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Safety assessment of a solid lipid curcumin particle preparation: Acute and subchronic toxicity studies

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ABSTRACT

Curcumin, a polyphenol, is obtained from turmeric, the ground rhizomes of *Curcuma longa* L. Extensive research over the past half century has revealed several health benefits of curcumin. The objective of the present study was to investigate potential adverse effects, if any, of a novel solid lipid curcumin particle (SLCP) preparation in rats following acute and subchronic administration. The oral LD_{50} of the preparation in rats as well as in mice was found to be greater than 2000 mg/kg body weight (bw). In the subchronic toxicity study, Wistar rats (10/sex/group) were administered via oral gavage 0 (control), 180, 360, and 720 mg/kg bw/day of SLCP preparation for 90 days. Administration of the curcumin preparation did not result in any toxicologically significant treatment-related changes in clinical (including behavioral) observations, ophthalmic examinations, body weights, body weight gains, feed consumption, and organ weights. No adverse effects of the curcumin preparation were noted on the hematology, serum chemistry parameters, and urinalysis. Terminal necropsy did not reveal any treatment-related gross or histopathology findings. Based on the results of this study, the No Observed-Adverse-Effect Level (NOAEL) for this standardized novel curcumin preparation was determined as 720 mg/kg bw/day, the highest dose tested.

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1. Introduction

Curcumin, the principal curcuminoid of the popular Indian spice turmeric, is obtained from the ground rhizomes of *Curcuma longa* L. It is the characteristic yellow coloring component and comprises 2–5% of the turmeric spice that has been consumed for centuries (Chattopadhyay et al., 2004). Curcumin (Fig. 1) is chemically known as 1,7-bis (4′-hydroxy-3′-methoxyphenyl)-1,6-heptadiene-3,5-dion or diferuloylmethane, and is a lipid soluble compound. In 1815, curcumin was isolated for the first time and subsequently in 1870 it was obtained in crystalline form (Shishodia et al., 2008; Daybe, 1870). In addition to its use as a dietary spice (flavoring agent), curcumin is used as a coloring agent in foods and textiles, and as a therapeutic agent for multiple health benefits (Aggarwal and Sung, 2008). Historically, turmeric, the natural source of curcumin, has been commonly used. However, in recent years, turmeric oleoresin that contains curcuminoids, primarily curcumin, is commonly used in place of turmeric. As compared to turmeric, the use of its oleoresin as a food additive is preferred as the organic extraction procedure removes microbial contaminants that might be found in ground powder (Govindarajan, 1980). Among several countries that use turmeric, the United States is the largest consumer of turmeric oleoresins, where it is primarily used for its yellow color and to impart a characteristic mild spicy aroma to multiple food products.

The history of turmeric (curcumin) use goes back to over 5000 years. In the traditional Indian systems of health care (Ayurveda, Unani, and Siddha), turmeric (curcumin) has been reported to possess a wide range of therapeutic uses. Ayurveda (*Ayur* = long life; *veda* = knowledge) describes the use of curcumin for a range of inflammatory conditions such as wound healing, sprains and swellings caused by injury, and abdominal complaints (Ammon and Wahl, 1991). Additionally, ingestion of curcumin has been suggested for the relief from abdominal pain in the Chinese texts on traditional medicine. The available evidence indicates that the majority of the curcumin effects may be associated with its ability to suppress inflammation (Sikora et al., 2010). Experimental research during the past few decades has revealed several important

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDA, food and drug administration; ICH, international conference on harmonization; NOAEL, no-observed-adverse-effect level; OECD, organization for economic co-operation and development; SLCP, solid lipid curcumin particle.

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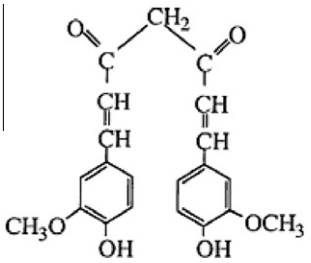

Fig. 1. Chemical structure of curcumin.

physiological properties such as antioxidant, anti-inflammatory, anti-cancer, and anti-atherogenicity of curcumin (Aggarwal et al., 2007).

In recent years, several investigators have attempted to unravel the underlying mechanisms of the beneficial effects of curcumin. These investigations suggest that curcumin can modulate several different transcription factors, cytokines, growth factors, kinases, and other enzymes (Aggarwal et al., 2007; Sikora et al., 2010; Zhou et al., 2010). Curcumin has been shown to alter the expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy (Aggarwal et al., 2003; Kuttan et al., 1985). Numerous lines of evidence suggest that curcumin is a potent anti-inflammatory agent as it suppresses the activation of the transcription factor NF-κB (regulates the expression of pro-inflammatory gene products), and down-regulates the expression of COX-2 (enzyme involved with inflammation). In spite of its increasingly claimed health-beneficial properties, one limiting factor for curcumin use is low bioavailability as demonstrated by data from studies using animal models (Wahlstom and Blennow, 1978; Ravindranath and Chandrasekhara, 1982; Shehzad et al., 2010). Clinical trials performed with healthy human subjects as well as cancer patients have all demonstrated low systemic bioavailability of curcumin following oral administration, even at doses of up to 12 g/day (Cheng et al., 2001; Dhillon et al., 2008). Attempts to increase the bioavailability of curcumin by dosing with glucuronidation inhibitors such as piperine have shown increased bioavailability in humans (Shoba et al., 1998), however alternative methods which do not interfere with systemic metabolism may be desirable. In a recent pharmacokinetic study in human subjects, Gota et al. (2010) reported relatively higher bioavailability of standardized novel solid lipid curcumin particle (SLCP) preparation compared to generic curcumin extract. The extended absorption in this study may be linked to key parameters such as curcumin/lipid/antioxidant ratio, globule-size distribution, and stability. The objective of the present study was to investigate the adverse effects, if any, of a novel SLCP preparation following acute administration to rats and mice, and subchronic administration to rats. The effects of the extract were investigated in a dose–response study.

2. Materials and methods

2.1. Acute studies

The acute toxicity study was based on OECD Guidelines for Testing of Chemicals (No. 420, Section 4, Health Effects). In two different acute toxicity studies, female Wistar rats and female Swiss albino mice bred at Cadila Pharmaceutical Limited (Dholka, India) were used. In two acute studies, Wistar rats (1 + 4/group; 10–11 weeks of age; body weight range: 127–228 g) and Swiss albino mice (1 + 4/group; 10–11 weeks of age; body weight range: 27–39 g) were administered a single oral (gavage) dose of solid lipid curcumin particle (SLCP) preparation (as Longvida®, Verdure Sciences, Noblesville, IN, USA) suspended in sodium carboxymethyl cellulose (CMC) at levels of 0 and 2000 mg/kg body weight. In these studies one animal was used sighting and four animal were included in the main study. In all these experiments, animals were observed for 15 days for clinical signs as well as for morbidity and mortality. On day 15 at completion, all the animals were euthanized and gross pathological examinations were undertaken. Based on the study design, Globally Harmonized System category 5/Unclassified was disclosed in both the study conducted for SLCP preparations.

2.2. Subchronic study

2.2.1. Study design

The subchronic study was performed according to a protocol based on Organization for Economic Co-operation and Development (OECD) Guidelines for Testing Chemicals, Health Effects Test Guidelines, for Repeated Dose 90-Day Oral Toxicity Study in Rodents, Section 408. The study was conducted in compliance with the OECD principles of Good Laboratory Practices.

2.2.2. Test item and formulation

Food grade solid lipid curcumin particle (SLCP) preparation (Longvida®) was provided for the present study. SLCP was produced using patent-pending methodology. Turmeric root extract containing curcumin was mixed with soy lecithin containing purified phospholipids, docosahexaenoic acid (DHA) and/or vegetable stearic acid, and inert ingredients. The formulation was manufactured under current good manufacturing practices and met internal and external specifications for precise chemical and physical characteristics deemed to be suitable by bioavailability-guided product development. The test item was yellowish orange dry granules and standardized to contain approximately 30% curcumin.

The appropriate amounts of the test item were suspended by thoroughly mixing with 0.5% sodium CMC to attain the desired concentration. The solutions containing SLCP concentration of 72, 36, 18, and 0 mg/ml were prepared in 0.5% sodium CMC for administration. The solution containing 36 and 18 mg/ml were prepared by appropriately diluting the 72 mg/ml stock solution. The test solutions were administered to rats daily orally via gavage. The solutions 0, 18, 36, and 72 mg/ml prepared for administration correlated to the gavage doses of 0, 180, 360, and 720 mg SLCP/kg body weight.

2.2.3. Animals

For the subchronic study, Wistar rats also from Cadila Pharmaceutical Ltd. were used. A total of 120 male and female rats 5–7 weeks old, were selected after physical and behavioral examination for the study. Selected females were nulliparous and non-pregnant. The animals were maintained according to standard guidelines. The animals were housed in groups of five in standard polypropylene cages with a stainless steel top grill under controlled conditions. Clean, autoclaved paddy husk was used as the bedding material. The room temperature was maintained at 22 ± 3 °C with relative humidity between 30% and 70% with 100% exhaust facility and a 12 h light/dark cycle. The animals were allowed to acclimatize for a minimum of 6 days before the initiation of experiments. Amrut standard rat pellet diet (Nav Maharashtra Chackan Mills Ltd., India) was provided *ad libitum* throughout the study period. Autoclaved drinking water was provided *ad libitum* in polypropylene bottles with stainless steel sipper tubes.

2.2.4. Treatment

In the subchronic study, Wistar rats (10/sex/group) were randomly divided into six groups. At randomization, the animals were approximately 5–7 weeks old and their body weight was within ±20% of the overall mean of each sex (male – 87–130 g; female – 79–118 g). Rats (10/sex/group) were treated orally (gavage) with SLCP preparation at dose levels of 0 (Group I – control), 180 (Group II – low dose), 360 (Group III – mid dose), and 720 (Group IV – high dose) mg/kg bw/day (dosing volume 10 mL/kg) for 90 days. Two additional groups of animals for the recovery study received 0 (Group V) and 720 (Group VI) mg/kg bw/day of the extract for 90 days, followed by no additional treatment for 28 days. During the course of the subchronic study, all animals were provided *ad libitum* feed, until the day prior to the scheduled euthanasia. At completion of the 90 day treatment period, all animals in Group I–IV were euthanized. In the recovery group, after completion of the 90 day treatment period, the animals were kept under post treatment observations for 28 days and then euthanized.

2.2.5. Parameters investigated

2.2.5.1. Clinical observations, body weights and feed consumption. All animals were observed twice daily for morbidity and mortality. Clinical examinations included any abnormal clinical signs and behavioral changes over the entire observation period. The cage side observations included changes in skin, fur, eyes and mucous membranes, occurrence of secretions and excretions; autonomic activity like lacrimation, piloerection, pupil size and unusual respiratory pattern, changes in gait, posture, response to handling, presence of clonic or tonic movements, stereotypes like excessive grooming and repetitive circling or bizarre behavior like self-mutilation, walking backwards, etc. Sensory reactivity to stimuli of different types (e.g. auditory, visual and proprioceptive stimuli), assessment of grip strength and motor activity assessment was conducted during the last week of exposure. The time of onset, intensity and duration of such symptoms, if any, were recorded. Ocular examinations were conducted on all animals prior to the initiation of experiments and during the day prior to euthanasia.

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