well tolerated, confirmation of linear pharmacokinetics was not possible and an explicit dose recommendation for further study was not identified (See Timerbaev, 2009, *supra*). Although an attempt was made to inhibit the loss of the ligand structure using an enteric coating, it was postulated that a significant amount of the drug was not absorbed, thus dramatically limiting bioavailability.

[0011] The results from this first clinical evaluation of GaQ3 suggested that the low solubility of the crystalline compound possessing a particle size range normally considered adequate for a conventional formulation resulted in poor bioavailability and non-linear pharmacokinetics. The data indicated that although a portion of GaQ3 survived intact after transit through the stomach, the absorption observed was somewhat erratic through the intestine.

[0012] Thus, the challenge in the advancement of oral GaQ3 in clinical development is keeping the GaQ3 intact during transit through the stomach and releasing a more soluble form of GaQ3 within the intestinal tract where the compound is stable and can be absorbed intact.

[0013] This challenge is met by: 1) formation of a non-crystalline solid form of GaQ3 and 2) using an enteric coating on the final dosage form or subunits within the final form to prevent exposure to the destabilizing effects of gastric acid.

Summary

[0014] Thus, in one example, the disclosure is directed to a dosage form for oral administration of GaQ3 which comprises an amorphous or nanocrystalline form of said GaQ3 protected by an enteric or delayed release coating. In some examples, the GaQ3 is admixed with a dispersant to maintain its amorphous or nanocrystalline form.

[0014a] In one aspect, the present disclosure refers to an oral dosage formulation comprising a dispersion of tris (8-quinolinolato) gallium (III) (GaQ3) in amorphous or nanoparticulate form dispersed in a dispersant, and wherein the dispersion of amorphous or nanoparticulate GaQ3 in said dispersant is protected by an enteric or delayed release coating, and wherein the weight ratio of GaQ3:dispersant is between 9:1 and 1:9.

[0015] The formulations of the disclosure result in desirable pharmacokinetics wherein when said encapsulated GaQ3 is administered to dogs at a dose of 10 mg/kg the Cmax in plasma is at least 100 times the Cmax in plasma of dogs administered 10 mg/kg of crystalline GaQ3 and the AUC in plasma is at least 200 times that of dogs administered comparable amounts of crystalline GaQ3. The formulations also have desirable solubility and in the case of amorphous forms, resistance to conversion back to a crystalline state under stress or exposure to moisture.

[0016] The disclosure also includes methods to administer GaQ3 utilizing the formulations of the disclosure. Such formulations are useful in treating cancer and conditions associated with calcium and bone metabolism.

[0016a] In another aspect, the present disclosure refers to use of the formulation as disclosed herein, in the manufacture of a medicament for the treatment for cancer, wherein the medicament is to be administered to a subject.

[0016b] In another aspect, the present disclosure refers to a method to prepare the formulation as disclosed herein which method comprises converting the GaQ3 to an amorphous state in the presence of said dispersant wherein both the GaQ3 and the dispersant are dissolved in a solvent and evaporating the solvent to obtain an amorphous dispersion; or suspending a nanoparticulate form of the GaQ3 in said dispersant dissolved in a solvent and evaporating the solvent to obtain said nanoparticulate surrounded by a dispersant layer.

Brief Description of the Drawings

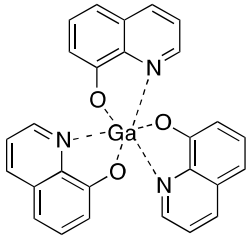
[0017] Figure 1 shows XRD curves for crystalline GaQ3 and amorphous GaQ3 dispersions.

[0018] Figure 2 shows retention of amorphous state of GaQ3 in a 1:1 dispersion with Eudragit L-100 when exposed to water.

[0019] Figure 3 shows the kinetics of dissolution for various dispersions of GaQ3 as compared to crystalline GaQ3.

Modes of Carrying Out the Invention

[0020] "GaQ3" refers to tris (8-quinolinolato) gallium (III), as shown in Formula 1**.**



Formula 1

[0021] "GaQ3," as used herein is as defined above.

[0022] Solubility of the GaQ3 is enhanced by converting crystalline GaQ3 to amorphous or nanocrystalline form. Since there is no crystal lattice in the amorphous form, dissolution of the solid is improved from a crystalline form. The amorphous state represents a complete loss of short and long range crystalline order and the energy required for a molecule of drug to dissolve in the gastrointestinal tract is much lower, resulting in a better rate and extent of absorption. The amorphous form or dispersion thereof may be prepared by spray drying, hot melt extrusion, rotary evaporation, freeze-drying or supercritical fluid processing.

[0023] An alternative to a completely amorphous state is a nanocrystalline form wherein, similarly, the crystalline lattice energy state is reduced, in this case, through a dramatically increased surface area. Particle size reduction of crystalline drugs to enhance solubility (or dissolution) can be pursued by various well-known mechanical and chemical means. Typical methods involve, chemical, mechanical grinding (wet milling), microfluidization, supercritical fluid processing, spray drying and precipitation techniques.

[0024] A mean particle size of less than about 400 nanometers (nm) is typically required for enhancement of the solubility (US 5,145,684), but the size range in the composition may be 80nm-500nm, or 100nm-300nm including intermediate values. The size distribution need not be uniform.