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Physico-pharmaceutical characteristics of steroid/crosslinked polyvinylpyrrolidone coground systems

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Summary

A high-energy milling technique was used for improving the biopharmaceutical properties of 6-methylenandrosta-1,4-diene-3,17-dione (FCE24304), an aromatase inhibitor, slightly soluble in water. Cogrinding with crosslinked polyvinylpyrrolidone (PVP-CL) was evaluated using different ratios of drug/polymer and powder/grinding media. The improved dissolution systems were then analysed and discussed in terms of the residual crystallinity of the drug (by DSC and X-ray), wettability, particle size analysis and dissolution rate behaviour. An accelerated short-term stability study was then carried out on a 1:3 w/w system.

Introduction

Swellable polymers, for example, crosslinked casein, crosslinked carboxymethylcellulose and crosslinked polyvinylpyrrolidone, have been used widely in pharmaceutical dosage forms in order to improve both the solubility and the dissolution rate of slightly soluble drugs. In particular, crosslinked polyvinylpyrrolidone (PVP-CL) has extensively been used (Lippold and Lûtshg, 1978; Lippold et al., 1978) to obtain molecular dispersions by swelling the polymer in an organic solvent containing the drug.

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The physico-chemical properties of the drug/PVP-CL systems thus obtained were extensively characterised and the dissolution behaviour of active substance investigated. Nevertheless, the solvent swelling method is limited by both the polymer swelling volume and the solubility of the drug in the chosen solvent: as a consequence, other methods such as cogrinding have been developed as an alternative loading technique.

Cogrinding versus solvent swelling has basic advantages (Carli, 1986, 1987): for example, the possibility of loading larger quantities of drug in the crosslinked polymer while avoiding, at the same time, toxicity problems related to the use of organic solvents.

More recently, as part of a wide study focused on the dissolution and bioavailibility characteristics of a slightly water-soluble synthetic steroid in

the class of aromatase inhibitors, namely, 6-methylenandrosta-1,4-diene-3,17-dione, FCE24304 (Giudici et al., 1988; Torricelli et al., 1990), we employed the cogrinding method and achieved interesting results on the improvement of its solubility, dispersibility and dissolution properties. The enhancement in these properties was related to the physico-chemical changes induced by the cogrinding process.

The objective of the present work is to describe the physico-pharmaceutical characterisation of steroid/PVP-CL coground powders according to the different technological parameters applied.

Materials and Methods

Pure crystalline 6-methylenandrosta-1,4-diene-3,17-dione (FCE24304, Farmitalia Carlo Erba) was used without further purification. A commercially marketed physically cross-linked polyvinylpyrrolidone (Kollidon CL, batch 371741, BASF), PVP-CL, was used as supplied. Part of the polymer was micronized before use by grinding in a semi-industrial mill (Sweco DM3) for 18 h.

Cogrinding method

A physical mixture was prepared from accurately weighing FCE24304 and PVP-CL, cosieving through a 60-mesh screen and tumble mixing with a Turbula mixer for 15 min. The mixture was then ground in a high-energy vibrational laboratory ball mill (IG W2/E, Giuliani). The mill consists of a porcelain jar filled with spherical grinding media of different sizes (10 balls, ϕ 18 mm; 10 balls, ϕ 16 mm; 64 balls, ϕ 10 mm) in order to obtain intimate contact between the powder and media themselves. The total volume developed by the grinding media is 91 cm^3 (d = 2.67 g/cm^3) and the grinding chamber volume is 386 cm^3. The volumetric ratio between the powder mass to be ground and the grinding media was assessed to range between 1:4 and 1:8. A preliminary study was carried out to determine the influence of grinding time: the optimum duration of grinding was found to be 2 h. Steroid/polymeric carrier weight ratio ranged from 1:1 to 1:5 w/w.

DSC measurements

Thermal analyses were carried out using a Mettler TA3000 apparatus (Mettler) equipped with a DSC20 cell under nitrogen flow (50 ml/min) at a heating rate of 10 °C/min. Calibration of the melting enthalpy was performed using indium as reference standard.

X-ray diffraction measurements

X-ray diffractograms were obtained by irradiating powder samples (CuKα as radiation source, Siemens P500II Diffractometer). The degree of residual crystallinity was calculated as the ratio between the area of the crystalline portion and that of the entire system (crystalline + amorphous). Since PVP-CL is naturally amorphous, the degree of crystallinity must be multiplied by a correction factor (drug/polymer weight ratio) and the result expressed as a percentage referred to pure crystalline FCE24304.

Wettability

Wettability was evaluated by solid/liquid contact angle measurements on compacts using a Lorentzen-Wettre wettability tester apparatus. For binary systems, it was possible to use the Cassie-Baxter equation (Colombo and Carli, 1984):

$$\cos\theta = f_1 \cdot \cos\theta_1 + (1 - f_1) \cdot \cos\theta_2$$

which allows the determination of the surface fraction of each component. θ denotes the contact angle of the binary system, θ_1 and θ_2 those of the pure drug and pure polymer, respectively, and f_1 is the surface fraction of the pure drug.

Particle size analysis

Particle size analyses and surface area were determined using a mercury porosimeter (Carlo Erba Instruments, Italy) applying the method developed by Carli (Carli and Motta, 1984).

Dissolution studies

Dissolution rate tests were carried out according to USPXXII no. 2 at 37 °C and 150 rpm in phosphate buffer (pH 7.4, 900 ml) on coground powdery samples containing 9 mg of FCE24304 (pure drug sink conditions). At appropriate time intervals, filtered samples were assayed by UV spectrophotometry at a wavelength of 250 nm in order to ascertain the amount of drug dissolved ($E^{1\%}_{1\,cm} = 513.0$). Corrections were made for cumulative dilutions.

Storage conditions

At temperatures of 35 and 55 °C, samples of the coground system were sealed in vials (glass type I); under the other storage conditions tested (25 °C + 80% R.H.; 25 °C + 90% R.H.; 35 °C + 80% R.H.), the powder was spread on glass disks such that a greater surface area was exposed to the moisturised atmosphere.

Chemical stability

The degradation products were detected by HPLC (SP8770 Knauer detector, 245 nm; Partisphere 5 μm; water/acetonitrile 60:40 v/v; 1 ml/min flow rate) and calculated by internal normalisation.

Results and Discussion

Information on the physical state of the loaded drug can be derived from differential scanning thermograms: both the shape and the melting temperature can be related to the degree of drug dispersion over the surface of the carrier (Monkhouse and Lach, 1972). There are dramatic differences (Fig. 1) between the thermograms of pure FCE24304 (sharp peak at 193–194 °C) and those of the crystalline drug loaded on PVP-CL that show broad peaks and lowering of melting temperatures for increasing amounts of carrier used. Such a phenomenon is often indicative of interaction between the two substances (Boscolo et al., 1990), however, in this case, no drug interaction was detected and it is reasonable to assume that the melting temperature is lowered when the drug is finely spread onto the polymeric

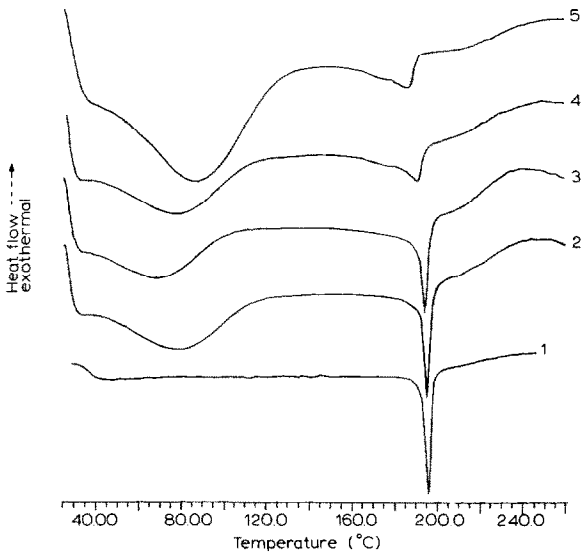

Fig. 1. DSC of (1) parent drug; (2) FCE24304/PVP-CL 1:2 mol/mol physical mixture; (3) FCE24304/PVP-CL 1:1 mol/mol coground system, batch A; (4) FCE24304/PVP-CL 1:2 mol/mol coground system, batch B; (5) FCE24304/PVP-CL 1:3 mol/mol coground system, batch D.

superficial network, the transition being related to crystal size (Carli and Colombo, 1988).

The above-described phenomenon is also accompanied by the partial amorphization of the steroid. The physical state of loaded FCE24304 has been assessed by both DSC and X-ray diffractometry: the two techniques are in good agreement with each other in the evaluation of the percentage of residual crystallinity as shown in Table 1. It is worth pointing out that the grinding process is unable to change the physical state of FCE24304 when ground alone: no amorphization results, nor is any change in melting temperature detectable, whereas amorphization is readily achieved when the association is with PVP-CL.

Some basic information can be drawn from Table 1: if PVP-CL is already micronized both amorphization and dispersion of the drug are promoted (Fig. 2); the degree of such dispersion and amorphization decreases when a higher ratio of powder/grinding media is used; the greater the amount of carrier, the larger is the melting point lowering.

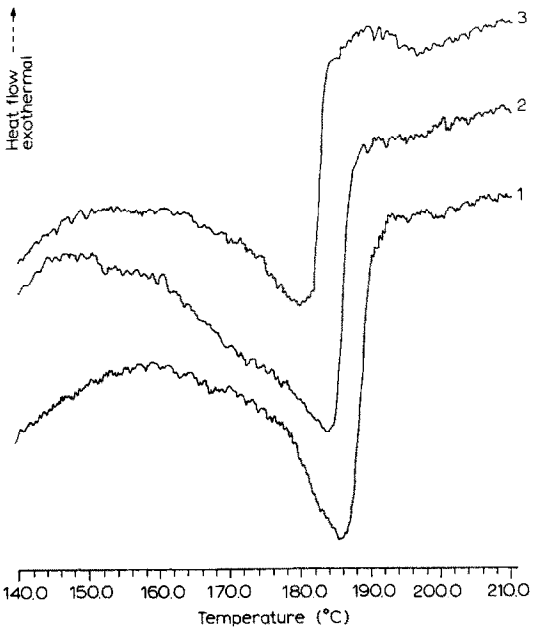

Fig. 2. DSC of (1) FCE24304/PVP-CL 1:3 mol/mol coground system, batch D; (2) FCE24304/PVP-CL 1:3 mol/mol coground system, batch C; (3) FCE24304/preground PVP-CL 1:3 mol/mol coground system, batch E.

Generally, contact angle measurements in water cannot be carried out on PVP-CL systems; in fact, the polymer is so highly and rapidly swellable that the dimensions of the drops cannot be measured. In this case, such behaviour was detected only when testing batches C and D; in contrast, the contact angles of the other systems were readily determined as reported in Table 2.

TABLE 2

Wettability measurements on FCE24304/PVP-CL systems

Batch	Contact angle (°)	Percentage of surface coated by drug
A	52	70
B	48	60
C	0	–
D	0	–
E	50	65
F	41	45
Untreated drug	63	100
PVP-CL	0	–

A high percentage of polymer surface is coated by FCE24304, as calculated according to Cassie-Baxter's equation. Obviously, with increasing polymer/steroid weight ratio, the characteristics of the tablet surface approach those of the pure polymer, i.e., swellable and more hydrophilic than the drug itself.

It is also interesting to observe that the value of the contact angle increases drastically when preground PVP-CL is used (see batches C–E in Table 2). This may be related to changes in the physical properties of the carrier: in fact, after prolonged grinding, both the rate and the quantity of water absorbed by the polymer decrease.

No substantial differences were detectable on measuring the surface areas as shown in Table 3.

TABLE 1

Batch characteristics and residual crystallinity determined by DSC and X-ray analyses

Batch	Drug/PVP-CL ratio (w/w)	Powder/grinding media (v/v)	DSC		X-rays (%)
			%	m.p. (°C)	
A	1:1	1:8	54	193	52
B	1:2	1:8	60	189–190	54
C	1:3	1:8	66	183–184	64
D	1:3	1:6	70	186–187	71
E [a]	1:3	1:8	32	181–182	50
F [a]	1:5	1:8	[b]	[b]	50
Untreated drug	1:0		100	194	100
Ground drug	1:0	1:8	100	194–195	100

[a] Preground PVP-CL.

[b] Undetectable. Thermal event related to drug superimposed on the glass transition of the polymer.

TABLE 3

Particle size analyses on FCE24304 / PVP-CL systems

Batch	Surface area (m^2/g)	Mean particle size (μm)
A	3.07	9.8
B	3.22	7.7
C	2.65	7.3
D	2.16	9.3
E	2.93	7.6
F	2.59	7.2
Untreated drug	2.16	6.0
PVP-CL	0.38	35.0
Preground PVP-CL	4.15	5.3

Nevertheless, from the analysis of samples C–E (drug/polymer weight ratio 1:3), it is evident that a favourable influence is exerted by lowering the powder/grinding medium volumetric ratio and increasing the area developed by the preground carrier.

In Table 4, the results obtained on the dissolution rate are listed: the process becomes faster with increasing polymer/drug ratio. No substantial differences are detectable between the 1:3 w/w samples obtained under different conditions while the dissolution profile of sample F is less favourable than that of sample E.

Generally speaking, the dissolution behaviour is influenced by parameters such as surface area, water contact angle and degree of amorphization (Carli et al., 1986). In this case, as the areas are quite similar, the predominant factor would appear to be the wettability of the powders, as pointed out in the case of the contact angle analyses.

According to the factors described above, we have tried to develop a 1:3 w/w system, since this drug/polymer ratio was found to be promising and since it avoids the disadvantages of experimental techniques, for example, the long pregrinding process.

Batch C was subjected to a short-term stability study under stress conditions. The results are here briefly summarised: with environmental moisture, the water content of samples increases as a result of the hydrophilic, swellable structure of the polymer. The degree of crystallinity and melting temperature of FCE24304 as determined by DSC and X-ray analyses remain unchanged after 3 months storage at 35 and 55 °C.

Humidity does exert a slight influence on the physico-chemical characteristics: recrystallization appears to occur, however, it is difficult to quantify; in fact, after the grinding process, the melting point of FCE24304 is within the same range as that of the glass transition temperature of PVP-CL. The water absorbed by the polymer modifies the relaxation behaviour of the polymer chain and increases the extent of the glass transition, and hence, does not allow accurate evaluation of the melting enthalpy for FCE24304. Moreover, X-ray diffractograms do not provide sufficiently precise data on this property.

TABLE 4

Dissolution rate behaviour under sink conditions of FCE24304 / PVP-CL systems

Time (min)	Percent in solution						
	Parent drug	A	B	C	D	E	F
5	0	36	65	84	84	86	74
10	0	57	86	88	96	95	88
15	4	73	89	89	100	97	90
30	17	91	93	91	100	97	94
60	43	95	94	91	100	97	96

TABLE 5

Percentage of related substances determined by normalization of samples stored under different conditions of temperature and humidity detected via HPLC

	Storage conditions	Initial	1 month	3 months
Parent drug	–	1.00		
	35 °C			1.23
	55 °C		2.23	
1:3 w/w system	–	1.35		
	35 °C		1.09	2.16
	55 °C		2.72	7.44
	25 °C + 80% R.H.			1.76
	25 °C + 90% R.H.			1.57
	35 °C + 80% R.H.			1.91

Finally, it is reasonable to conclude that storage under different conditions of humidity has no effect on the behaviour of drug dissolution, although storage under a very moist atmosphere reduced the rate of drug dissolution only in the first 5 min of the test.

PVP-CL does not protect FCE24304 against the effects of high temperature, as shown by the data in Table 5, in contrast to the results reported previously on an analogous formulation with β-cyclodextrin (Torricelli et al., 1991). A storage period of only 3 months at 35 °C is sufficient to cause significant degradation of FCE24304. Such behaviour was also confirmed via dissolution rate tests on samples stored for 3 months: the products of degradation reduced the rate of dissolution of FCE24304.

Conclusions

High-energy milling is an extremely useful technique for improving the biopharmaceutical properties of poorly soluble compounds. Solubility, dispersibility and dissolution were markedly improved and readily achieved. Enhancement of properties such as the afore-mentioned is strictly related to the physico-chemical changes induced by the process of cogrinding. Nevertheless, for drugs which involve problems due to limited stability, e.g., FCE24304, this experimental approach fails to lengthen the shelf-life of formulations.

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