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Cyclophosphamide film-coated tablets

The invention relates to cyclophosphamide film-coated tablets and to a process for their preparation. The invention can be used in the pharmaceutical industry.

Cyclophosphamide is an agent having a broad antitumor spectrum which has been introduced in chemotherapy for decades for the treatment of solid tumors such as breast carcinoma, bronchial carcinoma and hemoblastoses.

Until now, known pharmaceutical forms have been tablets, coated tablets and mainly lyophilizates with various auxiliaries such as mannitol or urea.

EP 0519099 describes tablets comprising cyclophosphamide and preswollen starch, prepared by a direct tableting process.
Since cyclophosphamide is harmful to health and for this reason direct contact with this substance represents a potential risk, the tablets prepared according to EP 0519099 are used as cores for press-coated tablets and thus coated by means of a second tableting. This process is technically complicated. Special tableting machines are furthermore needed for the preparation of press-coated tablets.

The need thus exists for a simple and economical preparation of a solid pharmaceutical form comprising cyclophosphamide for oral administration.
It is necessary to take into consideration here that the pharmaceutical forms have to be coated in order that direct contact with the cytotoxic active compound is avoided.
It is moreover known that cyclophosphamide is chemically labile, thus the stability of the

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pharmaceutical forms must also be taken into consideration.

Surprisingly, it has been possible to prepare film-coated tablets comprising cyclophosphamide without the use of preswollen starch.
Suitable auxiliaries were selected on the basis of the compatibility investigations mentioned in Example 1 . It was surprising in this context that the stability of cyclophosphamide is somewhat indifferent in the presence of preswollen starch.
It was moreover surprising that the finished film-coated tablets exhibit an adequate stability although the active compound, due to the preparation, is stressed during the film-coating process by moisture and heat.

According to one aspect, the present invention provides a film-coated tablet, comprising a tablet core containing cyclophosphamide as active ingredient, one or more fillers (1), one or more dry binders (2), one or more flow regulators (3) and one or more lubricants (4), and a suitable film coating thereof, whereby in the core at least one of the fillers (1) is lactose monohydrate and as a dry binder (2) no preswollen starch is present.

More particularly, the tablet core comprises cyclophosphamide, one or more fillers (1) selected from the group consisting of lactose monohydrate, D-mannitol and $CaHPO_4$, one or more dry binders (2) selected from the group consisting of non-preswollen corn starch and microfine cellulose, one or more flow regulators (3) selected from the group consisting of highly dispersed silica, and one or more lubricants (4) selected from the group consisting of magnesium stearate, stearic acid, glycerol palmitostearate, polyethylene glycol, talc and glycerol monobehenate.

Preferably the tablet core comprises cyclophosphamide, lactose monohydrate, non pre-swollen corn starch,

microfine cellulose, highly dispersed silica, magnesium stearate, and talc.

The tablet core may comprise per one part by weight of cyclophosphamide

0.2-1.5 parts by weight, preferably 0.5-1 parts by weight, more preferably 0.73 parts by weight of lactose monohydrate,

0.2-1.5 parts by weight, preferably 0.5-1 parts by weight, more preferably 0.74-0.75 parts by weight of microfine cellulose,

0.1-1.5 parts by weight, preferably 0.2-0.7 parts by weight, more preferably 0.37 parts by weight of non-preswollen corn starch,

0.01-1.5 parts by weight, preferably 0.05-0.08 parts by weight, more preferably 0.07-0.075 parts by weight of talc,

0.01-0.1 parts by weight, preferably 0.01-0.05 parts by weight, more preferably 0.037-0.04 parts by weight of highly dispersed silica, and

0.01-0.1 parts by weight, preferably 0.01-0.05 parts by weight, more preferably 0.028-0.03 parts by weight of magnesium stearate.

The film coating may comprise substances selected from the group consisting of polyethylene glycol, polysorbate 80, carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

According to a another aspect, the invention provides a tablet core, comprising cyclophosphamide as active ingredient, and having a composition as defined above.

According to further aspect, the invention provides a film-coated tablet obtainable by coating a tablet core as defined above with a suitable coating mixture. The film coating mixture may comprise substances selected from the group consisting of polyethylene glycol, polysorbate 80,

carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

According to a further aspect, the invention provides a method for producing a tablet core as defined above, comprising the steps of (a) sieving and adding of cyclophosphamide, one or more fillers (1), one or more dry binders (2), one or more flow regulators (3) and one or more lubricants (4), (b) homogenizing the so obtained mixture, (c) sieving and adding thereto the remaining one or more lubricants (4), mixing of the so obtained mixture and (d) processing of the so obtained mass into tablets.

Preferably in step (a) talc and in step (c) magnesium stearate is added as lubricant.

According to a further aspect, the present invention provides a method for producing a film-coated tablet comprising the step of coating a tablet core obtained by the method as defined above with a suitable film coating mixture. The film coating mixture may comprise substances selected from the group consisting of polyethylene glycol, polysorbate 80, carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

According to a further aspect, the invention provides a process for manufacturing a film-coated tablet containing cyclophosphamide as active ingredient comprising the steps of:
(a) sieving and homogenizing 1 part by weight of cyclophophamide and, each in relation to cyclophosphamide, 0.2-1.5 parts by weight, preferably 0.5-1 parts by weight, more preferably 0.73 parts by weight of lactose monohydrate, 0.2-1.5 parts by weight, preferably 0.5-1 parts by weight, more preferably 0.74-0.75 parts by weight of microfine cellulose, 0.1-1.5

parts by weight, preferably 0.2-0.7 parts by weight, more preferably 0.37 parts by weight of non-preswollen corn starch, 0.01-1.5 parts by weight, preferably 0.05-0.08 parts by weight, more preferably 0.07-0.075 parts by weight of talc, and 0.01-0.1 parts by weight, preferably 0.01-0.05 parts by weight, more preferably 0.037-0.04 parts by weight of highly dispersed silica, then adding thereto 0.01-0.1 parts by weight, preferably 0.01-0.05 parts by weight, more preferably 0.028-0.03 parts by weight of magnesium stearate, and then processing the so obtained mass into tablet cores, and then

(b) providing the so obtained tablet cores with a suitable film coating.

According to another aspect, the invention provides a film-coated tablet containing cyclophosphamide as active ingredient obtained by a process as defined above.

Example 1

Investigations on the compatibility of cyclophosphamide with various tableting auxiliaries

53.5 mg of cyclophosphamide and 86.5 mg of one of the auxiliaries defined below as 1-10 or 3.0 mg of one of the auxiliaries defined below as 11-18 were in each case mixed and compressed. The pressed tablets were stored at 31°C for 6 months. Decomposition of the active compound was assumed by means of chloride determination.
The results are summarized in the following table.

Function of the auxiliary		Auxiliary	Decomposition of cyclo-phosphamide	Dis-coloration
FILLER	1	Lactose, anhydrous	2.52	++
	2	Calcium phosphate	3.85	-
	3	Calcium phosphate anhydrous	2.02	-
	4	Emcompress($CaHPO_4$)	1.50	
	5	D-mannitol	1.15	-
	6	Lactose monohydrate	0.70	-
FILLER/DRY BINDER/ DISINTEGRATION PROMOTER	7	Microcrystalline cellulose	1.50-1.73*	-
	8	Cellulose (Elcema)	0.85-1.32*	-+
	9	Preswollen starch	1.02	-+
	10	Corn starch	0.75	-
DISINTEGRATION PROMOTER	11	Crosslinked poly-vinylpyrrolidone	1.5	++
FLOW REGULATOR	12	Highly disperse silica	0.46-1.72*	-+
FLOW REGULATOR/ LUBRICANT	13	Magnesium Stearate	1.51	-+
	14	Stearic acid	0.94	-+
	15	Glycerol palmitostearate	0.82	-
	16	Polyethylene glycol	0.68	-
	17	Talc	0.55	-
	18	Glycerol monobehenate	0.30	-

* Dependent on type

Example 2

Preparation of tablet cores (50 mg of cyclophosphamide) Direct tableting

0.535 mg of cyclophosphamide, 0.390 mg of lactose monohydrate, 0.400 mg of microfine cellulose, 0.200 mg of corn starch, 0.040 mg of talc and 0.020 mg of highly disperse silica are sieved and homogenized. 0.015 mg of magnesium stearate is then added and mixed. The mass prepared in this way is processed to give tablets:

Weight:	160 mg
Hardness:	> 30 N
Disintegration:	< 10 min.

Example 3

Preparation of film-coated tablets (50 mg of cyclophosphamide)

11.83 g of polyethylene glycol and 2.37 g of polysorbate 80 are dissolved in 75.21 g of water. 1.9 g of carboxymethylcellulose sodium are dissolved in 80.0 g of water. The solutions are brought together. 23.67 g of talc, 23.67 g of titanium dioxide and 0.24 g of simeticone are then added and the mixture is homogenized. 17.73 g of a 30% strength ethyl acrylate/methyl methacrylate copolymer dispersion in water are then added. The tablet cores are then sprayed with the prepared suspension in a suitable apparatus:

Theoretical weight of a film-coated tablet: 166 mg

Example 4

Investigation of the stability of cyclophosphamide film-coated tablets

Decomposition of cyclophosphamide after 3 months		
	26°C/60% RH	31°C/40%
Batch 1	0.30	4.12
Batch 2	0.17	2.36

Stability of the film-coated tablets of up to 3 years is expected on storage at < 25°C.

CLAIMS

1. A film-coated tablet, comprising a tablet core containing cyclophosphamide as active ingredient, one or more fillers (1), one or more dry binders (2), one or more flow regulators (3) and one or more lubricants (4), and a suitable film coating thereof, whereby in the core at least one of the fillers (1) is lactose monohydrate and as a dry binder (2) no preswollen starch is present.

2. A film-coated tablet according to claim 1, wherein the tablet core comprises cyclophosphamide, one or more fillers (1) selected from the group consisting of lactose monohydrate, D-mannitol and $CaHPO_4$, one or more dry binders (2) selected from the group consisting of non-preswollen corn starch and microfine cellulose, one or more flow regulators (3) selected from the group consisting of highly dispersed silica, and one or more lubricants (4) selected from the group consisting of magnesium stearate, stearic acid, gyceraol palmitostearate, polyethylene glycol, talc and glycerol monobehenate.

3. A film coated tablet according to claims 1 or 2, wherein the tablet core comprises cyclophosphamide, lactose monohydrate, non preswollen corn starch, microfine cellulose, highly dispersed silica, magnesium stearate, and talc.

4. A film-coated tablet according to any one of claims 1 to 3, wherein the tablet core comprises per one part by weight of cyclophosphamide

0.2-1.5 parts by weight of lactose monohydrate,

0.2-1.5 parts by weight of microfine cellulose,

0.1-1.5 parts by weight of non-preswollen corn starch,
0.01-1.5 parts by weight of talc,
0.01-0.1 parts by weight of highly dispersed silica, and
0.01-0.1 parts by weight of magnesium stearate.

5. A film-coated tablet according to any one of claims 1 to 4, wherein the tablet core comprises per one part by weight of cyclophosphamide
0.5-1 parts by weight of lactose monohydrate,
0.5-1 parts by weight of microfine cellulose,
0.2-0.7 parts by weight of non-preswollen corn starch,
0.05-0.08 parts by weight of talc,
0.01-0.05 parts by weight of highly dispersed silica, and
0.01-0.05 parts by weight of magnesium stearate.

6. A film-coated tablet according to any one of claims 1 to 5, wherein the tablet core comprises per one part by weight of cyclophosphamide
0.73 parts by weight of lactose monohydrate,
0.74-0.75 parts by weight of microfibe cellulose,
0.37 parts by weight of non-preswollen corn starch,
0.07-0.075 parts by weight of talc,
0.037-0.04 parts by weight of highly dispersed silica, and
0.028-0.03 parts by weight of magnesium stearate.

7. A film-coated tablet according to any one of claims 1 to 6, wherein the film coating comprises substances selected from the group consisting of polyethylene

glycol, polysorbate 80, carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

8. A tablet core containing cyclophosphamide as active ingredient, one or more fillers (1), one or more dry binders (2), one or more flow regulators (3), and one or more lubricants (4), whereby in the core at least one of the fillers (1) is lactose monohydrate and as a dry binder (2) no preswollen starch is present.

9. A tablet core according to claim 8, comprising cyclophosphamide, one or more fillers (1) selected from the group consisting of lactose monohydrate, D-mannitol and $CaHPO_4$, one or more dry binders (2) selected from the group consisting of non-preswollen corn starch and microfine cellulose, one or more flow regulators (3) selected from the group consisting of highly dispersed silica, and one or more lubricants (4) selected from the group consisting of magnesium stearate, stearic acid, gyceraol palmitostearate, polyethylene glycol, talc and glycerol monobehenate.

10. A tablet core comprising cyclophosphamide, lactose monohydrate, non preswollen corn starch, microcrystalline cellulose, highly dispersed silica, magnesium stearate, and talc.

11. A tablet core according to any one of claims 8 to 10, comprising per one part by weight of cyclophosphamide

0.2-1.5 parts by weight of lactose monohydrate,
0.2-1.5 parts by weight of microfine cellulose,
0.1-1.5 parts by weight of non-preswollen corn starch,
0.01-1.5 parts by weight of talc,

0.01-0.1 parts by weight of highly dispersed silica, and
0.01-0.1 parts by weight of magnesium stearate.

12. A tablet core according to any one of claims 8 to 11, comprising per one part by weight of cyclophosphamide
0.5-1 parts by weight of lactose monohydrate,
0.5-1 parts by weight of microfine cellulose,
0.2-0.7 parts by weight of non-preswollen corn starch,
0.05-0.08 parts by weight of talc,
0.01-0.05 parts by weight of highly dispersed silica, and
0.01-0.05 parts by weight of magnesium stearate.

13. A tablet core according to any one of claims 8 to 12, comprising per one part by weight of cyclophosphamide
0.73 parts by weight of lactose monohydrate,
0.74-0.75 parts by weight of microfine cellulose,
0.37 parts by weight of non-preswollen corn starch,
0.07-0.075 parts by weight of talc,
0.037-0.04 parts by weight of highly dispersed silica, and
0.028-0.03 parts by weight of magnesium stearate.

14. A film-coated tablet obtainable by coating a tablet core according to any one of claims 8 to 13 with a suitable film coating mixture.

15. A film-coated tablet obtainable by coating a tablet core according to any one of claims 8 to 13 with a film

coating mixture comprising substances selected from the group consisting of polyethylene glycol, polysorbate 80, carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

16. A method for producing a tablet core according to any one of claims 8 to 13, comprising the steps of (a) sieving and adding of cyclophosphamide, one or more fillers (1), one or more dry binders (2), one or more flow regulators (3) and one or more lubricants (4), (b) homogenizing the so obtained mixture, (c) sieving and adding thereto the remaining one or more lubricants (4), mixing of the so obtained mixture and (d) processing of the so obtained mass into tablets.

17. A method according to claim 16, wherein step (a) talc and in step (c) magnesium stearate is added as lubricant.

18. A method for producing a film-coated tablet comprising the step of coating the tablet cores obtained according to claim 16 or 17 with a suitable film coating mixture.

19. A method according to claim 18, wherein the film coating mixture comprises substances selected from the group consisting of polyethylene glycol, polysorbate 80, carboxymethylcellulose sodium, talc, titanium oxide, simeticone, a copolymer of ethyl acrylate and methyl methacrylate, and water.

20. A process for manufacturing a film-coated tablet containing cyclophosphamide as active ingredient comprising the steps of:
(a) sieving and homogenizing 1 part by weight of cyclophophamide and, each in relation to cyclophosphamide, 0.2-1.5 parts by weight of lactose monohydrate, 0.2-1.5 parts by weight of microfine cellulose, 0.1-1.5 parts by weight of non-preswollen corn starch, 0.01-1.5 parts by weight of talc, and 0.01-0.1 parts by weight of highly dispersed silica, then adding thereto 0.01-0.1 parts by weight of magnesium stearate, and then processing the so obtained mass into tablet cores, and then
(b) providing the so obtained tablet cores with a suitable film coating.

21. A process according to claim 20 wherein the components in step (a) in relation to 1 part by weight of cyclophosphamide are 0.5-1 parts by weight of lactose monohydrate, 0.5-1 parts by weight of microfine cellulose, 0.2-0.7 parts by weight of non-preswollen corn starch, 0.05-0.08 parts by weight of talc, 0.01-0.05 parts by weight of highly disperse silica, and 0.01-0.05 parts by weight of magnesium stearate.

22. A process according to claim 20 wherein the components in step (a) in relation to 1 part by weight of cyclophosphamide are 0.73 parts by weight of lactose monohydrate, 0.74-0.75 parts by weight of microfine cellulose, 0.37 parts by weight of non-preswollen corn starch, 0.07-0.075 parts by weight of talc, 0.037-0.04 parts by weight of highly disperse silica, and 0.028-0.03 parts by weight of magnesium stearate.

23. A film-coated tablet containing cyclophosphamide as active ingredient obtained by a process according to any of claims 20 to 22.