

Comparative Summary **SWELL vs. Analogous Carbomers**

SWELL

SWELL PS-100 (“SWELL”) is an ultra-high molecular weight, ingestible, pharmaceutical-grade (purity >99.995%), bioinert, carbomer fiber (CAS No. 27599-56-0) comprised of a highly proprietary lightly PEGylated [partial] sodium salt of Polyacrylic Acid used as a temporary gastric bulking agent determined to be useful as a weight management adjunct. SWELL is classified as a Type A Carbomer Homopolymer. SWELL is manufactured without the use of benzene, instead uses a proprietary supercritical fluid technology to form superabsorbent microspheres under fully compliant cGMP conditions. SWELL is self-affirmed to be GRAS and is currently commercialized in capsule form, mixed with L-Leucine (CAS No. 61-90-5) as a glidant. SWELL is sold in the United States as a dietary supplement, and elsewhere as a Class IIa Medical Device; and meets all current regulatory standards established for these designations, as well as the FDA’s newly proposed NDI guidelines.

Carbomers as a Subclass of SAP Compounds:

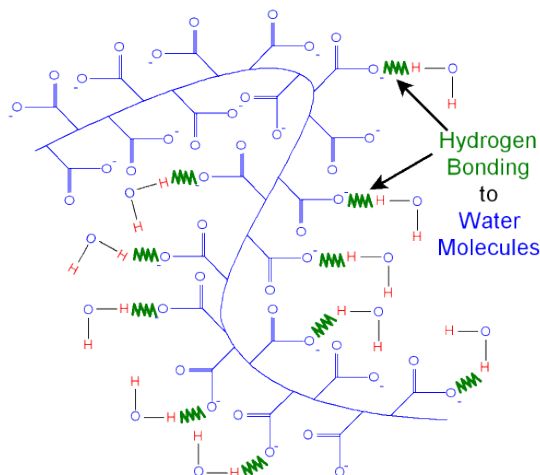
History, Structure and Synthesis

All Carbomers are Superabsorbent Polymers (SAP), but not all SAPs are Carbomers. Carbomers were first prepared and patented in 1957 and have been in wide commercial use in the medical, pharmaceutical and consumer products industries since. A number of ingestible applications including extended release tablet formulations, which involve Carbomer matrices, have been patented. Carbomers readily absorb water, get hydrated and swell - as much as 1,000x g/g. In addition to their hydrophilic nature, their cross-linked structure is essentially insoluble in water, making Carbomers ideal for use in controlled release drug delivery systems, dentifrices, and other ingestible forms. Hundreds of Carbomer Analogues are sold under many trade names to provide a wide variety of indications (See Appendix 1).

Carbomers are commonly made from the polymerization of acrylic acid blended with sodium hydroxide in the presence of an initiator to form a poly-acrylic acid sodium salt (Sodium Polyacrylate). Carbomers are the most common subclass of SAP made in the world today. When other side chain materials are used instead to make a superabsorbent polymer they are not classified as Carbomers. Such materials include: polyacrylamide copolymer, ethylene maleic anhydride copolymer, cross-linked carboxymethylcellulose, polyvinyl alcohol copolymers, cross-linked polyethylene oxide, and starch grafted copolymers of polyacrylonitrile (PAN); to name a few.

The starch-grafted PAN is one of the oldest SAP forms, but was discontinued in the late 1990's. Modern superabsorbent polymers are typically made using one of three synthesis methods: (1) suspension polymerization, (2) solution polymerization or (3) gel polymerization. Each process has certain advantages over the others and there are trade-offs between them. All yield a consistent quality of product.

One subset of Carbomers are the Carbomer Hydrogels. All Carbomer Hydrogels have three characteristics in common: a) They all are comprised of side chains of polymerized acrylic acid (PAA); b) they are extremely large; weighing into the billions of Daltons, and c) each is cross-linked with a smaller chemical moiety which defines an interpenetrating network that promotes the ingress and hydrogen bonding of free water into the polymer matrix (See Below). Common cross-linkers include: Polyethylene Glycol, methylenebisacrylamide (BIS), diacrylate, and many others.



Schematic of Carbomer Structure

Carbomer Classifications

Carbomers can be grouped together and further classified as:

1. Carbomer Homopolymers (Types A, B and C)
2. Carbomer Copolymers
3. Carbomer Interpolymers

This classification depends on a Carbomer's side chain composition, physical properties and the solvents used (benzene is common and has been determined to be of great concern due to its carcinogenic potential). See Appendix 2.

Ingestible Applications of Carbomers:

The readily water-swallowable Carbomer polymers are used in a diverse range of pharmaceutical and ingestible applications to provide:

1. Controlled release in tablets.
2. Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications.
3. Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
4. Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
5. Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

Several properties of Carbomers make them especially valuable as ingestible forms and pharmaceutical excipients for numerous applications. (See References Below).

International Carbomer Classification Nomenclature:

The USP-NF, European Pharmacopoeia, British Pharmacopoeia, United States Adopted Names Council (USAN), and International Nomenclature for Cosmetic Ingredients (INCI) have adopted the generic (i.e., non-proprietary) name “carbomer” for Type A Homopolymers. The Japanese Pharmacopoeia states, Type A Homopolymers as “carboxyvinyl polymer” and “carboxy polymethylene.” The Italian Pharmacopoeia also identifies Type A Homopolymers as “carboxy polymethylene” and the Deutschen Arzneibuch calls Type A Homopolymers “polyacrylic acid.” Carbomer copolymers, such as Carbopol 1342 NF and 1382, have also been named “carbomer” by the USP-NF, but are considered “Acrylates/C10-C30 Alkyl Acrylates Cross polymer” by the INCI.

Analogous Carbomer Toxicity Studies: The Carbopol Series

Type A Carbomer Homopolymers, like other high molecular weight polymers, demonstrate a low toxic and irritation potential based on their physical and chemical properties. Accordingly, such cross-linked, high molecular weight acrylic acid polymers have been found safe for use in a wide variety of cosmetics, detergents, ingestible forms and pharmaceuticals by appropriate regulatory and non-regulatory bodies concerned with such products. Acute oral studies with rats, guinea pigs, mice and dogs showed that Carbomers 910, -934, -940 and 941 have low toxicities when ingested. The inhalation LC₅₀ of Carbomers 910 in albino rats was 1.71mg/l. The dermal LD₅₀ of rats exposed to Carbopol 910 was greater than 3.0 g/kg. No mortalities occurred in rabbits injected intravenously with 1%, 2% or 3% Carbopol 934 in aqueous solution at a dose of 5 ml/kg. Rabbits showed minimal skin irritation when tested with 100% Carbopol 910 or 934, and zero to moderate eye irritation when tested with Carbomers 910, 934, 940, 941 and/or their various salts at concentrations of 0.20% to 100%. When Carbopol 934P was fed orally to dogs and rats, there was no significant effect on body weight, food consumption, mortality, behavior, and blood chemistry. The Cosmetic Ingredient Review Expert Panel called attention to the presence of benzene as an impurity in many Carbopol polymers and has recommended efforts to reduce it to the lowest possible level. SWELL contains no benzene in its manufacture.

SWELL: Analogous Carbomer Comparison

Carbomers that have a similar classification, macromolecular size, physical characteristics and chemical structures are called Analogous Carbomers. SWELL is analogous to all other Type A Carbomer Homopolymer Hydrogels in wide commercial use today (See Table 1. below). SWELL has: a) PAA side chains; b) it is cross-linked with PEG; c) it is billions of Daltons by weight; and uses supercritical CO₂ instead of Benzene as the solvent in the synthesis process. What most differentiates SWELL is its extreme purity (less than 50ppm acrylic acid monomer present; 99.995% pure USP grade) as compared to USP NF pharmaceutical grade Carbopols like 974P, 971P and 71G NF, which specify acrylic acid monomer content of <1,000ppm. (See Example 1. Below)

As a result of these attributes SWELL can be positively compared to any number of other Analogous Carbomers. One such group would include the Carbopol series of polymers by Lubrizol / Noveon (See Table 1 Below). Both SWELL and the Carbopol SAPs are Type A cross-linked Carbomer Homopolymers of Polyacrylic acid. They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a single molecule having a network structure of polymer chains interconnected via cross-linking weighing billions of Daltons (i.e., significantly larger than any human cell).

Carbopol Homopolymer Toxicology Studies

The following tests were performed on powdered Carbopol Homopolymers:

Human Repeated Insult Patch Tests

Carbopol homopolymer was impregnated into a 1" X 1" square piece of surgical gauze and moistened with 0.2 mL distilled water just prior to application to the skin of 54 human volunteers. In order to evaluate the skin irritation and sensitization potential of this product, a series of 12 applications was conducted with each panelist during the primary/induction phase. On four consecutive days of weeks 1, 2 and 3, the patch containing the test material was applied to its designated site. The patches were removed and the contact sites were examined 24 hours after each application. Following a one week rest period (week 4) a challenge phase was conducted on week 5 with 4 applications of the test material on a virgin site of each volunteer. Carbopol homopolymer produced no visible effect in 41 subjects out of 54 during the primary irritation/activation period. Faint or moderate reddening of the skin occurred on one occasion in 10 subjects, 2 times on one subject and 4 times on another subject. These effects would put Carbopol homopolymer in the category of a weak skin irritant. Two subjects out of 53 displayed solitary episodes of faint or moderate reddening in the challenge phase; however, the investigators concluded they did not display a sensitizing reaction. It was concluded that the results furnish no basis for contraindicating skin contact with Carbopol Homopolymers under similar or less stringent conditions than the testing conditions used.

Skin Irritation

The skin irritation potential of Carbopol homopolymer was evaluated in rabbits in accordance with FHSA regulations. Each of six rabbits received a 0.5g dose of the test article as dermal application to both an intact and abraded test site. The dose was held in contact with the skin under a semi-occlusive binder for an exposure period of 24 hours. Following the exposure period, the binder was removed, and the remaining test article was wiped from the skin using gauze and distilled water. The test sites were subsequently examined and scored for dermal irritation for up to three days following patch removal. Although slight well-defined erythema (redness of the skin) was noted at 25 hours, all responses had subsided by the 72 hours observation. No edema (swelling) was noted at any test site. Under the test conditions, Carbopol homopolymer is considered a slight irritant to rabbit skin. The calculated Primary Irritation Index for Carbopol homopolymer is 0.58.

Eye Irritation

The eye irritation potential of Carbopol homopolymer was evaluated. A standard amount, 0.1g (or 0.1 mL of the dilute solution) of the test material was administered to groups of six albino rabbits. The respective test material was instilled into the conjunctival sac of one eye of the test animals while the other eye served as a control. The eyes were not washed after instillation. A similar procedure was followed on an additional three animals, with the exception that saline rinse was used. In the no-rinse group, Carbopol homopolymer produced minimal conjunctivitis in 6 of 6 test animals at 24 hours. Redness and swelling persisted to the study termination (7 days) in 4 of 6 rabbits. Similar responses were seen in the rinse group. It was concluded that Carbopol homopolymer was not considered to be an eye irritant (rabbit) based on the no-rinse group according to FHSA evaluation criteria.





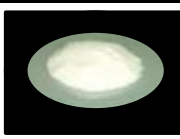
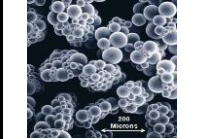
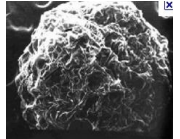
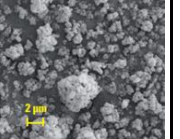
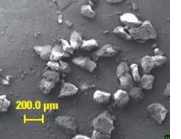
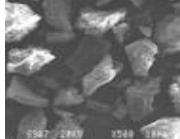
Summary

Type A Carbomer Homopolymers like SWELL are non-toxic and do not present any significant risk to human health.

Table 1.

Comparison of Analogous Type A Carbomer Homopolymers

The following summarizes a comparison of the principle characteristics and properties of SWELL vs. four Carbomer analogues. As can be readily appreciated, the similarities are evident.


Comparison of Properties and Specifications SWELL vs. Carbopol and Polycarbophil Analogues					
Properties/Specifications	SWELL PS-100	Carbopol Analogues			Carbopol EX83 (Polycarbophil)
		974P	971P	71G NF	
Powder					
Electronmicrograph					
CAS No.	27599-56-0	9003-01-4			126040-58-2
Safety	Self-directed GRAS	Self-directed GRAS			N/A
Avg Mol Weight	Billions of Daltons	Billions of Daltons			Billions of Daltons
Side Chains	Polyacrylic Acid	Polyacrylic Acid			Polyacrylic Acid
PAA Oral LD50 Rat	No Data Available	No Data Available			No Data Available
Cross-linker	PEG 400-600	allyl penta erythritol			Divinyl Glycol
Cross-link MW	500 pref	176.2			114.1
Cross-Link Oral LD50 Rat	30g/kg	19.5g/kg			1.6g/kg
Cross-link Density	1% to 10%	25% to 50%	15% to 25%	15% to 25%	15% to 25%
Absorptive Rate	1 - 2 minutes	30 - 60 minutes			30 - 60 minutes
Absorptive Capacity (DI H ₂ O)	Up to 1,000 g/g	Up to 1,000 g/g			Up to 70 g/g
Gastric pH Optimized	Yes	No			No
Bioadhesive Rating	0 (5 max)	3 to 4 (5 Max)	2 to 3 (5 Max)	2 to 3 (5 Max)	4 (5 max)
95% Particle Size Retention	40 Mesh	240 Mesh	240 Mesh	150 Mesh	N/A
Solvent	Supercritical CO ₂	Ethyl Acetate			N/A
Monomer Content	<50 ppm	<1,000 ppm			N/A
Ash Content	0.008 ppm (average) **	<20,000 ppm			N/A
Heavy Metals	ND	<20 ppm			N/A
Appearance	Fine, white, granular	Fluffy, white, powder	Fluffy, white, powder	White, granular powder	Off-white, granular
Bulk Density	730 kg/m ³	208 kg/m ³	208 kg/m ³	325-400 kg/m ³	N/A
Specific gravity	1.84	1.41	1.41	1.41	N/A
Moisture content	2.0% (max)	2.0% (max)	2.0% (max)	2.0% (max)	N/A
Equilibrium moisture content	8.3% (@ 50% rh)	8-10% (@ 50% rh)	8-10% (@ 50% rh)	8-10% (@ 50% rh)	N/A
pKa	5.5 ± 0.5	6.0 ± 0.5	6.0 ± 0.5	6.0 ± 0.5	N/A
pH of 1.0% water dispersion	3.0	2.5 - 3.0	2.5 - 3.0	2.5 - 3.0	N/A
Glass transition temperature	104C (219F)	100-105C (212-221F)	100-105C (212-221F)	100-105C (212-221F)	N/A

Conclusions:


As can be readily observed above, SWELL is Analogous to other Type A Carbomers in the Carbopol family of SAP materials. SWELL would compare favorably to all other Type A Carbomer Homopolymers in a similar analysis.

SWELL's most distinguishing features are: high purity, rapid swelling, highly lubricious, solvent selection (CO₂), pH optimization and selection of PEG 500 as its preferred cross-linker.

Attested:



Signed



September 17, 2014
Date

Name: Dr. Richard Davis, MD

Title: President and Chief Science Officer

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Appendix 1.

Common Trade Names For Acrylic Acid Homopolymers

1. 2-Propenoic acid homopolymer (9CI)
2. 801 * Haloflex 202
3. Acrylic acid homopolymer
4. Acrylic acid polymer
5. Acrylic acid resin
6. Acrylic polymer
7. Acrylic resin
8. Acrysol A 1
9. Acrysol A 3
10. Acrysol A 5
11. Acrysol AC 5
12. Acrysol ASE-75
13. Acrysol WS-24
14. Antiprex 461
15. Antiprex A
16. Arasorb 750
17. Arasorb S 100F
18. Arolon
19. Aron
20. Aron A 10H
21. Atactic
22. Atactic poly(acrylic acid)
23. Carbopol 940
24. Carbopol 941
25. Carbopol 960
26. Carbopol 961
27. Carboset 515
28. Carboset Resin No. 515
29. Carboxy vinyl polymer *
30. Carboxypolymethylene
31. Carpolene
32. Colloids 119/50
33. Dispex C40
34. G-Cure
35. Good-rite K 37
36. Good-rite K 702
37. Good-rite K-700
38. Good-rite K727
39. Good-rite WS
40. Good-rite WS 801
41. Haloflex 208
42. Junlon 110
43. Jurimer AC 10H
44. Jurimer AC 10P
45. Nalfloc 636
46. Neocryl A-1038
47. OLD 01
48. P 11H
49. PA 11M
50. PAA-25
51. Poly(acrylic acid)
52. Polyacrylate
53. Polyacrylate elastomers
54. Polymer, carboxy vinyl
55. Polytex

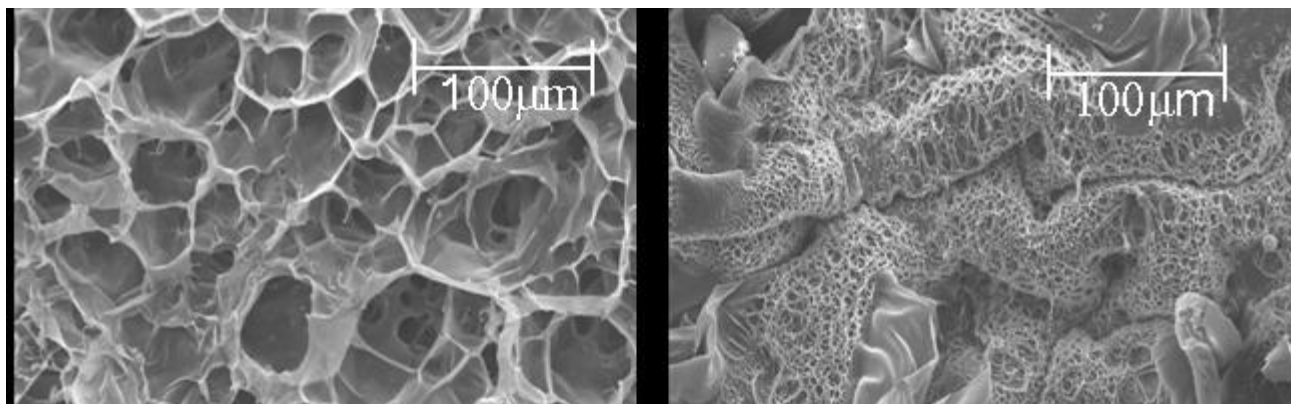
56. Primal ASE 60
57. R968
58. Racryl
59. Revacryl A 191
60. Rohagit SD 15
61. Sokalan PAS
62. Solidokoll N
63. Synthemul 90-588
64. TB 1131
65. Tecpol
66. Texcryl
67. Versicol E 7
68. Versicol E15
69. Versicol E9
70. Versicol S 25
71. Viscalex HV 30
72. Viscon 103
73. WS 24
74. WS-801
75. XPA

Carbomer Synonyms: [1/C3H4O2/c1-2-3\(4\)5/h2H,1H2,\(H,4,5, 101360-15-0, 10192-85-5, 104922-39-6, 105913-47-1, 10604-69-0, 11132-69-7, 125857-68-3, 14643-87-9, 15743-20-1, 165724-08-3, 174594-09-3, 2-propenoate, 2-Propenoic acid, 2-Propenoic acid, 2-methyl-, 2-hydroxyethyl ester, polymer with ethenyl acetate and 2-ethylhexyl 2-propenoate, 2-Propenoic acid, calcium salt, 2-Propenoic acid, homopolymer, 25987-55-7, 29862-29-1, 37241-23-9, 39341-22-5, 4-02-00-01455 \(Beilstein Handbook Reference\), 51142-25-7, 51366-35-9, 54182-57-9, 54578-44-8, 54990-82-8, 55488-18-1, 55927-87-2, 5651-26-3, 56747-65-0, 5698-98-6, 58197-53-8, 59233-19-1, 6292-01-9, 65742-16-7, 71767-27-6, 71767-28-7, 7446-81-3, 79-10-7, 81031-52-9, 82446-45-5, 87913-02-8, 88650-89-9, 9003-01-4, 9003-03-6, 9003-04-7, 9007-20-9, Acide acrylique \[French\], Acido acrilio \[Spanish\], Acroleic acid, Acrylate, Acrylic acid, Acrylic acid homopolymer, Acrylic acid polymer, Acrylic acid resin, Acrylic acid, calcium salt, Acrylic acid, glacial, Acrylic acid, inhibited \[UN2218\] \[Corrosive\], Acrylic acid, polymer, Acrylic acid, polymers, Acrylic polymer, Acrylic polymer resins, Acrylic resin, Acrysol A 1, Acrysol A 3, Acrysol A 5, Acrysol AC 5, Acrysol ase-75, Acrysol lmw-20X, Acrysol WS-24, A13-15717, AIDS-209945, AIDS209945, AKR, Antiprex 461, Antiprex A, Arasorb 750, Arasorb S 100F, Arolon, Aron, Aron A 10H, Atactic poly\(acrylic acid\), BRN 0635743, C00511, Calcium acrylate, Calcium diacrylate, Carbomer, Carbomer 1342, Carbomer 910, Carbomer 910 \[USAN\], Carbomer 934 \[USAN\], Carbomer 934p \[USAN\], Carbomer 940 \[USAN\], Carbomer 941 \[USAN\], Carbomer ;Carbopol 934P, Carbomere \[INN-French\], Carbomero \[INN-Spanish\], Carbomerum \[INN-Latin\], Carbopol, Carbopol 1342, Carbopol 910, Carbopol 934, Carbopol 934p, Carbopol 940, Carbopol 941, Carbopol 960, Carbopol 961, Carbopol 971P, Carbopol 974P, Carbopol 980, Carbopol 981, Carboset 515, Carboset Resin No. 515, Carboxy vinyl polymer, Carboxypolymethylene, Carboxypolymethylene resin, Carpolene, Caswell No. 009A, CCRIS 3234, CCRIS 737, CHEBI:18308, Colloids 119/50, Cyguard 266, Dispex C40, Dow Latex 354, EINECS 201-177-9, Ethylenecarboxylic acid, G-Cure, Glacial acrylic acid, Good-rite K 37, Good-rite K 702, Good-rite K 732, Good-rite K-700, Good-rite K727, Good-rite WS 801, Haloflex 202, Haloflex 208, HSDB 1421, Joncryl 678, Junlon 110, Jurimer AC 10H, Jurimer AC 10P, Kyselina akrylova \[Czech\], LMFA01030193, Nalfloc 636, Neocryl A-1038, NSC 106034, NSC 106035, NSC 106036, NSC 106037, NSC 112122, NSC 112123, NSC 114472, NSC 165257, NSC 4765, NSC4765, NSC8259, OLD 01, P 11H, P-11H, PA 11M, PAA-25, Pemulen TR-1, Pemulen TR-2, Poly\(acrylic acid\), Polyacrylate, Polyacrylate elastomers, POLYACRYLIC ACID, Polymer of 2-propenoic acid, cross-linked with allyl ethers of pentaerythritol, Polymer of 2-propenoic acid, cross-linked with allyl ethers of sucrose, Polymer of 2-propenoic acid, cross-linked with allyl ethers of sucrose or pentaerythritol, Polymer of acrylic acid, cross-linked with allyl ethers of pentaerythritol, Polymer of acrylic acid, cross-linked with allyl ethers of sucrose or pentaerythritol, Polymer, carboxy vinyl, Polymerized acrylic acid, Polytex 973, Primal ASE 60, prop-2-enoic acid, Propene acid, Propenoate, Propenoic acid, Propenoic acid polymer, R968, Racryl, RCRA waste no. U008, RCRA waste number U008, Revacryl A 191, Rohagit SD 15, Sokalan PAS, Solidokoll N, Synthemul 90-588, TB 1131, Tecpol, Texcryl, The viscosity of a neutralized 1.0 percent aqueous dispersion of Carbomer 1342 is between 9,500 and 26,500 centipoises, UN2218, Versicol E 7, Versicol E15, Versicol E9, Versicol K 11, Versicol S 25, Vinylformic acid, Viscalex HV 30, Viscon 103, WS 24, WS 801, XPA](#)

Hydrogel Synonyms: [1, 2-Bis\(methacryloyloxy\)ethane](#), [1,2-Bis\(methacryloyloxy\)ethane](#), [1,2-Ethanediy 2-methyl-2-propenoate](#), [108772-05-0](#), [121266-93-1](#), [121978-90-3](#), [12738-39-5](#), [130865-23-5](#), [135623-36-8](#), [138454-60-1](#), [138533-09-2](#), [141104-76-9](#), [154855-14-8](#), [156168-97-7](#), [156932-37-5](#), [156940-26-0](#), [170006-96-9](#), [2-Propenoic acid, 2-methyl-, 1, 2-ethanediy ester](#), [2-Propenoic acid, 2-methyl-, 1,2-ethanediy ester](#), [2-Propenoic acid, 2-methyl-, 1,2-ethanediy ester, homopolymer](#), [205501-13-9](#), [216753-70-7](#), [25721-76-0](#), [25852-47-5](#), [37211-46-4](#), [37311-07-2](#), [4-02-00-01532 \(Beilstein Handbook Reference\)](#), [51026-92-7](#), [56480-56-9](#), [62886-53-7](#), [73212-53-0](#), [81897-47-4](#), [92308-31-1](#), [97-90-5](#), [Ageflex EGDM](#), [BRN 1776663](#), [CCRIS 179](#), [Diglycol dimethacrylate](#), [EINECS 202-617-2](#), [Ethandiol dimethacrylate](#), [Ethylidiol metacrylate](#), [Ethylidiol methacrylate](#), [Ethylene dimethacrylate](#), [Ethylene glycol bis \(methacrylate\)](#), [Ethylene glycol bis\(methacrylate\)](#), [Ethylene glycol dimethacrylate](#), [Ethylene methacrylate](#), [Ethylenedimethacrylate](#), [Glycol dimethacrylate](#), [HSDB 5313](#), [Hydrogel](#), [Methacrylic acid ethylene ester](#), [Methacrylic acid, ethylene ester](#), [NSC 24166](#), [NSC24166](#), [Poly\(ethylene glycol dimethacrylate\)](#), [Poly\(oxy-1,2-ethanediy\)](#), [alpha-\(2-methyl-1-oxo-2-propenyl\)-omega-\(\(2-methyl-1-oxo-2-propenyl\)oxy\)-](#), [Poly\(oxy-1,2-ethanediy\)](#), [alpha-\(2-methyl-1-oxo-2-propenyl\)-omega-\(\(2-methyl-1-oxo-2-propenyl\)oxy\)-](#), [Polyethylene glycol dimethacrylate](#), [Sartomer SR 206](#), [SR 206](#), [ZINC01608917](#)

Example 1.

A team of scientists at Stanford and IBM have developed a novel synthesis method to control the porosity of hydrogels by varying monomer concentration. A model reaction for the cross-linking identified the critical monomer concentration dependent reaction regimes, and enhanced kinetic control was demonstrated by introducing a co-monomer which facilitated near quantitative conversion of monomer to polymer (>96%).



Scanning electron micrograph illustrating the variation in pore size of freeze-dried hydrogels as the starting compositions are varied by a factor of ~5

As submitted: V. Trang: *Biomacromolecules*.

Appendix 2.

USP NF Carbomer Homopolymer Monograph

Effective January 1, 2011

(Prior to January 1, 2011, the current practice of labeling the article of commerce with the name Carbomer 934, Carbomer 934P, Carbomer 940, or Carbomer 941, whichever is appropriate, may be continued.)

Carbomer Homopolymers are high molecular weight polymers of acrylic acid cross-linked with allyl ethers of polyalcohols. Carbomer Homopolymers, previously dried, contain not less than 56.0 percent and not more than 68.0 percent of carboxylic acid (–COOH) groups.

NOTE: The heading of this monograph does not constitute the official title for a Carbomer Homopolymer manufactured with the use of benzene. When benzene is used in the manufacturing process, the name of the article will be Carbomer 934, Carbomer 934P, Carbomer 940, or Carbomer 941, whichever is appropriate. Carbomer Homopolymers obtained from different manufacturers or produced in different solvents with different manufacturing processes may not have identical properties with respect to its use for specific pharmaceutical purposes, e.g., as tablet controlled-release agents, bioadhesives, gellants, etc. Therefore, types of Carbomer Homopolymer should not be interchanged unless performance equivalency has been ascertained.

Packaging and Storage: Preserve in tight containers, at a temperature not exceeding 45°.

Labeling: If benzene has been used in the manufacturing process, the name of the article will be Carbomer 934, Carbomer 934P, Carbomer 940, or Carbomer 941, whichever is appropriate. In addition, when benzene is used, the labeling requirements for the referenced individual Carbomer are applicable. If benzene is not used in the manufacturing process, label it to indicate whether it is Type A, B, or C; and also to state the measured viscosity, the solvent or solvents used in the polymerization process, and the nominal and residual solvent levels for each solvent.

Identification:

- A. Infrared Absorption $\langle 197K \rangle$ —The IR spectrum exhibits main bands at or near (± 5) wave numbers (cm⁻¹) 1710, 1454, 1414, 1245, 1172, 1115, and 801, with the strongest band at 1710.
- B. Adjust a 1 in 100 dispersion of it with 1 N sodium hydroxide to a pH of about 7.5: a viscous gel is produced.
- C. Add 2 mL of a 1 in 10 aqueous solution of calcium chloride, while stirring, to 10 mL of the gel obtained from Identification test B: a white precipitate is immediately produced.
- D. Prepare a 1 in 100 dispersion of it. Add 0.5 mL of thymol blue TS to 10 mL of the dispersion: an orange color is produced. To another 10 mL of the dispersion add 0.5 mL of cresol red TS: a yellow color is produced.

Viscosity $\langle 911 \rangle$: Carefully add 2.50 g of the resin, which has been previously dried, to 500 mL of water in a 800-mL beaker, while stirring continuously at 1000 \pm 50 rpm. The stirrer shaft is set at an angle of 60° and positioned at one side of the beaker, and the propeller is positioned near the bottom of the beaker. The stirrer used should be a three-blade, 2-inch marine impeller. Add Carbomer Homopolymer at a uniform rate over a period of 45 to 60 seconds, being sure that loose aggregates of

powder are broken up, and continue stirring at 1000 ± 50 rpm for 15 minutes. [NOTE: Proper dispersion of the Carbomer Homopolymer resin is imperative for accurate viscosity readings.] Remove the stirrer, and allow the beaker containing the dispersion to stand at controlled room temperature for 30 minutes. Insert a paddle stirrer to a depth necessary to ensure that the air is not drawn into the dispersion, and while stirring at 300 ± 25 rpm, titrate potentiometrically (see Titrimetry < 541 >) with sodium hydroxide solution (18 in 100) to the pH indicated on the label. (For example, if the pH is 7.3, then the total volume of sodium hydroxide would be about 5.4 ml.) After adding the sodium hydroxide solution, stir with a paddle mixer at 300 ± 25 rpm for 2 to 3 minutes. [NOTE: After neutralization, care must be taken to avoid excessively high shearing, as aggressive mixing will break the polymer chains and reduce the viscosity reading.] Take the final pH reading with a pH meter. If the final pH exceeds that indicated on the label, discard the mucilage, and prepare another using a smaller amount of sodium hydroxide for titration. Place the neutralized mucilage into a water bath maintained at $25 \pm 2^\circ$ for 1 hour, then perform the viscosity determination without delay.

Equip a suitable rotational viscometer (i.e., a Brookfield RVT or RVF viscometer) with a suitable spindle, as defined in the chart below. For spindle dimensions, consult the table under Carbomer Copolymer.

Expected Viscosity (cP)	Spindle Number	Multiplier
100–400	1	5
400–1600	2	20
1000–4000	3	50
2000–8000	4	100
4000–16,000	5	200
10,000–40,000	6	500
40,000–160,000	7	2000

With the spindle rotating at 20 rpm, observe and record the scale reading. Calculate the viscosity, in centipoise, by multiplying the scale reading by the multiplier defined in the table above for the spindle used at 20 rpm. The viscosity values, determined by the conditions specified herein, are within the limits specified in the accompanying table.

Carbomer Homopolymer	Viscosity Specified (cP)
A	4,000–11,000
B	25,000–45,000
C	40,000–60,000

Loss on drying < 731 >: Dry it in vacuum at 80° for 1 hour: it loses not more than 2.0% of its weight.

Residue on ignition < 231 >: not more than 4.0%, determined on 1.0 g.

Heavy metals, Method II < 231 >: not more than 0.002%.

Limit of ethyl acetate and cyclohexane: [NOTE: This test is required only for those Carbomer Homopolymers whose labeling indicates that ethyl acetate or a mixture of ethyl acetate and cyclohexane was used in the polymerization process.]

Standard stock solution: Transfer 5.0 mL of methanol to a 10-mL serum vial, insert a rubber septum, and seal with a metal cap. Add an accurately weighed quantity of about 25.0 µL of ethyl acetate and 20.0 µL of cyclohexane through the septum into the vial, and mix.

Standard solution: Transfer 20.0 mL of methanol to a 30-mL serum vial, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone (internal standard) and 50.0 µL of the Standard stock solution, and mix.

Test solution: Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 30-mL serum vial, add 20 mL of methanol, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone, and mix.

Chromatographic system (see Chromatography 〈 621 〉): Proceed as directed under Carbomer Copolymer.

Procedure: Proceed as directed under except to calculate the percentages of ethyl acetate and cyclohexane in the portion of Carbomer Homopolymer taken by the formula:

$$100(WS / WT)(RU / RS)$$

in which WS is the weight, in mg, of ethyl acetate or cyclohexane, as appropriate, in the Standard solution; WT is the weight, in mg, of Carbomer Homopolymer taken to prepare the Test solution; and RU and RS are the peak area ratios of the relevant analyte peak to the methyl ethyl ketone peak obtained from the Test solution and the Standard solution, respectively: not more than 0.5% of ethyl acetate and not more than 0.3% of cyclohexane is found.

Limit of benzene: [NOTE: This test does not apply to those articles titled Carbomer 934, Carbomer 934P, Carbomer 940 or Carbomer 941. Those articles meet the requirements for Limit of benzene in their respective individual monographs.]

Solvent solution: Quantitatively dissolve an accurately weighed quantity of benzene in dimethyl sulfoxide to obtain a solution having a concentration of about 1.0 mg per ml. Dilute this solution quantitatively, and stepwise if necessary, with organic-free water (see Organic Volatile Impurities 〈 467 〉, after July 1, 2008, see Residual Solvents 〈 467 〉) to obtain a solution having a concentration of about 0.1 µg per ml.

Test solution: Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). [NOTE: This preparation must be analyzed within 3 hours of preparation.]

Reference solution: Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Add 1.0 ml of the Solvent solution, dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). This solution contains about 0.01 µg of benzene per ml.

Chromatographic system: Proceed as directed in the test for Limit of benzene under Carbomer Copolymer.

Procedure: Proceed as directed in the test for Limit of benzene under Carbomer Copolymer. Calculate the percentage of benzene in the portion of Carbomer Homopolymer taken by the formula:

$$(C/W)(rU / rS)$$

in which C is the concentration, in µg per mL, of benzene in the Reference solution; W is the weight, in mg, of Carbomer Homopolymer taken to prepare the Test solution; and rU and rS are the benzene peak responses obtained from the Test solution and the Reference solution, respectively: not more than 0.0002% is found.

Organic volatile impurities, Method IV (467): meets the requirements for chloroform, 1,4-dioxane, methylene chloride, and trichloroethylene.

(Official until July 1, 2008)

Limit of acrylic acid: 0.01 M Phosphate buffer - Dissolve 1.361 g of monobasic potassium phosphate in 1000 mL of water, and mix.

Solution A: Use 0.01 M Phosphate buffer.

Solution B: Prepare a filtered and degassed mixture of 0.01 M Phosphate buffer and acetonitrile (1:1, v/v).

Mobile phase: Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography (621)).

Solvent: Dissolve 25 g of potassium alum in 1000 mL of water, and mix.

Standard solution: Dissolve an accurately weighed quantity of acrylic acid in the Solvent, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 12.5 µg per ml.

Test solution: Mix about 100 mg of Carbomer Homopolymer, accurately weighed, with Solvent, and add Solvent to obtain 20.0 mL of suspension. Heat the suspension at 50° for 20 minutes with occasional shaking. Then shake the suspension continuously at room temperature for 60 minutes. Centrifuge and use the clear supernatant.

Chromatographic system (see Chromatography (621)): The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 12-cm column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0	100	0	equilibration
0–8	100	0	isocratic
8–9	100@0	0@100	linear gradient
9–20	0	100	isocratic
20–21	0@100	100@0	linear gradient
21–30	100	0	isocratic

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than 5%.

Procedure: Separately inject equal volumes (about 20 µL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the response for the acrylic acid peaks. Calculate the percentage of free acrylic acid in the portion of Carbomer Homopolymer taken by the formula:

$$(C/W)(rU / rS)$$

in which C is the concentration, in µg per mL, of acrylic acid in the Standard solution; W is the weight, in mg, of Carbomer Homopolymer taken to prepare the Test solution; and rU and rS are the acrylic acid responses obtained from the Test solution and the Standard solution, respectively: not more than 0.25% is found.

Content of carboxylic acid: Proceed as directed in the test for Content of carboxylic acid under except to calculate the percentage of carboxylic acid in the portion of Carbomer Homopolymer taken by the formula:

$$100(45.02VN/W)$$

in which W is the weight, in mg, of the portion of Carbomer Homopolymer taken; and the other terms are as defined therein.

Auxiliary Information:

Staff Liaison: Hong Wang, Ph.D., Scientist

Expert Committee: (EM205) Excipient Monographs 2

USP31–NF26 Page 1096

Pharmacopeial Forum: Volume No. 34(1) Page 136

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Appendix 3.

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Appendix 4.

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