CNS Neurotoxicity of Bacterial Cellulose-Poly(acrylamide-sodium acrylate) Hydrogel: A Future Therapeutic Carrier

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Chemically, acrylamide is a vinyl monomer which is crystalline, odorless, and highly water-soluble have multiple chemicals, pharmaceuticals, and industrial applications. Acrylamide (Am) is a well-documented neurotoxicant in both experimental animal and human. This neurotoxicity is mainly due to the cerebellar Purkinje cell damage and central-peripheral distal axonopathy [1,2]. Am present as a residue impurity is evident in most of the polymeric preparations containing acrylamide as reactant [3,4]. Prior to the application of these polymers as therapeutic carrier, preliminary safety assessments on chemicals used in the drug delivery formulation are necessary according to the Organization for Economic Co-operation and Development (OECD) guidelines.

This study reports on the synthesis and toxicity of bacterial cellulose-poly(acrylamide-sodium acrylate) hydrogel using solubilized bacterial cellulose in NaOH/urea solution. The Am-grafted bacterial cellulose (BC) three-dimensional cross-link structure was synthesized by microwave irradiation [5]. As a new therapeutic carrier, several criteria are required to be fulfilled, and these include being noncytotoxic, biocompatible, and nonacute oral toxicity [6]. Hence, further application of polymer as oral therapeutic carrier needs in depth safety evaluation along with neurotoxicological investigation.

Adult female ICR mice (25–28 g), obtained from Laboratory Animal Centre of Universiti Kebangsaan Malaysia, were used in this study. The approval for the study protocol was given by Animal Ethics Committee (FF/2013/CAIRUL/15-MAY/522-MAY-2013-DEC-2013). The mice were housed in a controlled temperature maintained between 20 and 22°C with 50–60% relative humidity and dark-light cycles of 12 h. Water and food were freely accessible to the animals. All mice were in quarantine for a week before treatment. Acute oral toxicity of Am-grafted BC was performed as per OECD guidelines for the test of chemicals 425.

The mice were divided into two groups ($n = 6$). Group I was designated as a control which was fed with normal saline only, while Group II was designated as polymer-treated group with the dose of 2 g/kg. In Group II, one mouse was given, a total dosage of 2 g/kg body weight, bacterial cellulose-poly(acrylamide-sodium acrylate) hydrogel suspension thrice at an interval of 4 h by gavage. The mouse was given food again approximately 4 h after the last dosing. Thereafter, the mouse was monitored for 48 h for any mortal or toxic clinical signs. Additionally, the next five mice of Group II, corresponding doses of the suspension was orally administered and followed by monitoring of the mice for further 14 days. Observations were conducted twice daily, including mortality, injury, abnormal behavior, and the general condition of the mice such as the physical activities, color of feces, behavior patterns, and other clinical signs. At the end of the study, the brain was examined for gross pathological changes after sacrificing the mice by cervical dislocation. During the period of acute oral toxicity, none of the mice in Group II exhibited any sign of morbidity, and all of them survived during the observational period. The eyes, teeth, oral cavity, skin, and hairs of the mice were in normal conditions. Similarly, the physical activities such as reflection, breathing, and movements also displayed a normal behavior similarly with the control group (Group I). They were also not showing any vomit, salivation, and edema during the whole observation period.

Optical microscopic (Olympus, Fluoview FV1000) image (Figure 1A) of cytotoxicity test by direct contact method using V79 fibroblast cells recommended by International Organization for Standardization guidelines (ISO/EN, 10993-5) revealed that the cells possess normal morphology, and no significant difference in percentage cell viability compared with the control group (data not shown).

Figure 1 Optical microphotographs obtained after 48-h incubation of V79 cell with polymer (A), photograph of brain of ICR mice (B), mice cerebellum and cerebrum histological section of control group (C, E), and polymer-treated group (D, F), respectively.

Figure 1B showed that there is no difference in terms of the shape, size, and weight of the brain in comparison with the control group. The CNS neurotoxicity of Am is expressed through the Purkinje cell injury, which controls the somatic motor activity coordination and muscle tone regulation, and is the cerebellum's sole efferent source [1]. However, the microscopic image of the cerebellum (Figure 1D) appears as a highly ordered tissue with distinct layers including the cell dense granular layer and molecular layer, between which the large Purkinje cells are located. There is no sign of degeneration and damage as compared to the control group (Figure 1C and D). Similarly, the morphology of the cerebrum is within the normal limit (Figure 1F), nonetheless

scattered red neurons are present which is also appears in control (Figure 1E).

These results suggested that the use of bacterial cellulose-poly (acrylamide-sodium acrylate) hydrogel as an oral therapeutic carrier showed no signs of neurotoxicity and any histopathological changes response up to 2 g/kg when administered orally in comparison with the control group.

Conflict of Interest

The authors declare no conflict of interests.

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