

Carbopol[®] ETD 2020 NF Polymer Toxicology Summary

GENERAL INFORMATION

Carbopol[®] ETD 2020 NF polymer is a proprietary cross-linked, polyacrylic acid copolymer that contains a proprietary processing aid. It is manufactured using a toxicologically preferred cosolvent system of ethyl acetate (class III solvent) and cyclohexane (low toxic class II solvent with high PDE). The polymer is one of a family of Carbopol[®] polymers sold for pharmaceutical applications and manufactured under cGMP conditions. Carbopol[®] ETD 2020 NF polymer is made to meet the current USP Monograph for "Carbomer Interpolymers", Type B.

As with other Carbopol[®] polymers, Carbopol[®] ETD 2020 NF polymer is a high molecular weight polymer estimated to be in the billions of Dalton. The toxicology studies summarized below were performed on polymer samples with chemical compositions representative of Carbopol[®] ETD 2020 NF polymer and on a sample of the proprietary processing aid. Therefore, this toxicology data described below and the data on Carbopol[®] polymers is expected to be predictive of the toxicology of Carbopol[®] ETD 2020 NF polymer and supports the safety of its use in oral care applications.

BIOAVAILABILITY

Because Carbopol[®] ETD 2020 NF polymer has a high molecular weight (billions of Daltons), it is not expected to be absorbed by the body. In the 1984 final polymer exemption rule (49 FR No. 226, Nov. 21, 1984) EPA established 1000 Dalton as the threshold for exempting polymers. The agency noted that molecular weight is a determinant of risk and stated that,

"For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response."

The Agency went on to state that,

"If a chemical cannot penetrate the protective membranes to access a target site, it usually cannot elicit a response in the organism no matter what inherent potential it may have to do so. It can be further reasoned that if a chemical cannot elicit a response, it will not present a risk."

The Agency concluded that,

"—substances with molecular weights greater than 400 are not readily absorbed through the intact skin and that substances with molecular weights greater than 1000 are not readily absorbed through the gastrointestinal tract."

Independent studies by Riley et al (2001)¹ also support this conclusion. C¹⁴ labeled cross-linked and uncross-linked polyacrylic acids (3% in water) were administered by gavage to rats. No evidence of systemic absorption was detected.

¹ Riley et al. (2001) "The Gastrointestinal Transit Profile of C¹⁴ Labeled Poly (Acrylic Acids): an In Vivo Study." Biomaterials, 22:1861-1867.

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ACUTE TOXICOLOGY STUDIES WITH CARBOPOL® ETD 2020 NF POLYMER

Human Repeated Insult Patch Tests

The test material was applied evenly over 2 cm x 2 cm surgical gauze pads which were moistened with distilled water just prior to application to the skin of 100 human volunteers in order to evaluate its skin irritation and sensitization potential. 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.

The test material did not produce any evidence of skin irritation or skin sensitization under the conditions of the test. The investigators concluded that the results furnish no basis for contraindicating skin contact with the test material.

Skin Irritation

The skin irritation potential of the test material was evaluated undiluted and as a 1% neutralized solution in rabbits according to international OECD guidelines. The test material (0.5 g of dry polymer or 0.5 ml of 1% neutralized solution) was applied to the intact skin on each of three animal backs. The dose was held in contact with the skin under a semi-occlusive binder for an exposure period of 4 hours. Following the exposure period, the binder was removed, and the remaining test article was wiped from the skin using tap water and paper towels. The test sites were subsequently examined and scored for dermal irritation for up to seven days following patch removal. Although very slight erythema (redness of the skin) and edema (swelling) were noted with the undiluted lots, all responses had subsided by the day 7 observation. Very slight erythema also was noted with one lot of the 1% test solution. However, even with this lot, the observation was limited to one of the three animals and was only seen at the 4 hour observation.

Under the test conditions, the test material is considered a non-irritant to a slight irritant to rabbit skin when undiluted (Primary Irritation Index 0.0 - 1.5), and a non-irritant to a very slight irritant when tested as a 1% solution (Primary Irritation Index 0.0 - 0.1).

Eye Irritation

The eye irritation potential of the test material was evaluated undiluted and as a 1% neutralized solution (pH 6.9 - 7.0) according to international OECD guidelines. A standard amount of the test material (0.1 ml or the weight equivalent, 0.04 g) was administered to groups of three 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.

Under the test conditions, the test material (undiluted) produced slight to moderate corneal irritation, and conjunctival irritation which cleared by the study termination (day 7). Only slight iridal and conjunctival irritation was noted with the 1% solution and all irritation was found to clear by 72 hours.

REPEAT DOSE AND GENOTOXICITY STUDIES WITH CARBOPOL® ETD 2020 NF POLYMER

Repeat dose and genotoxicity studies have not been conducted. The bioavailability studies described above indicate that the polymer is too large to be absorbed. These data are consistent with the results of the toxicology studies on our family of Carbopol® polymers. These studies indicate that Carbopol® ETD 2020 NF polymer is expected to have a low order of toxicity.

REPEAT DOSE AND GENOTOXICITY STUDIES WITH PROPRIETARY ETD PROCESSING AID

ETD processing aid was administered for 28 days to groups of Sprague-Dawley rats (10/sex/group) in their diet at concentrations of 0, 12,500, 25,000, and 50,000 ppm. Cageside exams were conducted daily and physical exams, body weight measurements, and food consumption measurements were conducted weekly. Hematology and clinical chemistry blood analyses were conducted on Day 30. Gross pathology was conducted at termination. Histopathological examinations were conducted on selected tissues from the control and top dose groups as well as any gross lesions that were observed in the other treatment groups. No adverse treatment-related effects were observed.

The genotoxic potential of ETD processing aid was evaluated using *Ames/Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without S-9 metabolic activation system.

Based on a preliminary test the final doses of 16.7, 50, 167, 500, 1670, and 5000 µg/plate were used in the main study. ETD processing aid was not toxic to any of the doses evaluated. However, the test article precipitated from solution at dose \geq 50 µg/plate. ETD processing aid was evaluated in triplicate for the selected doses. Statistically significant increases in revertant frequency, to approximately 1.6 fold, was observed in testor strain TA1535 at 16.7, 500, and 5000 µg/plate. With S9. However, these increases were not dose dependent and all were within acceptable historical control ranges. ETD processing aid was re-evaluated in a confirmatory assay under identical conditions. All revertant frequencies for all doses in all tester strains with and without activation were similar or lower than the control values. Therefore, ETD processing aid was consider negative in the Ames. *Salmonella* Plate Incorporation Assay.

The genotoxic potential of ETD processing aid also was evaluated in the *In Vitro* Micronucleus Test to determine its potential to induce micronuclei in the bone marrow erythropoietic cells of mice. A preliminary toxicity assay was conducted to select the appropriate doses for tha main study. Nine groups of mice (5/sex/group) were given i.p. injections of ETD processing aid at doses of 400, 2000, and 4000 mg/kg. The negative control, corn oil, was dosed concurrently to 3 groups of mice. Cyclophosphamide (60 mg/kg), the positive control, was also administered concurrently to a group of mice. Bone marrow was collected, pooled, and scored for the number of micronucleated PCEs in 1000 PCEs/mouse as well as the number of micronucleated normochromatic erythrocytes present in the optical fields containing those 1000 PCEs. The ratio polychromatic to normochromatic erythrocytes per 1000 erythrocytes was determined for each mouse as an index of toxicty. A statistically significant increase in MPCE frequency, as compared to the concurrent negative control group was observed in mice treated with ETD processing aid at 4000 mg/kg. However, the MPCE frequency was within the range of acceptable historical control frequency and a statisital assessment indicated that it was not dose dependent. MPCE frequencies for all other doses were not statistically greater than controls. Therefore, ETD processing aid was considered to be non-clastogenic in this assay.