[0005] Anal cancer accounts for 2.5 percentage of all digestive system malignances in the US, and approximately 8,000 new cases are diagnosed annually. The incidence of anal cancer in the general population has increased over the last three decades. Additionally, colorectal cancer (CRC) is a common and lethal disease. It is estimated that approximately 134,490 new cases of large bowel cancer are diagnosed annually in the US, including approximately 95,270 colon and 39,220 rectal cancers. This cancer remains the third most common cause of cancer death in the United States. Approximately 49,190 Americans are expected to die of large bowel cancer each year.

[0006] One of the differences between colorectal cancer and anal cancer are the risk factors that can cause each. Primary risk factors for colorectal cancer include age, genetics, race, diabetes, obesity, lack of exercise and smoking. In contrast, the primary cause of anal cancer has been the increase in prevalence of human papillomavirus (HPV).

[0007] These cancers, oral, colorectal and anal cancer, can all be treated with cisplatin, a platinum-containing drug with widespread anti-tumor activity. This drug is an alkylation agent, used for treating solid tumors such as testicular, ovarian, bladder and epithelial malignancies and cancers of the esophagus, lung, and head and neck. Following entry into the target cells via diffusion, **t**he substitution of water for one or more chlorine atoms gives it a positive charge, with the resulting positively charged complex reacting with DNA to inhibit DNA replication. This property of cisplatin, however, makes it prone to hydrolysis. The addition of sodium chloride can mitigate this risk by improving the chemical stability of cisplatin. Improved methods of delivering cisplatin to treat oral, anal and colorectal cancers are needed. The present invention meets this and other needs.

BRIEF SUMMARY

[0007a] In an aspect, there is provided a system comprising:

a polymeric matrix comprising chitosan, and a plurality of microparticles each comprising chitosan, a chloride salt of a monovalent cation having a concentration of from about 10 to about 18 % (w/w) of the polymeric matrix, and a therapeutic agent, wherein the microparticles have an average diameter between 500 nm and 2000 nm.

[0007b] In another aspect, there is provided a use of a system as defined above in the manufacture of a medicament for administering a therapeutic agent to a subject in need

thereof, wherein at least 50% of the therapeutic agent of the system is to be released from the system in less than 30 minutes.

[0007c] In another aspect, there is provided a method of preparing a system as defined above, comprising forming a first mixture comprising water, chitosan, a chloride salt, a hydration promoter, a particle adhesion inhibitor, and a particle aggregation inhibitor, to prepare a matrix mixture;

forming a second mixture comprising the matrix mixture, a first platinum antineoplastic agent, and chitosan microparticles comprising a second platinum antineoplastic agent;

removing the water from the second mixture, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing the system.

[0007d] In another aspect, there is provided a method of preparing a system as defined above, comprising

forming a first mixture comprising water, chitosan, and acetic acid;

forming a second mixture comprising a chloride salt, a therapeutic agent, and sodium tripolyphosphate;

forming a third mixture comprising the first mixture and the second mixture, thereby forming microparticles;

forming a fourth mixture comprising water, chitosan, acetic acid, a hydration promoter, and a particle adhesion inhibitor;

forming a fifth mixture comprising the fourth mixture, a particle aggregation inhibitor, and the micorparticles, to form the polymer matrix;

removing the water from the polymer matrix, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing a system as defined above.

[0007e] In another aspect, there is provided a use of a system as defined above in the manufacture of a medicament for treating a skin disease of a subject in need thereof, wherein

the system is to be applied to the skin of the subject such that a therapeutic agent of the system is to be released from the system and is to be administered to the skin of the subject.

[0007f] In another aspect, there is provided a use of the system as defined above in the manufacture of a medicament for treating a mucosal cancer in a subject in need thereof.

[0007g] In another aspect, there is provided a system as defined above for use in therapy.

[0008] In one example, the present disclosure provides a system for delivery of cisplatin to a site in mucosal tissue, the system comprising a porous, mucoadhesive, freeze-dried polymeric matrix, having first and second opposed surfaces, the matrix formed by a composition including chitosan in an aqueous solution of a chloride salt of a monovalent cation, the chloride salt having a concentration of between about 10 wt % and about 18 wt %; and a plurality of microparticles, the microparticles comprising chitosan and having an average diameter between 500 nm and 2000 nm, the microparticles being embedded within the matrix so as to be directly surrounded by, and in contact with, the matrix, the

microparticles containing cisplatin. In this example, (i) the first surface of the matrix is configured to attach to the site in the mucosal tissue; (ii) the matrix is configured to provide controlled release of the microparticles, through the first surface, when the first surface of the matrix is thus attached to the site; and (iii) the microparticles are configured so as to provide controlled release of the cisplatin.

[0009] In another example, the present disclosure provides a system comprising: a polymeric matrix comprising chitosan, and a plurality of microparticles each comprising chitosan, a chloride salt of a monovalent cation having a concentration of from about 10 to about 18 % (w/w) of the polymeric matrix, and a therapeutic agent, wherein the microparticles have an average diameter between 500 nm and 2000 nm.

[0010] In another example, the chloride salt of a monovalent cation is chosen from the group consisting of NaCl, KCl, LiCl, RbCl, CsCl, NH4Cl, and combinations thereof. Optionally, the chloride salt of a monovalent cation is NaCl. Also optionally, the aqueous solution of a chloride salt of a monovalent cation includes propylene glycol in a concentration of from about 5 weight percent to about 25 weight percent. As a further option, the aqueous solution of a chloride salt of a monovalent cation includes hydroxypropylmethylcellulose (HPMC) in a concentration of from about 0.1 weight percent to about 10 weight percent. In yet another related example, the aqueous solution of a chloride salt of a monovalent cation includes sucralose in a concentration of from about 0.1 weight percent to about 30 weight percent. In a further related example, the microparticles are present in the matrix in a concentration of about 10 to about 40 weight percent. Optionally, the system further includes a water-permeable backing layer applied to the matrix.

[0011] In another example, the present disclosure provides a method of administering a therapeutic agent to a subject in need thereof, comprising applying a system of the present disclosure to the subject such that at least 50% of a therapeutic agent of the system is released from the system in less than 30 minutes.

[0012] In another example, the present disclosure provides a method of preparing the system of the present disclosure, comprising

forming a first mixture comprising water, chitosan, a chloride salt, a hydration promoter, a particle adhesion inhibitor, and a microparticle aggregation inhibitor, to prepare a matrix mixture;

forming a second mixture comprising the matrix mixture, a first platinum antineoplastic agent, and chitosan microparticles comprising a second platinum antineoplastic agent;

removing the water from the second mixture, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing the system.

[0013] In another example, the present disclosure provides a method of preparing a system of the present disclosure, comprising:

forming a first mixture comprising water, chitosan, and acetic acid;

forming a second mixture comprising a chloride salt, a therapeutic agent, and sodium tripolyphosphate;

forming a third mixture comprising the first mixture and the second mixture, thereby forming microparticles;

forming a fourth mixture comprising water, chitosan, acetic acid, a hydration promoter, and a particle adhesion inhibitor;

forming a fifth mixture comprising the fourth mixture, a particle aggregation inhibitor, and the micorparticles, to form the polymer matrix;

removing the water from the polymer matrix, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing a system of the present disclosure.

[0014] In another example, the present disclosure provides a method of treating a skin disease of a subject in need thereof, comprising applying a system of the present disclosure to the skin of the subject such that a therapeutically effective amount of a therapeutic agent of the system is released from the system and administered to the skin of the subject, thereby treating the skin disease.

[0015] In another example, the present disclosure provides a method of treating a mucosal cancer, comprising applying the system of the present disclosure to the mucosal cancer of a subject in need thereof, thereby treating the mucosal cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The foregoing features of embodiments will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

WHAT IS CLAIMED IS:

1. A system comprising:

a polymeric matrix comprising chitosan, and a plurality of microparticles each comprising chitosan, a chloride salt of a monovalent cation having a concentration of from about 10 to about 18 % (w/w) of the polymeric matrix, and a therapeutic agent, wherein the microparticles have an average diameter between 500 nm and 2000 nm.

2. The system of claim 1, wherein the polymeric matrix is a porous, mucoadhesive, freeze-dried polymer matrix.

3. The system of claim 1 or 2, wherein the chitosan has a molecular weight of from about 25 kDa to 1000 kDa.

4. The system of any one of claims 1 to 3, wherein the chitosan has a molecular weight of from about 25 kDa to 500 kDa.

5. The system of any one of claims 1 to 4, wherein the chitosan has a molecular weight of from about 80 kDa to 200 kDa.

6. The system of claim 1 or 2, wherein the chloride salt of a monovalent cation is NaCl, KCl, LiCl, RbCl, CsCl, NH_4Cl, or combinations thereof.

7. The system of claim 1 or 6, wherein the chloride salt of a monovalent cation is NaCl.

8. The system of any one of claims 1 to 7, wherein the chloride salt of a monovalent cation is NaCl and is present in the polymeric matrix in an amount of about 18% (w/w) of the polymeric matrix.

9. The system of any one of claims 1 to 8, wherein the therapeutic agent comprises an antineoplastic agent.

10. The system of any one of claims 1 to 9, wherein the therapeutic agent comprises cisplatin.

11. The system of any one of claims 1 to 10, wherein the polymeric matrix further comprises a hydration promoter.

12. The system of claim 11, wherein the hydration promoter is ethylene glycol, propylene glycol, beta-propylene glycol, glycerol, or combinations thereof.

13. The system of claim 12, wherein the propylene glycol is present in the polymeric matrix in an amount of from about 5 to about 25% (w/w).

14. The system of claim 13, wherein the propylene glycol is present in an amount of about 7.75 % (w/w).

15. The system of any one of claims 1 to 14, wherein the polymeric matrix further comprises a particle adhesion inhibitor.

16. The system of claim 15, wherein the particle adhesion inhibitor comprises hydroxypropylmethylcellulose (HPMC).

17. The system of claim 16, wherein the hydroxypropylmethylcellulose (HPMC) is present in the polymeric matrix in an amount of from about 0.1 to about 10 % (w/w).

18. The system of claim 17, wherein the hydroxypropylmethylcellulose (HPMC) is present in the polymeric matrix in an amount of about 3.7% (w/w).

19. The system of any one of claims 1 to 18, wherein the polymeric matrix further comprises a particle aggregation inhibitor.

20. The system of claim 19, wherein the particle aggregation inhibitor is present in an amount of from about 0.1 to about 30 % (w/w).

21. The system of claim 19 or 20, wherein the particle aggregation inhibitor is a monosaccharide, disaccharide, sugar alcohol, chlorinated monosaccharide, chlorinated disaccharide, or combinations thereof.

22. The system of any one of claims 19 to 21, wherein the particle aggregation inhibitor is sucralose.

23. The system of any one of claims 19 to 22, wherein the sucralose is present in the polymeric matrix in an amount of from about 0.1 to about 30 % (w/w).

24. The system of claim 22 or 23, wherein the sucralose is present in the polymeric matrix in an amount of about 22.25% (w/w).

25. The system of any one of claims 1 to 24, wherein the polymeric matrix further comprises a free amount of the therapeutic agent in an amount of from about 20 to about 80 % of the total amount of the therapeutic agent in the system.

26. The system of any one of claims 1 to 25, wherein the microparticles are embedded within the matrix so as to be directly surrounded by, and in contact with, the polymeric matrix.

27. The system of any one of claims 1 to 26, wherein the microparticles are present in the polymeric matrix in an amount of from about 10 to about 40 % (w/w).

28. The system of any one of claims 1 to 27, wherein the platinum antineoplastic agent comprises cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, satraplatin, or combinations thereof.

29. The system of any one of claims 1 to 28, wherein the platinum antineoplastic agent comprises cisplatin.

30. The system of any one of claims 1 to 29, comprising from about 1 to about 50 % (w/w) of cisplatin.

31. The system of any one of claims 1 to 30, comprising about 22.5 % (w/w) of cisplatin.

32. The system of any one of claims 1 to 31, wherein the microparticles further comprise sodium tripolyphosphate.

33. The system of claim 32, comprising from about 0.1 to about 10% (w/w) of sodium tripolyphosphate.

34. The system of claim 32 or 33, comprising about 3.0% (w/w) of sodium tripolyphosphate.

35. The system of claim 1, wherein the polymeric matrix comprises:

chitosan in an amount of from about 20 to about 30% (w/w);

cisplatin in an amount of from about 20 to about 30% (w/w);

NaCl in an amount of from about 10 to about 18 % (w/w);

propylene glycol in an amount of from about 5 to about 25 % (w/w);

hydroxypropylmethylcellulose (HPMC) in an amount of from about 0.1 to about 10 % (w/w);

sucralose in an amount of from about 0.1 to about 30 % (w/w); and

the microparticles in an amount of from about 10 to about 40 % (w/w).

36. The system of any one of claims 1 to 35, wherein the polymeric matrix comprises:

chitosan in an amount of about 22.5% (w/w);

cisplatin in an amount of about 22.5% (w/w);

NaCl in an amount of about 18 % (w/w) of the polymeric matrix;

propylene glycol in an amount of about 7.75% (w/w);

hydroxypropylmethylcellulose (HPMC) in an amount of about 3.7% (w/w); and

sucralose in an amount of about 22.25% (w/w).

37. The system of any one of claims 1 to 36, wherein the polymer matrix has first and second opposed surfaces, and wherein the system further comprises a water-permeable backing layer applied to the first surface of the polymeric matrix.

38. The system of any one of claims 1 to 37, wherein the second surface comprises a polyacrylate adhesive, a non-woven polyester fabric, or combinations thereof.

39. Use of a system of any one of claims 1 to 38 in the manufacture of a medicament for administering a therapeutic agent to a subject in need thereof, wherein at least 50% of the therapeutic agent of the system is to be released from the system in less than 30 minutes.

40. The use of claim 39, wherein the system is to be applied to a mucosal membrane of the subject.

41. The use of claim 39, wherein the system is to be applied to an oral cavity of the subject.

42. The use of claim 39, wherein the system is to be applied to the skin of the subject.

43. The use of any one of claims 39 to 42, wherein at least 75% of the therapeutic agent of the system is to be released from the system in less than 30 minutes.

44. The use of any one of claims 39 to 43, wherein at least 90% of the therapeutic agent of the system is to be released from the system in less than 30 minutes.

45. The use of any one of claims 39 to 44, wherein at least 90% of the therapeutic agent of the system is to be released from the system in less than 15 minutes.

46. A method of preparing a system of any one of claims 1 to 38, comprising

forming a first mixture comprising water, chitosan, a chloride salt, a hydration promoter, a particle adhesion inhibitor, and a particle aggregation inhibitor, to prepare a matrix mixture;

forming a second mixture comprising the matrix mixture, a first platinum antineoplastic agent, and chitosan microparticles comprising a second platinum antineoplastic agent;

removing the water from the second mixture, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing the system.

47. The method of claim 46, comprising

forming the first mixture comprising water, chitosan, a chloride salt, propylene glycol, hydroxypropyl methyl cellulose, and sucralose, to prepare the matrix mixture;

forming a second mixture comprising the matrix mixture, cisplatin, and chitosan microparticles comprising chitosan, cisplatin and sodium tripolyphosphate;

removing the water from the second mixture, to prepare the dried mixture; and

applying the dried mixture to the backing layer, thereby preparing the system of any one of claims 1 to 38.

48. A method of preparing a system of any one of claims 1 to 38, comprising

forming a first mixture comprising water, chitosan, and acetic acid;

forming a second mixture comprising a chloride salt, a therapeutic agent, and sodium tripolyphosphate;

forming a third mixture comprising the first mixture and the second mixture, thereby forming microparticles;

forming a fourth mixture comprising water, chitosan, acetic acid, a hydration promoter, and a particle adhesion inhibitor;

forming a fifth mixture comprising the fourth mixture, a particle aggregation inhibitor, and the micorparticles, to form the polymer matrix;

removing the water from the polymer matrix, to prepare a dried mixture; and

applying the dried mixture to a backing layer, thereby preparing a system of any one of claims 1 to 38.

49. The method of claim 46, comprising

forming the first mixture comprising water, chitosan, and acetic acid;

forming the second mixture comprising sodium chloride, cisplatin, and sodium tripolyphosphate;

forming the third mixture comprising the first mixture and the second mixture, thereby forming the microparticles;

forming the fourth mixture comprising water, chitosan, acetic acid, propylene glycol, and hydroxypropyl methyl cellulose;

forming the fifth mixture comprising the fourth mixture, sucralose, and the micorparticles, to form the polymer matrix;

removing the water from the polymer matrix, to prepare the dried mixture; and

applying the dried mixture to the backing layer, thereby preparing the system.

50. Use of a system of any one of claims 1 to 38 in the manufacture of a medicament for treating a skin disease of a subject in need thereof, wherein

the system is to be applied to the skin of the subject such that a therapeutic agent of the system is to be released from the system and is to be administered to the skin of the subject.

51. The use of claim 50, wherein at least 50% of the therapeutic agent is released from the system in less than 30 minutes.

52. The use of claim 50, wherein the skin disease is skin cancer, inflammatory skin disease, autoimmune skin disease, acne, atopic dermatitis, contact dermatitis, eczema, impetigo, rashes, psoriasis, plaque psoriasis, or Behcet's disease.

53. The use of any one of claims 50 to 52, wherein the skin disease is basal cell carcinoma, squamous cell carcinoma, or melanoma.

54. The use of any one of claims 50 to 52, wherein the skin disease is an inflammatory skin disease.

55. The use of any one of claims 50 to 52, wherein the skin disease is an autoimmune skin disease.

56. Use of the system of any one of claims 1 to 38 in the manufacture of a medicament for treating a mucosal cancer in a subject in need thereof.

57. The use of claim 56, wherein the mucosal cancer is an oral cancer, anal cancer, or colorectal cancer.

58. The use of claim 56, wherein the system of claim 36 is to be applied to a tumor in an oral cavity of the subject in need thereof.

59. A system of any one of claims 1 to 38 for use in therapy.