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 or a derivative thereof which comprises an amorphous or nanocrystalline form of said GaQ3 or a derivative thereof protected by an enteric or delayed release coating. In some examples, the GaQ3 or its derivative 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 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.

[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 or its derivative 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 a gallium complex 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 GaQ3 to an amorphous state in the presence of said dispersant wherein both GaQ3 and dispersant are dissolved in a solvent and evaporating the solvent to obtain an amorphous dispersion; or suspending a nanoparticulate form 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

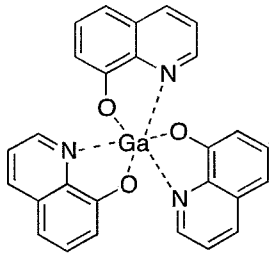
[0017] Figure 1 shows XRD curves for crystalline GaQ3 and amorphous GaQ3 dispersions.

[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.

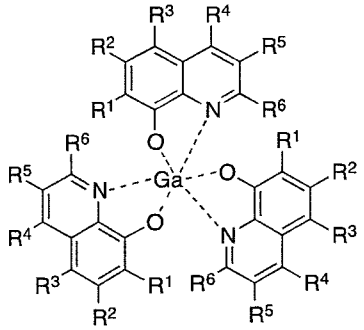
Modes of Carrying Out the Invention

[0020] "GaQ3" refers to tris (8-quinolinolato) gallium (III), as shown in Formula 1 and also includes derivatives as described in Formula 2.



Formula 1

Derivatives of tris (8-quinolinolato) gallium (III), includes those of Formula 2.



Formula 2

CLAIMS

1. An oral dosage formulation comprising a dispersion of 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.

2. The formulation of claim 1 which is prepared by a process comprising either:

converting GaQ3 to an amorphous state in the presence of said dispersant wherein both GaQ3 and dispersant are dissolved in a solvent and evaporating the solvent to obtain an amorphous dispersion; or

suspending a nanoparticulate form in said dispersant dissolved in a solvent and evaporating the solvent to obtain said nanoparticulate surrounded by a dispersant layer.

3. The formulation of claim 2, wherein the GaQ3 is amorphous and the GaQ3 and dispersant are dissolved and spray-dried together.

4. The formulation of any of claims 1-3, wherein the weight ratio of GaQ3:dispersant is between 9:1 and 1:9.

5. The formulation of any of claims 1-4, wherein the dispersant comprises a methacrylic acid : methacrylate copolymer.

6. The formulation of any of claims 1-4, wherein the enteric or delayed release coating comprises a methacrylic acid : methacrylate copolymer.

7. The formulation of any of claims 1-6, wherein the GaQ3 is tris (8-quinolinolato) gallium (III).

8. The formulation of claim 1, wherein said GaQ3 is amorphous tris (8-quinolinolato) gallium (III) in a 1:1 wt/wt dispersion with Eudragit L-100 and has the powder X-ray diffraction pattern (XRD) shown in Figure 1, curve A.

9. The formulation of any of claims 1-8, wherein said GaQ3 exhibits an immediate peak of dissolution when mixed with aqueous medium.

10. The formulation of any of claims 1-8, wherein said GaQ3 maintains its amorphonanocrystalline state when exposed to water vapor or to 75% relative humidity.

11. The formulation of any of claims 1-8,

wherein the formulation provides an AUC in plasma of dogs which have been administered a dose of GaQ3 of 10 mg/kg, that is at least 200 times the AUC in plasma of dogs which have been administered 10 mg/kg of crystalline GaQ3; or

wherein the formulation provides a Cmax of at least 2336 ng/ml in plasma of dogs which have been administered a dose of GaQ3 of 10 mg/kg; or

wherein the formulation provides an AUC of at least 60546 ng*hr/ml in plasma of dogs which have been administered a dose of GaQ3 of 10 mg/kg; or

wherein the formulation provides an AUC of at least 4381 ng*hr/ml in plasma of fasted female dogs which have been administered a dose of GaQ3 of 1 mg/kg; or

wherein the formulation provides an AUC of at least 4227 ng*hr/ml in plasma of fasted male dogs which have been administered a dose of GaQ3 of 1 mg/kg; or

wherein the formulation provides a Cmax of at least 330 ng/ml in plasma of fasted female dogs which have been administered a dose of GaQ3 of 1 mg/kg; or

wherein the formulation provides a Cmax of at least 310 ng/ml in plasma of fasted male dogs which have been administered a dose of GaQ3 of 1 mg/kg.

12. Use of the formulation of any of claims 1-8, in the manufacture of a medicament for the treatment for cancer, wherein a gallium complex is to be administered to a subject.

13. The use of claim 12, wherein the subject is human or a laboratory animal model.

14. A method to prepare the formulation of claim 1 which method comprises

converting GaQ3 to an amorphous state in the presence of said dispersant wherein both GaQ3 and dispersant are dissolved in a solvent and evaporating the solvent to obtain an amorphous dispersion; or

suspending a nanoparticulate form in said dispersant dissolved in a solvent and evaporating the solvent to obtain said nanoparticulate surrounded by a dispersant layer.