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 solid pharmaceutical form [sic] 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

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 I [sic]. 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.

Example 1

Investigations on the compatibility of cyclophosphamide with various tableting auxiliaries

53.5 mg of cyclophosphamide and 86.5 mg of (auxiliary 1-10) [sic] or 3.0 mg of (auxiliary 11-18) [sic] were in each case mixed and compressed. The pressed tablets were stored at 31°C for 6 months. The decomposition of the active compound took place [sic] 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 sterate [sic]	1.51	-+
	14	Stearic acid	0.94	-+
	15	Glycerol palmitostearate	0.82	-
	16	Polyethylene glycol	0.68	-
	17	Talc	0.55	-
	18	Glycerol monobeherate [sic]	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 [sic] are then added and the mixture is homogenized. 17.73 g of a 30% strength ethyl acrylate/methyl metharcrylate [sic] 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.

Patent claims

1. A film-coated tablet with cyclosphosphamide [sic] as active compound, comprising in the core cyclophosphamide, one or more fillers, one or more dry binders but no preswollen starch, flow regulators and lubricants.

2. The film-coated tablet as claimed in claim 1, comprising in the core as a filler lactose monohydrate, D-mannitol or $CaHPO_4$, nonpreswollen corn starch or microfine cellulose as a dry binder, highly disperse silica as a flow regulator and magnesium stearate, stearic acid, glycerol palmitostearate, polyethylene glycol, talc or glycerol monobehenate as a lubricant.

3. The film-coated tablet as claimed in claim 2, where the cores can comprise the auxiliaries either individually or alternatively in any desired mixture.

4. The film-coated tablet as claimed in claims 1 to 3, comprising, per part of cyclophosphamide in the core, lactose monohydrate, microfine cellulose, nonpreswollen corn starch, talc, highly disperse silica and magnesium stearate in the following ratio:

lactose monohydrate 0.2-1.5, preferably 0.5-1, particularly 0.73

microfine cellulose 0.2-1.5, preferably 0.5-1, particularly 0.74

nonpreswollen corn starch 0.1-1.5, preferably 0.2-0.7, particularly 0.37

talc 0.01-1.5, preferably 0.05-0.08, particularly 0.07

highly disperse silica 0.01-0.1, preferably 0.01-0.5, particularly 0.04

magnesium stearate 0.01-0.1, preferably 0.01-0.05, particularly 0.03.

This Sheet Has Been Replaced