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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING GEMCITABINE AND CYCLODEXTRINES

(57) Abstract: The present invention provides a pharmaceutical composition comprising gemcitabine and cyclodextrin. The pharmaceutical formulation is suitable for liquid parenteral administration.

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PHARMACEUTICAL COMPOSITIONS COMPRISING GEMCITABINE AND CYCLODEXTRINES

The present invention relates to a liquid composition comprising the known compound gemcitabine. In particular, the present invention relates to a liquid composition comprising gemcitabine and a cyclodextrin; which liquid composition is stable and pharmaceutically elegant.

Gemcitabine hydrochloride is an anti-tumor agent, with known antiviral action, that is currently produced and marketed as Gemzar®, a lyophilised, powder formulation for treatment of various cancers.

Gemcitabine was first described in US Patent 4,808,614, herein incorporated by reference, as an antiviral compound. The anti-tumor properties of gemcitabine were later described in US Patent 5,464,826, herein incorporated by reference. The formulation teachings of US Patents 4,808,614 and 5,464,826 provide that the compounds claimed therein can be administered parenterally, and that a dried powder, which is then reconstituted in an aqueous solution, is preferred. Currently, Gemzar is marketed as a freeze-dried parenteral that is then reconstituted by the administrating personnel prior to administration by injection or infusion.

A ready to use stable solution that could be stored at room temperature is particularly desired for a pharmaceutical such as gemcitabine, wherein such ready to use formulation provides easier, safer handling, storage, and distribution. Further, a stable, ready to use formulation is more acceptable to the customer.

It has now been discovered that pharmaceutically acceptable, concentrated, ready to use, liquid solutions of gemcitabine may be prepared when the formulation includes a sulfobutyl ether derivative of beta-cyclodextrin (SBECD) and a suitable buffer. This formulation does not require expensive freeze-drying and is ready to use with no reconstitution required. The novel formulation can be adjusted to be isotonic and may be directly administered or further diluted prior to administration.

The claimed formulation is expected to exhibit acceptable stability, less than 0.5% decomposition or precipitation of active ingredient for two years at room temperature; solubility, contains at least 40 mg/mL of active ingredient; and fulfils the health care

provider's desire for a stable, ready to use liquid formulation. Additionally, the formulation provided herein, is suitable for parenteral dosage and can be delivered to the health care provider as an aqueous solution.

The present invention addresses the need for a pharmaceutically stable liquid gemcitabine formulation having acceptable shelf life stability with regard to retaining the solution dosage form and avoiding unacceptable degradation to undesired related substances. Additionally, the claimed formulations can be administered directly or diluted to the desired administration concentration by the health care provider. Finally, the formulations provided herein do not require freeze-drying to maintain stability of the compound.

The present invention particularly provides a pharmaceutical composition comprising:

a) gemcitabine; and

b) a cyclodextrin.

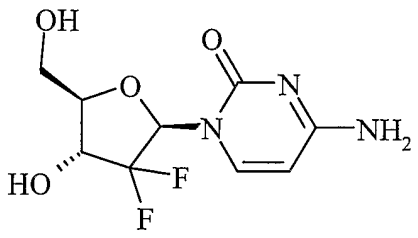
Preferrably the pharmaceutical composition is a liquid formulation suitable for parenteral administration, wherein the cyclodextrin is a sulfobutylether beta-cyclodextrin. Most preferred is the pharmaceutical composition wherein the sulfobutylether beta-cyclodextrin is Captisol®.

Another aspect of the present invention is a gemcitabine-captisol complex.

The term "cyclodextrin" as used herein means a cyclic oligosacchride consisting of a variable number of D-glucose residues attached by α-(1,4) linkages, as defined in "Water Insoluble Drug Formulation," edited by Rong Liu, pp 112, 2000, Interpharm Press. Preferred cyclodextrins are the sulfobutyl ether beta-cyclodextrins. Sulfobutylether beta-cyclodextrins (hereinafter refered to as "SBECD") are uniquely effective for the claimed formulation. A most preferred SBECD is commercially available as Captisol® from CyDex in Lawerance, Kansas, USA. Surprisingly, cyclodextrins significantly improved the stability and solubility of the novel.

The concentration of cyclodextrin to gemcitabine for use in the present invention is a mole to mole ratio of about 0.1:1.0 to about 2.0:1.0. Preferably the concentration of cyclodextrin to gemcitabine is about 0.5:1.0 to 1.0:1.0.

As used herein, the term "gemcitabine" refers to the stable salts, acids and free base forms of 2'-deoxy-2',2'-difluorocytidine as represented in formula I. The term includes, for example, the free base of gemcitabine, gemcitabine HCl, or Gemzar®. The skilled artisan will appreciate that Captisol® can and does form a novel complex with gemcitabine. Nuclear magnetic resonance studies including chemical shift changes, nuclear overhauser enhancements and diffusion data confirm the formation of an inclusion complex of gemcitabine with sulfobutyl ether derivative of beta cyclodextrin. Gemcitabine HCl is particularly preferred for use in the present formulation.



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The skilled artisan would appreciate the formulation should be adjusted to a range of about 5 to about 8 for human use. This adjustment is traditionally achieved through the use of buffers or pH adjusting exipients. Preferred buffers and exipients include but are not limited to phosphate buffer, acetate buffer, phosphoric acid, hydrochloric acid, and sodium hydroxide.

The pH of the formulation is most preferably from about 4.5 to about 9. The formulation is more preferably from about pH 5.0 to about 8. It is especially desired that the pH of the formulation is from 5.5 to 7.0. The artisan will appreciate that combinations of the components of the formulation can provide new preferred pH ranges. Standard modifications of the composition can provide compositions of various pH within the contemplation of this invention.

The artisan will appreciate that the use of depyrogenated prewashed vials is desired for the storage of a sterile liquid formulation that is intended for parenteral use. The vial may be colored; however, a clear vial is acceptable for storage of the formulation. Any pharmaceutically acceptable material may be used to make the formulation container; however, glass is an especially preferred container material. A

glass vial is a preferred container. Other packaging materials for parenterals like plastic vials are preferred options as well. For example, plastic vials may be useful.

The resulting formulation can be sterilized using methods known to the artisan. Such sterilisation methods may include, for example, sterile filtration or heating. It is especially beneficial that the presently claimed formulation is stable during heat sterilization.

The pharmaceutical formulation provided herein is suitable for both human clinical use and veterinarian use for animals.

Gemcitabine can be prepared using the processes described in United States Patent 5,464,826, hereby incorporated by reference in its entirety. Compositions of gemcitabine are useful to treat cancer, as described in the '826 patent.

Description of Preferred Embodiments.

The present invention is seen more fully by the examples given below.

Preparation of gemcitabine free base

To prepare the free-base of gemcitabine, add gemcitabine hydrochloride (5.0g) and potassium carbonate (4.0 g, 1.5 molar equivalents) to a 1.0 L round bottom flask. Then add dichloromethane (350 mL) and ethanol (300 mL). Stir vigorously the contents of the flask at room temperature overnight. Filter the milky white solution with a fritted funnel to a clean bottle. Remove a majority of the solvent by evaporation with the aid of forced dry air. Place the solids under high vacuum for 8 hours at 30° C. Free-base verification was done by ^{1}H-NMR. Yeild = 86wt%

Preparation of plates

Glass plates having reaction wells and a means of sealing these wells were used for these experiments. Prepare four plates in accordance with Table 1. Create plate 1 with 40 mg of gemcitabine per well, and create plates 2-4 with 50 mg gemcitabine per well. Dispense gemcitabine hydrochloride in column 1, and dispense the free base of gemcitabine to column 2. Prepare and dispense aqueous solutions of Captisol (1 molar equivalent to gemcitibine) to the appropriate wells. Dry the plates and then appropriately dispense water and co-solvent to the plates.

Table 1

Row		% water	Column 1 Hydrochloric acid	Column 2 Captisol
A	Ethanol	100		
B		80		
C		60		
D		40		
E	Propylene Glycol	100		
F		80		
G		60		
H		40		

Storage Conditions

Seal the vessels, shake for 42 hours at room temperature to allow the samples to reach solution equilibrium for solubility measurements. For stability measurements, heat plate 2 to 55°C, plate 3 to 70°C, and plate 4 to 85°C. Take and dilute aliquots, then store in a refrigerator at approximately 5°C until analyzed.

Results

Room Temperature solubility

Table 2 shows the gemcitibine solubility measured after equilibrium for 42 hours at room temperature. The table shows that both formulations were highly soluble in water.

Table 2

Row		% water	Hydrochloric acid mg/mL	pH	Captisol mg/mL	pH
A	Ethanol	100	42.1	2.3	35.0	9.8
B		80	43.1	2.2	31.8	10.1
C		60	46.6	2.2	33.2	10.3
D		40	39.4	2.3	32.0	10.6
E	Propylene Glycol	100	47.9	2.3	37.0	9.8
F		80	43.7	2.1	32.3	9.9
G		60	40.9	2.1	31.4	10.1
H		40	37.7	2.0	26.7	10.3

β-uridine formation, rate constants, and $t_{5\%}$ from 1st order kinetic model

To follow the stability of gemcitibine in these solutions, heat plates 2, 3, and 4 to 55, 70, and 85°C, respectively, and draw aliquots over 18 days and analyze for gemcitabine potency and the formation of its β-uridine analog degradation product by HPLC. Use the concentrations of the β-uridine analog of gemcitibine to calculate the degradation rate constants of gemcitibine at the three temperatures. Use these rate constants to construct an Arrhenius plot which then is used to calculate the degradation rate constant at 25°C (see Jansen, P.J, et al. The degradation of the Antitumor Agent Gemcitibine HCl in an Acidic Aqueous Solution at pH 3.2 and Identification of Degradation Products. J. Pharmaceutical Sciences, 89(7) 885-891). Tables 3-5 show pseudo first-order degradation rate constants for gemcitibine in $days^{-1}$.

Table 3: 55°C—plate 2

Row		% water	Column 1 Hydrochloric acid	Column 2 Captisol
A	Ethanol	100	2.86×10^{-2}	4.05×10^{-6}
B		80	3.70×10^{-2}	6.29×10^{-6}
C		60	5.77×10^{-2}	1.48×10^{-5}
D		40	4.66×10^{-2}	6.88×10^{-6}
E	Propylene Glycol	100	2.86×10^{-2}	2.57×10^{-6}
F		80	2.91×10^{-2}	9.24×10^{-6}
G		60	2.09×10^{-2}	3.04×10^{-6}
H		40	1.96×10^{-2}	-

Table 4: 70°C—plate 3

Row		% water	Column 1 Hydrochloric acid	Column 2 Captisol
A	Ethanol	100	1.61×10^{-1}	2.51×10^{-5}
B		80	1.37×10^{-1}	2.44×10^{-5}
C		60	1.28×10^{-1}	4.92×10^{-5}
D		40	1.34×10^{-1}	2.13×10^{-5}
E	Propylene Glycol	100	1.32×10^{-1}	2.84×10^{-5}
F		80	8.15×10^{-2}	3.10×10^{-5}
G		60	7.29×10^{-2}	3.61×10^{-5}
H		40	6.62×10^{-2}	3.55×10^{-5}

Table 5: 85°C—plate 4

Row		% water	Column 1 Hydrochloric acid	Column 2 Captisol
A	Ethanol	100	2.16×10^{-2}	8.27×10^{-4}
B		80	-	2.04×10^{-3}
C		60	1.59×10^{-1}	3.11×10^{-3}
D		40	-	3.10×10^{-3}
E	Propylene Glycol	100	1.49×10^{-2}	8.86×10^{-4}
F		80	1.07×10^{-2}	1.27×10^{-3}
G		60	4.00×10^{-1}	2.00×10^{-3}
H		40	-	1.19×10^{-3}

Table 6 shows the $t_{5\%}$ for degradation of gemcitabine at 25°C in days.

Table 6: 25°C

Row	Column 1 Hydrochloric acid	Column 2 Captisol
A	53.8	10000+
B	39.8	10000+
C	3.9	10000+
D	40.7	10000+
E	22.6	10000+
F	26.8	10000+
G	38.7	10000+
H	92.3	10000+

Scale up #1

Add gemcitabine (148 mg) and captisol (1200mg) to a 3 mL vial. Add water (1.0 mL) and shake the vial at room temperature for 15 hours. Add a solution of HCl (190 µL, 1.0M) to bring the pH to 6.0. The concentration determined by HPLC was 48 mg/mL.

Heat the vial to 85°C, and monitor the formation of β-uridine.

Time (days)	Normalized Concentration of β-uridine
0	0.000
1	0.008
4	0.069
6	0.042

Scale up #2

Prepare a dry mixture of gemcitabine HCl/captisol (1:1 mole ratio). Slowly add the mixture to water (1.0 mL) until there remains a small amount of solids that will not dissolve (150 mg gemcitabine HCl, 1075 mg of captisol). Add a solution of NaOH (450 µL, 1.0M) to bring the pH to 5.5. The concentration determined by HPLC was 63.7 mg/mL.

Heat the vial to 85°C, and monitor the formation of β-uridine.

Time (days)	Normalized Concentration of β-uridine
0	0.000
3	0.015
5	0.071

Formulations of gemcitabine with captisol have significantly improved stability over the hydrochloride salt with room temperature stability predicted to be measured in years. The solubility of the captisol complex formulations is high (>40 mg/mL). Scale-up of the captisol formulations demonstrate that the pH of such formulations can be adjusted to be between 5 and 7 while maintaining high solubility.

Set up plate 8, as shown in Table 7, containing an 8 x 2 array of 8 mL vials containing stir bars. Dispense 300 mg of gemcitabine HCl to column 1 and 300 mg of gemcitabine freebase to columns 2. Dispense 2500 mg (1 molar equivalent) Captisol to each vial in rows 1 - 4. Dispense 1250 mg (1/2 molar equivalent) Captisol to each vial on rows 5 - 8. Add 2.5 mL water to each vial of the plate and seal and stir all 16 vials for

four days. Subsequently, measure the pH of each vial in plate 8 and then adjust to its target pH using concentrated HCl and NaOH solutions. Allow solutions to equilibrate for an additional two days (six total days in solution). Measure and record the final pH of each vial. Aspirate 1.0 mL aliquots from each vial on plate 8 (the source plate) and transfer to three plates (Plates 9, 10 and 11).

Table 7

Row		pH	Column 1 Hydrochloric acid	Column 2 Captisol
A	1.0 Equivalent Captisol	5.5		
B		6.5		
C		7.0		
D		7.5		
E	0.5 Equivalent Captisol	5.5		
F		6.5		
G		7.0		
H		7.5		

For stability measurements, heat plate 9 to 55°C, Plate 10 to 70°C, and Plate 11 to 85°C. Draw aliquots from the sealed plates using a piercing needle. Dispense aliquots to a microtiter vial plate and dilute to a concentration appropriate for subsequent HPLC analysis. Store aliquots taken and diluted in a refrigerator at 5°C until analyzed. Table 8 shows the extrapolated first-order degradation rate constant for gencitibine from these experiments in day^{-1}.

Table 8

Row		pH	Column 1 Hydrochloric acid	Column 2 Captisol
A	1.0 Equivalent Captisol	5.5	4.04×10^{-4}	3.06×10^{-5}
B		6.5	2.89×10^{-5}	9.59×10^{-6}
C		7.0	1.54×10^{-5}	8.90×10^{-5}
D		7.5	2.29×10^{-5}	5.95×10^{-6}
E	0.5 Equivalent Captisol	5.5	7.91×10^{-5}	3.16×10^{-4}
F		6.5	4.76×10^{-5}	1.29×10^{-4}
G		7.0	3.08×10^{-5}	5.33×10^{-4}
H		7.5	3.33×10^{-5}	2.40×10^{-5}

The time, in days, for 5% gemcitibine degradation is calculated from these data and shown in Table9.

Table 9.

Row		pH	Column 1 Hydrochloric acid	Column 2 Captisol
A	1.0 Equivalent Captisol	5.5	127	1676
B		6.5	1774	5344
C		7.0	3335	579
D		7.5	2235	8619
E	0.5 Equivalent Captisol	5.5	648	162
F		6.5	1077	399
G		7.0	1668	96
H		7.5	1538	2117

We Claim:

1. A pharmaceutical composition comprising:
a) gemcitabine and
b) a cyclodextrin.

2. The pharmaceutical composition as claimed by Claim 1 wherein the composition is a liquid formulation suitable for parenteral administration.

3. The pharmaceutical composition as claimed by any one of Claims 1 and 2 wherein the cyclodextrin is a sulfobutylether beta-cyclodextrin.

4. The pharmaceutical composition as claimed by Claim 3 wherein the sulfobutylether beta-cyclodextrin is Captisol®.

5. The pharmaceutical composition as claimed by any one of Claims 1-4 wherein the composition further comprises a buffer or pH adjusting exipient.

6. The pharmaceutical composition as claimed by any one of Claims 1-5 wherein the gemcitabine is gemcitabine HCl.

7. The pharmaceutical composition as claimed in any one of Claims 1 -6 wherein the gemcitabine/cyclodextrin mole ratio is from about1.0:0.1 to about 1.0:2.0.

8. The pharmaceutical composition of Claim 7 wherein the gemcitabine/captisol mole ratio is from about 1.0:0.5 to about 1.0:1.0.

9. A gemcitabine-captisol complex.

10. The complex of claim 9 for use in the manufacture of a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

Ir onal Application No
I ..., JS2004/018928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7068 A61K31/724 A61K47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/032161 A1 (ON NINH ET AL) 14 March 2002 (2002-03-14) the whole document	1-10
A	EP 0 719 788 A (LILLY CO ELI) 3 July 1996 (1996-07-03) the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2004	03/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Albayrak, T

INTERNATIONAL SEARCH REPORT

Int[illegible]onal Application No
PCT/US2004/018928

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THORSTEINN LOFTSSON ET AL: "Pharmaceutical Applications of Cyclodextrins. 1. Drug Solubilization and Stabilization" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 85, no. 10, 1 October 1996 (1996-10-01), pages 1017-1025, XP002080430 ISSN: 0022-3549 page 1023, left-hand column, paragraph 2 - page 1024, left-hand column, paragraph 3	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ›nal Application No
PCT/US2004/018928

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