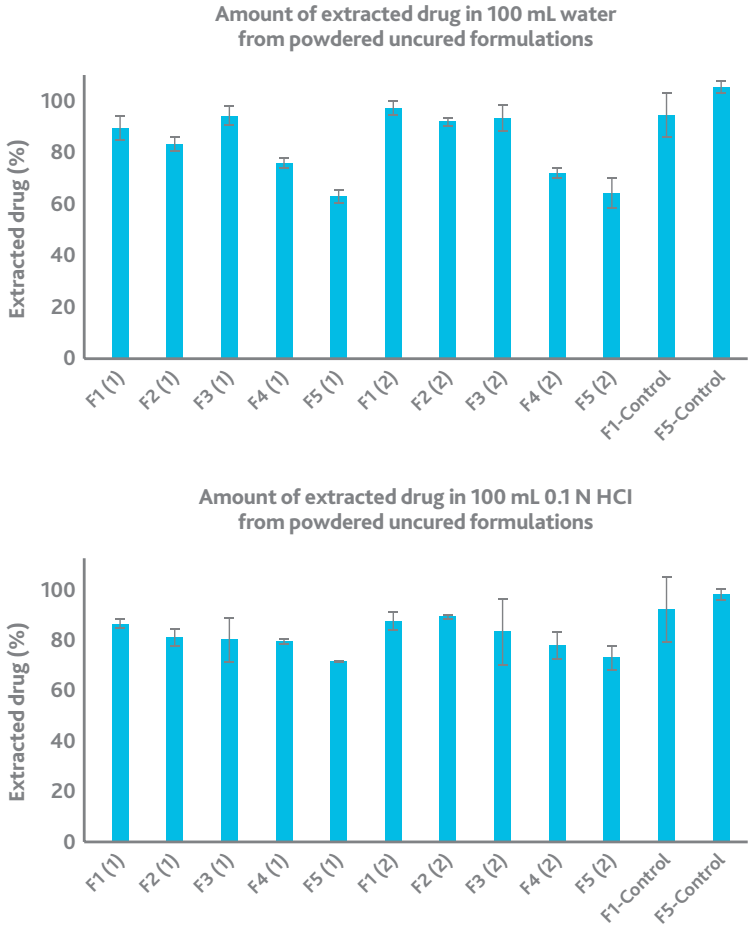
Oral and parenteral abuse assessments

Abusers attempt to extract the drug in commonly used solvents and then ingest or inject for immediate euphoric effect. Extraction studies were performed on intact and powdered tablets to evaluate the potential of pseudoephedrine extraction using various solvents and conditions (Table 5). Intact tablets or powdered tablets were added to a beaker containing 100 mL or 10 mL of solvent. The sample container was stirred for 15 seconds before withdrawing a sample of 100 µL for analysis. Samples were diluted before injecting into HPLC system. All studies were performed in triplicate.

Table 5. Conditions for extraction of pseudoephedrine HCl

Extraction solvent	Solvent volume	Temperature	Sample	Time
Water	100	RT	Intact and powdered	5 min and 30 min
Ethanol	100	RT	Intact and powdered	5 min and 30 min
0.1 N HCl	100	RT	Intact and powdered	5 min and 30 min
0.1 NaOH	100	RT	Intact and powdered	5 min and 30 min

Figure 5. Extractions of uncured powdered formulations



The addition of SAIB decreases the amount of extracted drug by 41.3%–42.5%, 24.8%–26.1%, and 37.4%–50.6% in water, 0.1 N HCl, and 0.1 N NaOH solvents, respectively, when compared with control formulations.

Extraction of powdered cured and uncured formulations with ethanol and evaporation of the solvent leads to a sticky mass unsuitable for parenteral or nasal delivery.

Dissolution

Dissolution testing was performed in USP apparatus 1 with spindle speed of 100 rpm. All tablets were tested in dissolution medium of 900 mL of water at 37°C for 9 h. Samples of 1 mL were withdrawn and filtered through nylon filters (0.45 µm, 25 mm). The drug dissolved was determined by HPLC method. The experiments were performed in triplicate.

Figure 6. Dissolution of uncured formulations

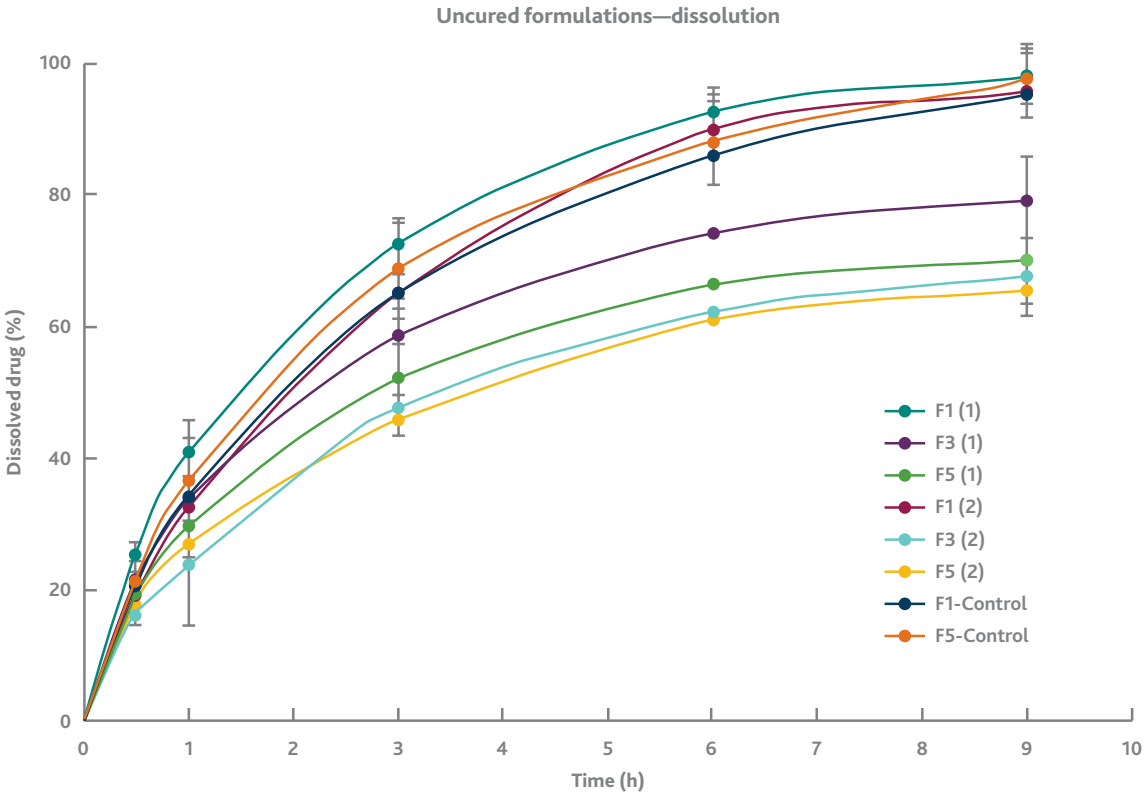
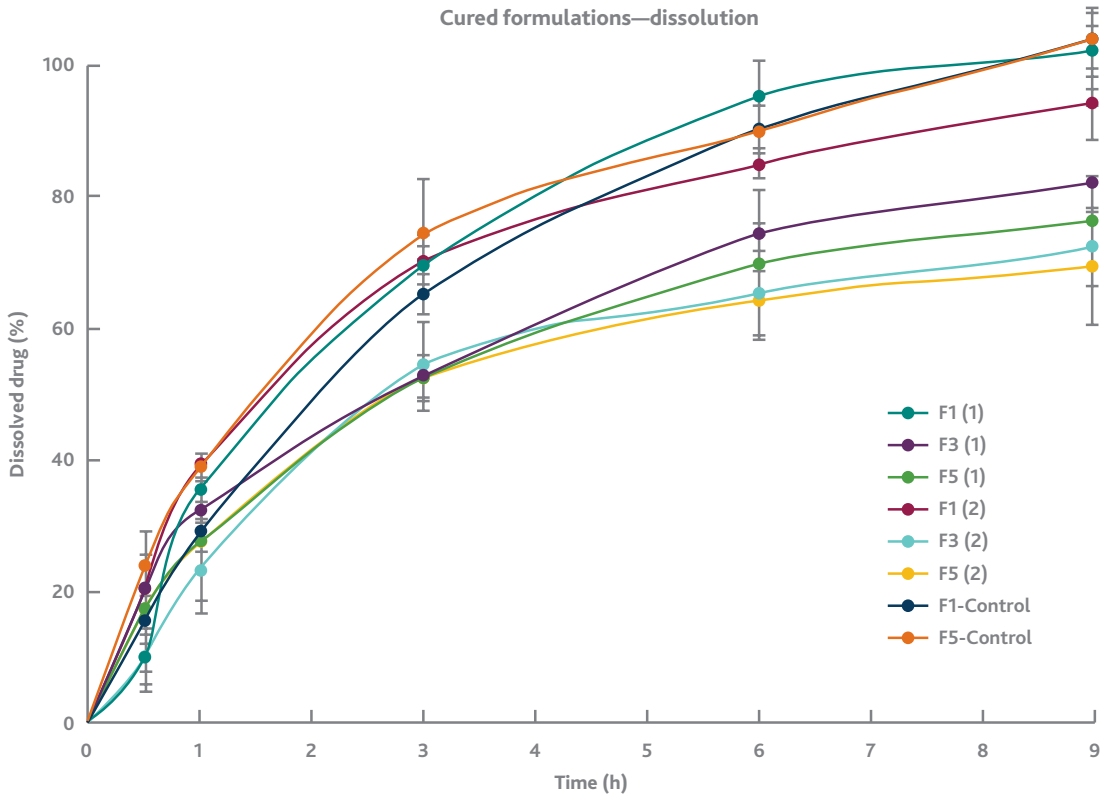


Figure 7. Dissolution of cured formulations



Note: Additional data available on request through your Eastman representative.

Conclusions

- SAIB is a legitimate deterrence tool for opioid drug formulations based on results from experiments involving particle size reduction, tablet hardness, and water and alcohol extraction.
- When compared with control formulations, addition of SAIB decreases the amount of extracted drug by 41.3%–42.5%, 24.8–26.1%, and 37.4%–50.6% when extracted with water, 0.1 N HCl, and 0.1 N NaOH, respectively. It is expected that formulations containing SAIB will deter abusers from pursuing oral, nasal, and parenteral routes.
- Extraction with organic solvents yields sticky residues that are difficult to abuse by various routes (injection, ingestion, nasal, etc.).
- Opioid dissolution profile is heavily influenced by the amount of SAIB in the formulation.

Regulatory status

Eastman BioSustane™ SAIB NF is manufactured in a dedicated facility in accordance with Current Good Manufacturing Practices as provided for in the *Joint International Pharmaceutical Excipient Council—Pharmaceutical Quality Group Good Manufacturing Practices Guide for Pharmaceutical Excipients 2006* and meets specifications listed in the current product sales specification (Specification No. 21404). Drug Master File 19694 is on file with the U.S. FDA. BioSustane (sucrose acetate isobutyrate) is listed in the FDA Inactive Ingredient Database (IID) and has a published United States Pharmacopeia-National Formulary (USP-NF) monograph.

Packaging

Eastman BioSustane™ SAIB NF is packaged in epoxy phenolic-lined 215.4-kg (475-lb) net weight steel drums.

Storage and handling

Stability studies have been conducted on samples of BioSustane stored in epoxy phenolic-lined steel drums. The drums of material were stored in stability chambers under controlled conditions of 30°C/60% relative humidity in Kingsport, Tenn. Based on these studies, BioSustane should retain its sales specification properties for three years when stored in its original unopened container and protected from excessive light, moisture, and extremes in temperature.

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PHMA-7888A 5/21