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Research paper

Polyvinylalcohol substituted with triethyleneglycolmonoethylether as a new material for preparation of solid dispersions of hydrophobic drugs

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Abstract

Among the different methods used to increase the aqueous drug solubility, the preparation of a solid dispersion with a soluble carrier represents an interesting formulative approach. We substituted polyvinylalcohol with triethyleneglycolmonoethylether and obtained a suitable material for the formulation of a solid dispersion of progesterone, by spray-drying. In particular, we evaluated the influence of the polyvinylalcohol substitution degree and the polymer–drug weight ratios in the preparative mixture on the progesterone dissolution rate in the aqueous environment. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Substituted polyvinylalcohol; Diethoxyethylether; Progesterone; Drug–polymer affinity; Free drug availability

1. Introduction

The solubility of a drug is an important factor in determining the rate and extent of absorption and thus the appearance and intensity of the therapeutical effect. Poorly soluble drugs are characterized by a low tendency to dissolve in the aqueous fluids of the administration environment. After their oral administration, this results in poor bioavailability, whereas after parenteral administration, the therapeutic effect is delayed resulting in a weak therapeutic response. To overcome these problems many chemical and formulation approaches aim to improve the release rate of poorly soluble drugs. Chemical approaches are mainly based on the formation of soluble prodrugs or salts. Formulation approaches are mainly based on the use of polymorphous [1] or amorphous [2] forms of the drug, complexation, a decrease of particle size and drug dispersions in soluble solid carriers. Drug dispersions are now receiving increasing attention for their easy preparation, the possibility to use a wide range of carriers and their suitability for any drug. Polyethylene glycol, polyvinylpyrrolidone, polyvinylalcohol (PVA), cellulose derivatives (HPMC, HPC, CMEC, HPMCP), polyacrylates and polymethacrylates have been extensively tested as carriers for solid dispersions with many drugs [3–9]. The physico-chemical characteristics of the polymer and the polymer–drug ratio influence drug release from the solid dispersions [10–13]. In the presence of a high polymer–drug ratio, the increased drug dissolution rate, based on the increased surface area of the dispersed drug that comes into contact with the dissolution medium after carrier dissolution, may be counterbalanced by an increased viscosity in the diffusion boundary layer adjacent to the dissolving surface due to the presence of the polymer in solution. The choice of the polymer and the polymer–drug ratio is thus very important in the preparation of solid drug dispersion suitable for a drug dissolution increase. This work describes the use of PVA substituted with triethyleneglycolmonoethylether (TEGME) as a carrier for the preparation of solid dispersions of progesterone chosen as a poorly soluble drug model. We substituted PVA with TEGME at different substitution degrees and evaluated the functional properties of these derivatives both in terms of their physico-chemical characteristics and their ability to provide solid dispersions of progesterone increasing its dissolution rate in an aqueous environment. To obtain substituted polymers also suitable for parenteral use, PVA 10,000 Mw was used in the present study providing, after substitution, polymers not exceeding 40,000, the molecular weight threshold for renal excretion [14].

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2. Materials and methods

2.1. Chemicals and supplies

PVA (Mw 10,000, 80% hydrolyzed) was purchased from Sigma-Aldrich, 1,2-bis(2-chloroethoxy)ethane, ethyl alcohol, 1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5) (DBU) and progesterone were from Fluka, and *N*-methylpyrrolidone was from Carlo Erba. Other organic and inorganic chemicals were commercially available and used without further purification.

2.2. Synthesis of PVA derivatives

PVA (5.24 g; 100 mmol of monomer) was dissolved in 50 ml of *N*-methylpyrrolidone, and the solution was supplemented with DBU and stirred at room temperature for 24 h. The polymer was subsequently precipitated by addition of diethyl ether, recrystallized twice from methanol and desiccated under vacuum. The dry solid was subsequently solubilized in *N*-methylpyrrolidone 30 ml and a solution of 1-chlorodiethoxyethylether (3.84 g, 10 mmol; 11.52 g, 30 mmol; 19.20 g, 50 mmol) in *N*-methylpyrrolidone was added and stirred for 24 h to obtain PVA substituted with TEGME at different substitution degrees: PVA-TEGME10, PVA-TEGME30, PVA-TEGME50. The solution of 1-chlorodiethoxyethylether was prepared by stirring anhydrous ethanol with DBU for 24 h at room temperature and then adding bis-chloroethoxyethane (BCEE) and stirring for an additional 3 h at room temperature (ethanol, DBU and BCEE were added in a 1:1:1 molar ratio). The substituted polymer was separated from the solution by precipitation with diethyl ether. The precipitate obtained was dissolved in 100 ml of a mixture of ethanol/water (1:1; v/v) and dialyzed against the same mixture for 48 h. The dialyzed solution was subsequently spray-dried. The products were characterized by IR spectroscopy, elemental analysis and ^{1}H-NMR. The IR spectra were obtained using a Jasco FT-IR-410 spectrophotomer in KBr disks. Elemental analysis (C,H,N) was carried out on a Perkin-Elmer model 240B elemental analyzer. The ^{1}H-NMR spectra were recorded on a Gemini 200 instrument in $(CD_3)_2SO/D_2O$ (10:1; v/v).

2.3. Evaluation of polymer–drug interactions by solubility studies

To evaluate the interactions between the drug and the polymers in solution, an excess of drug (10 mg of progesterone) was added to 10 ml of a pH 7.4 aqueous buffer/polyethylene glycol 400 (1:1; v/v) mixture containing the polymer at increasing concentrations up to 8 mg/ml. The suspensions were magnetically stirred at 37 °C for 24 h and then ultracentrifugated and the solutions obtained were spectrophotometrically analyzed for the drug content. The solutions of the polymers in the same mixture were used as blanks.

2.4. Preparation of polymer–drug spray-dried mixtures

The drug–polymer solid mixtures were prepared by dessication of solutions of drug and polymer in a water/ethanol mixture (1:1; v/v) at the following polymer–drug weight ratios by spray-drying: 2:1, 4:1, 6:1, 8:1, 10:1. The solutions were prepared by dissolving 100 mg of progesterone in 400 ml of the aqueous mixture and subsequently adding the appropriate amount of polymer. The spray-drying process was carried out under the following conditions: inlet temperature 90 °C, outlet temperature 40 °C air flow. As a comparison, the pure drug was spray-dried in the same conditions.

2.5. Differential scanning calorimetry (DSC) on the spray dried mixtures

DSC curves were recorded on a Mettler FP 80 HT differential scanning calorimeter. Mettler FP 85 and FP 89 HT system software was used for data acquisition. All samples (7–10 mg) were heated in crimped aluminium pans at a scanning rate of 20 °C min^{-1} in the temperature range 40–350 °C.

2.6. Release studies

To detect the amount of free drug available from the polymer–drug mixtures, the solid mixtures (100 mg) were placed in a donor cell containing 3 ml of a pH 7.4 aqueous buffer/polyethylene glycol 400 (1:1; v/v) mixture separated by a dialysis membrane (Mw cut off: 10,000) from a receiving compartment containing 10 ml of the same aqueous buffer, which was replaced after time intervals suitable to guarantee sink conditions throughout the runs. The system was thermostatted at 37 °C. The drug was spectrophotometrically detected in the receiving phase over time. The polymers were used in the same conditions to avoid any interference.

3. Results and discussion

3.1. Characterization of the substituted polymers

The infrared spectra (KBr, cm^{-1}) of the substituted polymers showed bands at 1100 ($\nu_{c\text{-}o\text{-}c}$). Elemental analysis indicated that substitution had occurred and the percentage of substitution on the polymer (mol of TEGME per 100 mol of vinylmonomer) was 4.5%, 17%, and 33%, in the presence of 10%, 30%, and 50% respectively (mol substituent per 100 mol of vinylmonomer) in the preparative mixture. By ^{1}H-NMR analysis the ratios of TEGME groups to acyl groups of the PVA (80% hydrolyzed then containing 20% vinylacetate) were obtained by comparing the signals at 3.63 ppm of the six protons of triethyleneglycol and at 1.95 ppm of the three protons of the PVA acyl group [15]. The substitution was 6.3%, 16.4%, and 37.8% in the presence of 10%, 30%,

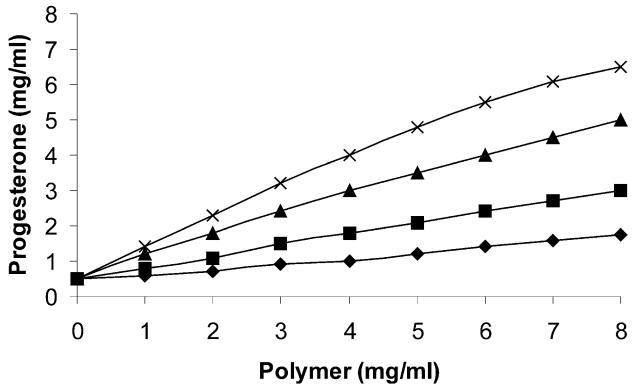

Fig. 1. Phase-solubility diagrams of progesterone in the presence of PVA (◆), PVA-TEGME10 (■), PVA-TEGME30 (▲), and PVA-TEGME50 (×) in pH 7.4 aqueous buffer/polyethylene glycol 400 (1:1; v/v). Each value represents the mean of three experiments.

and 50%, respectively (mol of substituent per 100 mol of vinylmonomer), in the preparative mixture.

3.2. Drug–polymer interactions by solubility studies

The phase-solubility diagrams of progesterone in the presence of the substituted polymers analyzed and PVA revealed an increase in drug solubility on raising the polymer concentration (Fig. 1). This is probably due to hydrophobic interactions between the drug and the amphiphilic tetraethylene moiety of the polymer. The increased drug solubility expressed by the slope of the linear trend of the diagrams (Table 1) was more evident in the presence of PVA-TEGME50 than PVA-TEGME30, PVA-TEGME10 and PVA, respectively. This indicated a greater tendency of the substituted polymers than PVA to interact with the drug in solution and a favourable effect of the substitution degree on this interaction.

3.3. Characterization of the polymer–drug spray-dried mixtures

The polymer–drug spray-dried mixtures analyzed by optical microscopy were spherical and the dimensions ranged from 0.5 to 3 μm. No significant differences were observed among the different mixtures.

Table 1
Slopes of the linear trends of the phase-solubility diagrams of progesterone in the presence of the substituted PVA at 37 °C in pH 7.4 aqueous buffer/polyethylene glycol 400 (1:1; v/v)[a]

Polymer type	Slope
PVA	0.305
PVA-TEGME10	0.988
PVA-TEGME30	1.352
PVA-TEGME50	2.167

[a] Each value represents the mean of three experiments.

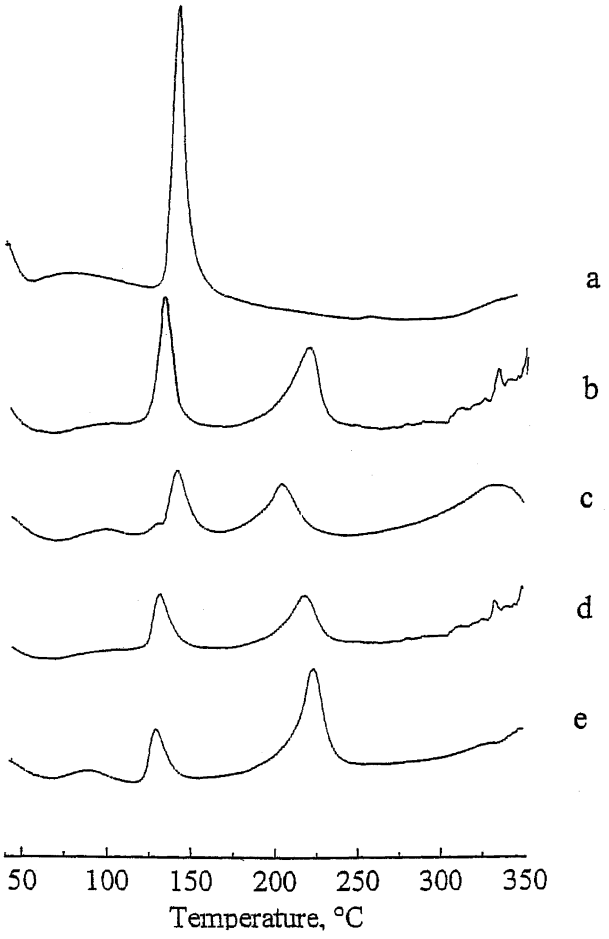

Fig. 2. DSC curves of progesterone (a) and the different polymer–drug mixtures at 2:1 polymer–drug weight ratio: PVA/progesterone (b), PVA-TEGME10/progesterone (c), PVA-TEGME30/progesterone (d) and PVA-TEGME50/progesterone (e).

3.4. DSC studies

The DSC curves reported in Fig. 2 revealed some information on solid-state interactions of progesterone with PVA and PVA-TEGME. Spray-dryed progesterone showed the characteristic endothermic peak at 135.21 °C (Table 2). The melting point of progesterone remained approximately constant in the polymer–drug mixtures until a 4:1 polymer–drug weight ratio, while it decreased significantly at the higher polymer–drug ratios. The enthalpic values of progesterone decreased in the mixtures, and the decrease was more evident in the presence of PVA-TEGME than PVA, and in the presence of the higher substitution degrees and the higher polymer–drug weight ratios. This indicated that solid dispersions of the drug in the polymers are obtained in each case and the degree of drug dispersion is higher in the presence of PVA-TEGME than PVA, the higher substitution degrees and the higher polymer–drug weight ratios. This is in accordance with the establishment of a polymer–drug interaction in solution influencing the dispersion degree of the drug in the solid mixture obtained following

Table 2
Progesterone peaks and relative enthalpy collected from the DSC thermograms

Type of polymer–drug mixture	Polymer–drug weight ratio	Progesterone peak (°C)	Enthalpy (J/g) relative to progesterone peaks
Progesterone		135.21	73.47
PVA/progesterone	2:1	134.00	59.63
	4:1	132.05	51.23
	6:1	100.56	47.39
	8:1	91.23	43.02
	10:1	87.01	40.85
PVA-TEGME10/progesterone	2:1	133.93	17.72
	4:1	130.80	10.61
	6:1	92.86	5.03
	8:1	82.80	4.98
	10:1	78.42	3.79
PVA-TEGME30/progesterone	2:1	132.22	15.43
	4:1	126.06	10.15
	6:1	88.53	3.96
	8:1	78.42	2.91
	10:1	75.30	1.86
PVA-TEGME50/progesterone	2:1	130.63	13.16
	4:1	128.00	8.15
	6:1	85.46	2.19
	8:1	76.08	2.07
	10:1	71.43	1.50

the spray-drying process. Indeed, the polymer–drug mixtures characterized by the stronger interactions in solution are expected to provide the more dispersed drug solid mixtures.

3.5. Free drug availability from the polymer–drug spray-dried mixtures

The availability of progesterone in aqueous solution was enhanced in the presence of the polymers analyzed, as the fractional amount of the free drug released increased from the polymer–drug mixtures with respect to the pure drug (Fig. 3). The increase in availability was more evident for PVA-TEGME50 than PVA-TEGME30, PVA-TEGME10 and PVA, respectively, according to the formation of solid dispersions of the drug in the polymers characterized by an increased dispersion degree with the increase in the polymer substitution. Moreover, the drug availability increased by raising the polymer–drug weight ratio up to 6:1 (w/w) and decreased with the higher weight ratios (Fig. 4). This trend may be attributed to a counterbalance of two opposite effects on the free drug availability from a polymer–drug dissolving system: increased drug dispersion in the solid suspension on increasing the amount of the polymer in the mixture, providing an enhanced drug dissolution rate [16]; establishment of polymer–drug interactions in solution which, in the presence of high amounts of polymer, strongly decrease the free drug concentration in solution and therefore the free drug availability from the polymer–drug

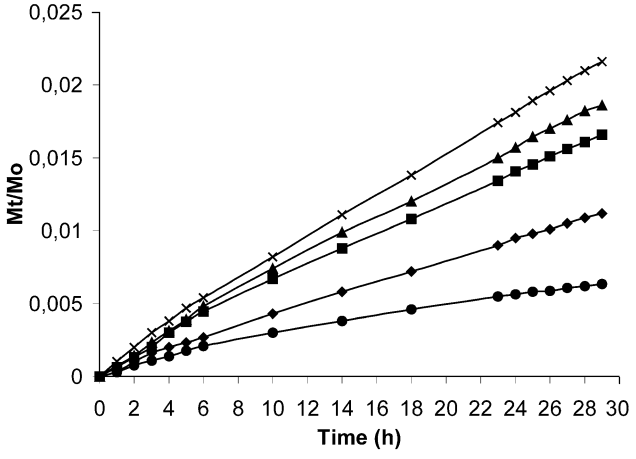

Fig. 3. Release profiles of progesterone in pH 7.4 aqueous buffer/polyethylene glycol (1:1; v/v) from the pure drug (●) and from PVA (◆), PVA-TEGME10 (■), PVA-TEGME30 (▲) and PVA-TEGME50 (×) (polymer–drug ratio 2:1). Each value represents the mean of three experiments.

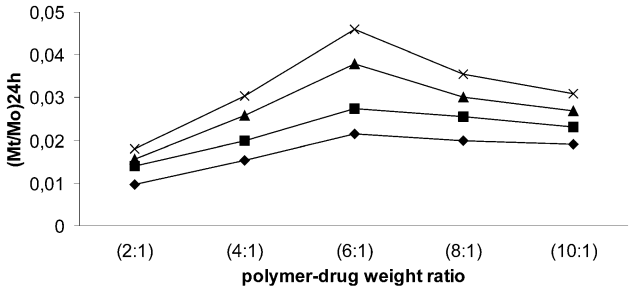

Fig. 4. Fractional amount of free drug released after 24 h at pH 7.4 aqueous buffer/polyethylene glycol (1:1; v/v) from PVA/progesterone (◆), PVA-TEGME10/progesterone (■), PVA-TEGME30/progesterone (▲), and PVA-TEGME50/progesterone (×) spray-dried mixtures of different polymer–drug weight ratios. Each value represents the mean of three experiments.

Table 3
Diffusional exponent values (n) obtained from the release profiles of progesterone from the different substituted polymers in the presence of pH 7.4 aqueous buffer/polyethylene glycol 400 (1:1; v/v)[a]

Polymer type	Polymer–drug weight ratio	n
PVA	2:1	0.8032
	4:1	0.9120
	6:1	0.9407
	8:1	0.9638
	10:1	0.9953
PVA-TEGME10	2:1	0.8297
	4:1	0.8823
	6:1	0.9462
	8:1	0.9693
	10:1	0.9996
PVA-TEGME30	2:1	0.8971
	4:1	0.9135
	6:1	0.9593
	8:1	0.9703
	10:1	1.0060
PVA-TEGME50	2:1	0.9120
	4:1	0.9382
	6:1	0.9921
	8:1	1.0330
	10:1	1.0459

[a] Each value represents the mean of three experiments.

system. The kinetic analysis of release, conducted according to the general equation $M_t/M_o = kt^n$ [17], revealed that the release of the drug from the polymers analyzed was almost constant over time, the diffusional exponent values approaching unity (Table 3). The approach to unity was more evident in the presence of the higher substitution degree and the higher polymer–drug weight ratio mixtures. This was due to the increase in polymer–drug interactions in solution maintaining constant concentrations of the free drug in solution when the free drug diffusion outside the dissolution environment provides the drug dissociation from the complex [18].

4. Conclusions

PVA substituted with TEGME is a suitable material for the preparation of solid dispersions with progesterone. The increasing PVA substitution degree and polymer–drug weight ratio yield high free drug amounts released from the solid dispersions due to an increase in the drug dispersion in the polymer raising the drug dissolution rate. For the polymer–drug characterized by strong interaction in solution this effect was counterbalanced by the slow drug dissociation from the complex. As the drug release was controlled by the dissolution process, the release kinetics approached zero order in particular for the higher substitution degrees and for the higher polymer–drug weight ratios.

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