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(54) **HCG LIQUID FORMULATIONS**

FLÜSSIGE HCG-FORMULIERUNGEN

COMPOSITIONS LIQUIDES DE GONADOTROPHINE CHORIONIQUE DE L'HOMME

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Description

[0001] The present invention relates to gonadotropin containing liquid pharmaceutical compositions. More precisely, it concerns liquid formulations of recombinant hCG (human Chorionic Gonadotropin) stabilised with mannitol.

[0002] It is known that highly purified proteins easily undergo degradation, even due to the contact with atmospheric agents. This characteristic is even more evident for proteins produced by recombinant DNA techniques.

[0003] Such proteins are usually stabilised with saccharides, such as lactose. or with mannitol, or else with proteins or aminoacids, such as albumin and glycin.

[0004] The injectable stabilised formulations of gonadotropins are obtained with a process which includes always a step of lyophilisation to obtain a dry powder; in such a way the stabilised formulations are able to maintain a longer cycle life, even if stored at room temperature.

[0005] WO 93/11788 describes lyophilised gonadotropin-containing pharmaceutical compositions stabilised with sucrose, alone or in combination with other stabilising agents. In said patent application it is shown that the stability provided to the lyophilised compositions under study by sucrose was better than that provided by lactose or mannitol.

[0006] No liquid stabilised formulations of gonadotropins have been described until now. It is highly desirable to obtain such liquid formulations so as to have the compositions ready to be injected and to avoid the reconstitution of the lyophilised powder, thus simplifying the way of use.

[0007] We have surprisingly found that it is possible to obtain such liquid stabilised formulations.

[0008] The main object of the present invention is to provide a liquid pharmaceutical composition containing recombinant hCG stabilised with mannitol.

[0009] The solution is preferably a buffered aqueous solution and the buffer according to the invention is selected from the group consisting of phosphate, acetate or succinate buffer. The preferred buffer is phosphate and the pH is preferably 7.00.

[0010] The recombinant hCG can be prepared, for example, by expression in CHO (Chinese Hamster Ovary) cells, transformed with the corresponding DNA, according to the technique described in European Patent 160699.

[0011] A further object of the present invention is to provide a process for the preparation of said liquid pharmaceutical composition comprising diluting a hCG bulk solution in a buffer solution containing the excipients.

[0012] Still another object of the present invention is to provide a form of presentation of said liquid pharmaceutical composition comprising such formulation hermetically closed in a sterile condition in a container suitable for the storage before the use.

[0013] In order to optimise the stability of the hCG formulations of the invention a series of preliminary experiments have been carried out with different buffers at various pH, ionic strength, dielectric constant and concentration of rec-hCG.

[0014] In order to evaluate the effect of pH and of the buffer, 0.01 M solutions of phosphate, succinate or acetate buffers were prepared with water for injection. The pH was adjusted to 6.0, 7.0 or 8.0 with NaOH 1 M. The bulk solution of rec-hCG was added to the buffer systems to obtain solutions at 5,000 IU/ml. The solutions were then filtered and poured into 3 ml glass vials. The composition of the formulations thus prepared is reported in Table 1. The accelerated stability of these formulations has been studied, so that the stability of the same can be foreseen when they are stored in containers at room temperature, through the extrapolation of the data at higher temperatures. In this case the samples were stored at 40° and 50°C and the stability of rec-hCG was checked by determining its purity by HPSEC analyses according to the following standard conditions:

Phase A	0.1 M phosphate pH 6.7 + 0.1 M Na_2SO_4
Isocratic conditions	100% phase A
Column	TSK G 2000 SWXL
Flow Rate	0.5 ml/min
UV Detector	214 nm
Injection Volume	20 µl (10.000 IU strength)
	40 µl (5,000 IU strength)

[0015] Table 3 reports the percentage of rec-hCG monomer peak determined by HPSEC. The results show that the solutions at pH 6.0 and 8.0 are less stable in comparison with the solutions at pH 7.0 and that no remarkable stability differences were observed among the buffers.

[0016] The effect of the ionic strength was evaluated on rec-hCG 5,000 IU/ml solutions, prepared with phosphate and succinate buffers 0.01M at pH 7.0, adjusted with NaCl to the following values of osmolality: 150, 300 and 400 mOsm. The composition of the formulations is reported in Table 2. The samples were stored at 4°, 25°, 40° and 50°C and tested for the stability of rec-hCG by HPSEC. The results, reported in table 4, show that the increase of ionic

strength negatively affects the stability of rec-hCG.

[0017] The effect of the dielectric constant was evaluated on 5,000 IU/ml solutions of rec-hCG, prepared with phosphate and succinate buffers 0.01 M at pH 7, containing 5, 10 and 15% propylene glycol. The composition of the formulations is reported on Table 2. The samples were stored at 4°, 25°, 40° and 50°C and tested for the stability of rec-hCG by HPSEC. The results, reported in Table 4, show that increasing the percentage of propylene glycol negatively affects the stability of rec-hCG.

[0018] In order to evaluate the effect of the rec-hCG concentration, the stability at 50°C of the solutions in phosphate buffer 0.01 M at pH 7.0, containing respectively 2,500, 5,000, 7,500 and 10,000 IU/ml of rec-hCG was monitored by HPSEC for 2 weeks. The results reported in Table 5 showed that the stability was higher for the more concentrated solutions.

[0019] In order to compare the effects of various stabilisers and/or excipients on the stability of rec-hCG, six liquid formulations, in phosphate buffer 0.01 M at pH 7.0 containing 10,000 IU/ml rec-hCG were prepared, as a first step. Sucrose, glycine, glucose, mannitol, lactose and NaCl were used, as stabilisers/excipient. Experiments with sucrose, glycine, glucose, lactose and NaCl were carried out for comparison with mannitol.

[0020] The composition of the formulations is reported in Table 6. These formulations were submitted to the stability tests by storing samples at 4°, 25°, 40° and 50°C and tested by a Bioassay and HPSEC. Subsequently, based on the results of said first step, four lots of two selected liquid formulations were prepared, using as stabilisers sucrose and mannitol. Table 7 reports the composition of such formulations.

[0021] The Bioassay has been carried out in accordance with the European Pharmacopoeia Monograph.

[0022] In Table 8 the HPSEC stability data are reported and in Table 9 the values of bioactivity are reported . The results showed the following:

1. the bioactivity of the formulations containing glucose and lactose remarkably decreased at 50°C after 1 week storage. Also monomer peak was lower compared to that measured in the other formulations.
2. in the presence of glycine and NaCl a more evident decrease of bioactivity and of purity was measured in comparison to the formulations containing sucrose and mannitol. Also in this case the decrease of the percentage of the rec-hCG monomer peak, was not due to the formation of aggregates forms, but to the increase of free subunits.

[0023] Tables 10 and 11 report the purity determined by HPSEC for the 5,000 and 10,000 IU strength respectively. Data show that even after three weeks at 50°C the purity is higher in the formulations containing mannitol compared to the formulations containing sucrose. Tables 12 and 13 report the purity of the α subunit determined by reverse phase HPLC after 1 week storage at 50°C for the sucrose and mannitol formulations. The data confirm the better stability of the formulation containing mannitol in comparison to that containing sucrose.

[0024] Reverse Phase HPLC analyses have been performed with the following standard conditions:

Phase A	1 ml TFA in 1 liter of bidistilled water		
Phase B	0.79 ml TFA in 1 liter of acetonitrile		
Gradient conditions	time	A%	B%
	0	85	15
	20'	60	40
	21'	20	80
	22'	85	15
Column	Aquapore RP 300 25 cm		
Column temperature	40°C		
Flow Rate	1 ml/min		
UV detector	214 nm		
Injection volume	10 µl		

[0025] In the Tables 14 and 15 the results of the bioactivity assay are reported. No appreciable bioactivity decrease was observed after 24 weeks at 4° and 25°C in the mannitol formulation.

[0026] According to the present invention, the liquid pharmaceutical compositions contain from 1,000 to 40,000 IU/ml, preferably 10,000 IU/ml, of hCG and from 10 to 180 mg/l, preferably 54.6 mg/l, of mannitol in a 0.01 M buffer solution.

EXAMPLES OF PHARMACEUTICAL MANUFACTURING

[0027] Materials: Phosphoric acid 85% RPE ACS (Carlo Erba); Mannitol DAB, Ph Eur BP, FU, USP, FCC, E421 (Merck), NaOH 1 M (Merck), water for injections.

[0028] The primary container for the formulated vials consists of: 3 ml glass vials (DIN 2R) (borosilicate glass type I), Rubber closures (Pharmagummi W1816 V50), Aluminium rings and flip off caps (Pharma Metal GmbH).

Preparation of rec-hCG solution containing mannitol

[0029] The phosphoric acid (0.98 g) is added to the water for injections (600 ml). If necessary, the pH is adjusted to 7.0 with NaOH 1 M. Mannitol (54.6 g) is added to the phosphoric acid solution and the pH is again checked and, if necessary, adjusted to 7.00 ∓ 0.2 with NaOH 1 M or with phosphoric acid diluted 1:5. The rec-hCG bulk (10 MIU or 20 MIU, if the final desired strenght is 5,000 or 10,000 IU respectively) is then added to the excipient solution and the pH is again checked and, if necessary, adjusted to 7.00 ∓ 0.2 with NaOH 1 M or with phosphoric acid diluted 1:5.

[0030] The solution is brought to 1 liter with water for injections. Such solution is then filtered through a 0.22 μm Millipak 20 filter under a pressure not higher than 1.5 atm, under laminar flow, collecting the solution intoa flask and stirring gently for about 1 minute.

[0031] The vials are then filled up with 0.5 ml of the rec-hCG solution.

TABLE 1 -

COMPOSITION OF r-hCG SOLUTIONS pH/buffer effect	
Acetate buffer solution	**Amount/ml**
r-hCG bulk	5000 IU
Acetic acid glacial	0.6 mg
NaOH 1M	q.s. to pH 6.0,7.0,8.0
Succinate buffer solution	
r-hCG bulk	5000 IU
Succinic acid	1.18 mg
NaOH 1M	q.s. to pH 6.0,7.0,8.0
Phosphate buffer solution	
r-hCG bulk	5000 IU
Phosphoric acid 85%	0.98 mg
NaOH 1M	q.s. to pH 6.0,7.0,8.0
Filling volume: 1 ml	

TABLE 2 - COMPOSITION OF r-hCG SOLUTIONS

Ionic strength/dielectric constant

Lot	r-hCG	NaCl	Prop. glyc.	Phosp. buffer 0.01 pH 7.0	Succinate buffer 0.01 M pH 7.0
Fos/7.0/PG 5	5000 IU/ml	-	50 mg/ml	q.s. to 1 ml	-
Fos/7.0/PG 10	5000 IU/ml	-	100 mg/ml	q.s. to 1 ml	-
Fos/7.0/PG 15	5000 IU/ml	-	150 mg/ml	q.s. to 1 ml	-
Suc/7.0/PG 5	5000 IU/ml	-	50 mg/ml	-	q.s. to 1 ml
Suc/7.0/PG 10	5000 IU/ml	-	100 mg/ml	-	q.s. to 1 ml
Suc/7.0/PG15	5000 IU/ml	-	150 mg/ml	-	q.s. to 1 ml

Filling volume: 1 ml
FOS = Phosphate buffer
SUC = Succinate buffer
7.0 = pH 7.0
PG 5 = propylene glycol 5%
PG 10 = propylene glycol 10%
PG 15 = propylene glycol 15%

TABLE 2 (CONT.)

LOT	r-hCG	NaCl	Prop. glyc.	Phosp. buffer 0.01 pH 7.0	Succinate buffer 0.01 M pH 7.0
Fos/7.0/150	5000 IU/ml	4.4 mg/ml	-	q.s. to 1 ml	-
Fos/7.0/300	5000 IU/ml	8.8 mg/ml	-	q.s. to 1 ml	-
Fos/7.0/400	5000 IU/ml	11.7 mg/ml	-	q.s. to 1 ml	-
Suc/7.0/150	5000 IU/ml	4.4 mg/ml	-	-	q.s. to 1 ml
Suc/7.0/300	5000 IU/ml	8.8.mg/ml	-	-	q.s. to 1 ml
Suc/7.0/400	5000 IU/ml	11.7 mg/ml	-	-	q.s. to 1 ml

Filling volume: 1 ml
150, 300, 400: osmolarity
FOS = Phosphate buffer
SUC = Succinate buffer
7.0 = pH 7.0

TABLE 3 - r-hCG PURITY (%)

HPSEC DATA

pH/Buffer effect

		50 °C			40° C	
LOT	T=0	1 W	3 W	5 W	3 W	5 W
ACE/6	100	95.85	92.70	84.99	97.51	94.10
ACE/7	100	96.62	93.26	88.02	97.27	94.05
ACE/8	100	96.51	92.70	87.10	97.45	95.12
SUC/6	100	94.56	91.28	82.11	96.92	93.11
SUC/7	100	95.78	94.20	88.05	96.91	93.99
SUC/8	100	95.36	90.12	83.00	97.61	94.02
FOS/6	100	94.10	90.76	81.00	97.50	93.00
FOS/7	100	96.09	93.12	86.93	96.72	93.74
FOS/8	100	94.21	82.52	74.96	96.77	93.55

W = week
ACE = acetate buffer
SUC = succinate buffer
FOS = phosphate buffer
6/7/8 = pH 6.0, 7.0, 8.0

TABLE 4 - r-hCG PURITY (%)
HPSEC DATA

Ionic strength/dielectric constant

LOT		50°C			40°C		25°C	4°C
	T=0	1 W	2 W	4 W	3 W	6 W	6 W	4 W
Fos/7.0/PG 5	100	91.9	85.7	80.8	96.5	94.3	100	100
Fos/7.0/PG 10	100	91.9	81.0	77.7	93.9	93.9	100	100
Fos/7.0/PG 15	100	89.2	79.3	76.2	94.4	93.8	100	100
Suc/7.0/PG 5	100	90.6	84.3	-	91.7	-	-	-
Suc/7.0/PG 10	100	88.9	81.4	-	94.1	-	-	-
Suc/7.0/PG15	100	89.3	79.9	-	93.5	-	-	-

- = not tested
FOS = Phosphate buffer
SUC = Succinate buffer
7.0 = pH 7.0
PG 5 = propylene glycol 5%
PG 10 = propylene glycol 10%
PG 15 = propylene glycol 15%
W= week

TABLE 4 (CONT.)

LOT		50°C			40°C		25°C	4°C
	T=0	1 W	2 W	4 W	3 W	6 W	6 W	4 W
Fos/7.0/150	100	88.5	79.2	72.2	93.0	93.0	100	100
Fos/7.0/300	100	80.5	75.0	67.9	93.4	92.1	100	100
Fos/7.0/400	100	81.5	74.8	67.4	94.6	93.8	100	100
Suc/7.0/150	100	83.1	87.4	-	94.3	-	-	-
Suc/7.0/300	100	82.4	76.7	-	93.9	-	-	-
Suc/7.0/400	100	81.8	74.6	-	93.5	-	-	-

- = not tested
FOS = Phosphate buffer
SUC = Succinate buffer
7.0 = pH 7.0
150, 300, 400 = osmolarity
W = week

TABLE 5 - r-hCG PURITY (%)

HPSEC DATA

concentration effect

LOT		50°C	
	T=0	1 W	2 W
Fos /2500	100	87.3	84.0
Fos/5000	100	90.8	89.1
Fos/7500	100	92.9	89.8
Fos/10000	100	92.5	90.9

Fos/2500: 2,500 IU/ ml of r-hCG
Fos/5000 :5,000 IU/ ml of r-hCG
Fos/7500: 7,500 IU/ ml of r-hCG
Fos/10000:10,000 IU/ml of r-hCG

TABLE 6 - LIQUID FORMULATIONS

Vial composition

COMPONENTS/ LOT	r-hCG/ SAC	r-hCG/ MAN	r-hCG/ GLY	r-hCG/ GLU	r-hCG/ LAT	r-hCG/ NaCl
r-hCG IU/ml	10,000	10,000	10,000	10,000	10,000	10,000
SUCROSE mg/ml *	102.6	-	-	-	-	-
MANNITOL mg/ml	-	54.6	-	-	-	-
GLYCINE mg/ml *	-	-	22.52	-	-	-
GLUCOSE mg/ml *	-	-	-	54.6	-	-
LACTOSE mg/ml *	-	-	-	-	102.6	-
NaCl mg/ml *	-		-		-	9.0

Buffer : H_3PO_4 0.01 M , pH 7.0
Filling volume: 0.5 ml

Experiments marked with an asterisk were carried out for comparison

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TABLE 7 - LIQUID FORMULATIONS

Vial composition

Comparison Experiment:

COMPONENT	UNIT	r-hCG/5000/S01	r-hCG/10000/S01
r-hCG	IU/ml	10,000	20,000
SUCROSE	mg/ml	102.6	102.6
O. PHOSPHORIC ACID	mg/ml	0.98	0.98
SODIUM HYDROXIDE		q.s. to pH 7.0	q.s. to pH 7.0

Example according to the invention:

COMPONENT	UNIT	r-hCG/5000/M01	r-hCG/1000/M01
r-hCG	IU/ml	10,000	20.000
MANNITOL	mg/ml	54.6	54.6
O. PHOSPHORIC ACID	mg/ml	0.98	0.98
SODIUM HYDROXIDE		q.s. to pH 7.0	q.s. to pH 7.0

Filling volume : 0.5 ml

TABLE 8 - COMPATIBILITY WITH DIFFERENT EXCIPIENTS

HPSEC stability data: purity (%)

LOT		50°C			40° C				25° C				4°C	
	T=0	1 W	2 W	6 W	2 W	4 W	6 W	11 W	4 W	6 W	8 W	11 W	8 W	12 W
FOS/SAC*	100	94.1	90.3	83.0	98.0	95.5	96.1	94.8	100	100	100	100	100	100
FOS/GLY*	100	94.2	90.4	81.5	97.5	96.3	95.5	95.5	100	100	100	100	100	100
FOS/GLU*	100	85.0	74.9	N.T	88.0	N.T	N.T	N.T	N.T	N.T	N.T	N.T	N.T	N.T.
FOS/MAN	100	94.0	91.7	83.5	97.9	97.1	95.8	95.4	N T	100	100	100	100	100
FOS/LAT*	100	88.3	71.6	N.T	89.0	N.T	N.T	N.T	N.T	N.T	N.T	N.T	N.T	N.T
FOS/NaCl*	100	89.7	85.6	71.7	97.2	95.2	94.2	94.1	N T	100	100	98.5	100	100

W = week
Filling volume = 0.5 ml
FOS = Phosphate buffer
SAC = Sucrose, GLY = glycine, GLU = glucose, MAN = mannitol, LAT = lactose
N.T. = not tested

Experiments marked with an asterisk were carried out for comparison

TABLE 9 - COMPATIBILITY WITH DIFFERENT EXCIPIENTS

Bioassay data (IU/ml)

LOT		50°C			40° C				25° C		4° C	
	T=0	1 W	2 W	7 W	2 W	4 W	7 W	10 W	8 W	11 W	8 W	12 W
FOS/SAC *	9473	7854	8245*	N.V.	8098	10368	9126	8269	8809*	11222	9588	8489
FOS/GLY*	7850*	5642	4913	-	6421	8112	6780	6635*	-	7159	-	6821*
FOS/GLU*	8370	N.V.	-	-	-	-	-	-	-	-	-	-
FOS/MAN	9498	7031	7224	6321*	10605	13216	9374*	6904	7285	7941	10079	8762
FOS/LAT*	7976	N.V.	-	-	-	-	-	-	-	-	-	-
FOS/NaCl*	8486	8394	6433	-	9262	10576		7578	9151*	9353*	8804	8377

W= week
Filling volume=0.5 ml
* = one valid assay
n.v.= not valid assay
- = not tested
FOS: Phosphate buffer, SAC = Sucrose, GLY = glycine, GLU = glucose, MAN = mannitol, LAT = lactose

Experiments marked with an asterisk were carried out for comparison

TABLE 10 - LIQUID FORMULATION: CONC. 5,000 IU/vial

HPSEC Stability data: purity (%)

Formulation development

LOT		50°C		40° C
	T=0	1 W	3 W	3 W
HCG/5000/S01	100	90.0	86.3	97.2
HCG/5000/M01	100	89.5	88.3	97.6

W=week
S01=sucrose (Comparison Experiment)
M01=mannitol

TABLE 11 - LIQUID FORMULATION: CONC. 10,000 IU/vial

HP-SEC Stability data: purity (%)

Formulation development

LOT		50°C		40 ° C
	T=0	1 W	3 W	3 W
HCG/10000/S01	100	91.8	88.9	97.9
HCG/10000/M01	100	93.4	92.1	97.2

W=week
S01=sucrose (Comparison Experiment)
M01=mannitol

TABLE 12 - LIQUID FORMULATION

α subunit purity by RP-HPLC

LOT		50°C
	T=0	1 W
HCG/5000/S01 α(%)	100	90.2
HCG/5000/M01 α(%)	100	94.7

W= week
S01 = Sucrose (Comparison Experiment)
M01= Mannitol

TABLE 13 - LIQUID FORMULATION

α subunit purity by RP-HPLC

LOT		50°C
	T=0	1 W
HCG/10000/S01 α(%)	100	92.4
HCG/10000/M01 α(%)	100	95.1

W= week
S01 = Sucrose (Comparison Experiment)
M01= Mannitol

TABLE 14 - LIQUID FORMULATION
Bioassay data (IU/ml)

LOT		50°C			
	T=0	1 W	3W	4W	5W
HCG/5000/S01	09194 (7484-11298)	6427 (4770-8660)	6757 (5454-8371)	-	N V
HCG/5000/M01	8548 (6376-11459)	9249 (7495-11414)	6977 (5649-8618)	6207 (4767-8082)	3219* (1436-5150)

LOT	40°C			
	4 W	6 W	10 W	13 W
HCG/5000/S01	8682* (6082-12393)	10102 (7733-13195)	8192 (6276-10692)	-
HCG/5000/M01	10203 (7813-13325)	7959 (6118-10356)	-	7309 (5932-9005)

W = Week
N V = not valid assay
S01 = Sucrose (Comparison Experiment)
M01 = Mannitol
* = one valid assay

TABLE 14 (CONT.)

LOT		25°C		
	T=0	5 W	13 W	24 W
HCG/5000/S01	9194 (7484-11298)	-	-	-
HCG/5000/M01	8548 (6376-11459)	6660* (3855-10118)	8969 (7007-11479)	8232* (5787-11712)

LOT	4°C		
	5 W	13 W	24 W
HCG/5000/S01	7555 (5904-9667)	-	-
HCG/5000/M01	8869* (5968-12826)	10330 (8167-13065)	9799 (7714-12447)

W=week
NV= not valid assay
*=one valid assay
S01=sucrose (Comparison Experiment)
M01=mannitol

TABLE 15 - LIQUID FORMULATION : 10,000 IU/VIAL

Bioassay data (IU/ml)

LOT		50 °C		
	T = 0	1 W	2 W	4 W
HCG/10000/S01	20273 (15170-27091)	15531 (11842-20368)	14971 (11307-19824)	-
HCG/10000/M01	18919 (14150-25295)	15880 (12605-20006)	13495 (9994-18222)	14855 (11579-19058)

LOT	40°C		
	4 W	6 W	13 W
HCG/10000/S01	22201 (16648-29607)	14977 (12075-18576)	-
HCG/10000/M01	19508 (14201-26797)	14680 (11328-19022)	14606 (11580-18423)

W = Week
N V = not valid assay
S01 = Sucrose (Comparison Experiment)
M01 = Mannitol
* = one valid assay

TABLE 15 (CONT.)

LOT		25 ° C			
	T = 0	5 W	10 W	13 W	24 W
HCG/10000/S01	20273 (15170-27091)	-	17812* (11809-26112)	-	-
HCG/10000/M01	18919 (14150-25295)	17890 (14467-22122)	15494 (12638-18996)	16419 (12890-20915)	18991 (15311-23556)

LOT	4°C		
	5 W	13 W	24 W
HCG/10000/S01	21616 (17596-26555)	-	-
HCG/10000/M01	20666 (17390-24559)	17096 (13503-21646)	19553 (14494-26377)

W = Week
N V = not valid assay
S01 = Sucrose (Comparison Experiment)
M01 = Mannitol
* = one valid assay

Claims

1. A stable, liquid pharmaceutical composition comprising recombinant human Chorionic Gonadotropin and a stabilizing amount of mannitol.

2. A liquid pharmaceutical composition according to Claim 1, wherein the solution is a buffered aqueous solution.

3. A liquid pharmaceutical composition according to Claim 2, wherein the buffer solution is selected from the group consisting of acetate, succinate and phosphate buffer.

4. A liquid pharmaceutical composition according to Claim 3, wherein the buffer is phosphate buffer.

5. A liquid pharmaceutical composition according to any of Claims 2 to 4, wherein the buffer solution is at pH 7.00.

6. A liquid pharmaceutical composition according to any of Claims 2 to 5, wherein the buffer solution is 0.01 M.

7. A liquid pharmaceutical composition according to Claim 1, comprising from 1,000 to 40,000 IU/ml of hCG and from 10 to 180 mg/l of mannitol in a 0.01 M phosphate buffer at pH 7.00.

8. A process for the preparation of a liquid pharmaceutical composition according to Claim 1, comprising diluting a hCG bulk solution in a buffer solution containing the excipients.

9. A form of presentation of a liquid pharmaceutical composition of Claim 1 hermetically closed in a sterile condition in a container suitable for the storage before the use.

Patentansprüche

1. Stabile flüssige pharmazeutische Zusammensetzung umfassend rekombinantes menschliches Choriongonadotropin und eine stabilisierende Menge Mannit.

2. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1, worin die Lösung eine gepufferte wässrige Lösung ist.

3. Flüssige pharmazeutische Zusammensetzung nach Anspruch 2, worin die Pufferlösung ausgewählt ist aus der Gruppe bestehend aus Acetat-, Succinat- und Phosphatpuffer.

4. Flüssige pharmazeutische Zusammensetzung nach Anspruch 3, worin der Puffer Phosphatpuffer ist.

5. Flüssige pharmazeutische Zusammensetzung nach den Ansprüchen 2 bis 4, worin die Pufferlösung einen pH von 7,00 hat.

6. Flüssige pharmazeutische Zusammensetzung nach den Ansprüchen 2 bis 5, worin die Pufferlösung 0.01 M ist.

7. Flüssige pharmazeutische Zusammensetzung nach Anspruch 1, umfassend 1.000-40.000 IU/ml von hCG und 10-180 mg/l Mannit in einem 0,01 M Phosphatpuffer bei pH 7,00.

8. Verfahren zur Herstellung einer flüssigen pharmazeutischen Zusammensetzung nach Anspruch 1, umfassend das Verdünnen einer hCG-Stammlösung in einer die Arzneimittelträger enthaltenden Pufferlösung.

9. Darreichungsform einer flüssigen pharmazeutischen Zusammensetzung nach Anspruch 1 hermetisch in einem sterilen Zustand in einem Behälter verschlossen, welcher für die Lagerung vor der Verwendung geeignet ist.

Revendications

1. Composition pharmaceutique liquide stable comprenant une chorio-gonadotrophine humaine (hCG) recombinante et une quantité stabilisante de mannitol.

2. Composition pharmaceutique liquide suivant la revendication 1, dans laquelle la solution est une solution aqueuse tamponnée.

3. Composition pharmaceutique liquide suivant la revendication 2, dans laquelle la solution tampon est choisie dans le groupe consistant en un tampon à l'acétate, . un tampon au succinate et un tampon au phosphate.

4. Composition pharmaceutique liquide suivant la revendication 3, dans laquelle le tampon est un tampon au phosphate.

5. Composition pharmaceutique liquide suivant l'une quelconque des revendications 2 à 4, dans laquelle la solution tampon est à un pH de 7,00.

6. Composition pharmaceutique liquide suivant l'une quelconque des revendications 2 à 5, dans laquelle la solution tampon est une solution 0,01 M.

7. Composition pharmaceutique liquide suivant la revendication 1, qui comprend de 1000 à 40 000 UI/ml de hCG et de 10 à 180 mg/ml de mannitol dans un tampon au phosphate 0,01 M à pH 7,00.

8. Procédé pour la préparation d'une composition pharmaceutique liquide suivant la revendication 1, qui comprend la dilution d'une solution de hCG en quantité dans une solution tampon contenant les excipients.

9. Forme de présentation d'une composition pharmaceutique liquide suivant la revendication 1 enfermée de façon hermétique à l'état stérile dans un récipient convenable pour le stockage avant l'utilisation.