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Studies in dissolution enhancement of atenolol. Part I

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Abstract

The objective of this study was to design atenolol tablets with fast in vitro release rates. Different polymers were screened as possible carriers to enhance atenolol dissolution. Binary systems using povidone (PVP), crospovidone (PVP-CL), polyvinilpyrrolidone/vinylacetate (PVP/VA), and Eudragit®E were prepared. The physical properties of solid dispersions, compared to physical mixtures, were analysed using X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The solubility and the release rate of atenolol from solid dispersions were compared to the drug alone. The influence of various parameters (type of polymer, drug to polymer ratio, pH) on the solubility and dissolution rate of the drug was also evaluated. The results of DSC and X-ray analyses of solid dispersions attested that the drug was always present in a crystalline form in the PVP-CL and Eudragit®E systems, while with the high content of PVP and PVP/VA an amorphisation of the atenolol was detectable. On the other hand, the diffraction patterns and the DSC thermograms of the physical mixtures revealed that to some extent the drug was always present in a crystalline form. An improvement in solubility and dissolution rate of atenolol with PVP and PVP-CL was obtained.

Keywords: Atenolol; Dissolution enhancement; Hydrophilic polymers; Physico-chemical characterisations; Solid dispersions

1. Introduction

Atenolol is a cardioselective β-blocker agent which is widely used in the management of hypertension and angina pectoris. Its slight solubility in water, low bioavailability (50%) and use in cardiac diseases make it a suitable candidate for increase of its release from solid dosage forms (Caplar et al., 1984).

Povidone (PVP) and crospovidone (PVP-CL) are commonly used as carriers to modify the solubility and the dissolution of poorly soluble drugs in several solid dosage forms (i.e. solid

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dispersions, microspheres, granules and tablets). Furthermore, because of its highly hydrophilic character, rapid water uptake, and good swelling properties, PVP-CL is widely used as a tablet disintegrant (Adeyeye and Barabas, 1993; Gordon et al., 1993; Barabas and Adeyeye, 1996; Kesavan and Peck, 1996; Suzuky et al., 1996; Tantishaiyakul et al., 1996; Gohel et al., 1996; Bolhuis et al., 1997; Yen et al., 1997). As reported in the literature a copolymer of polyvinilpyrrolidone/vinylacetate (PVP/VA) has been employed as water-soluble carrier in certain rapid-dissolution dosage forms (Moneghini et al., 1992; Zingone et al., 1992; Zingone and Rubessa, 1994). Eudragit® E is a cationic copolymer of dimethylaminoethyl methacrylate and of neutral methyl and butyl methacrylic esters. This polymer is soluble up to pH 5 and above this pH value is capable of swelling and is water-permeable (De Filippis et al., 1991; Suzuky et al., 1996).

The objective of this study was to analyse the influence of these four hydrophilic polymers on the physical state and dissolution properties of atenolol, preparing solid dispersions by the solvent method. Their characterisations were carried out using X-ray diffraction (XRD) and differential scanning calorimetry (DSC).

2. Materials and methods

2.1. Materials

Atenolol was kindly provided by Zeneca (Milano, Italy) PVP (Kollidon® K-30) and PVP-CL (Kollidon®CL) were provided by BASF (Ludwigshafen, Germany) PVP/VA S630 and Eudragit® E were from GAF (Milano, Italy). Solvents were of analytical grade.

2.2. Methods

2.2.1. Preparation of solid dispersions

Atenolol and polymer in different weight ratios (1:1, 1:3, 1:5 w/w) were dissolved in a minimum amount of methanol, the solvent was removed under reduced pressure in a rotary evaporator at 50 ± 1°C. The dispersions were kept for 5 days in a desiccator under vacuum at room temperature. The residue was ground and the 50–160 μm particle size fraction was obtained by sieving.

2.2.2. Preparation of physical mixtures

Physical mixtures of atenolol and each carrier, recrystallised from methanol, were prepared in the same weight ratios previously reported by simple mixing in a mortar and selecting the same particle size fraction of solid dispersions.

2.2.3. Properties of the systems

Analysis of drug content was evaluated by dissolving a weighed amount of the solid dispersion in ethanol. The drug was determined spectrophotometrically at 275 nm (Mod. 552, Perkin-Elmer, Padova, Italy).

Thermal analyses were carried out using a differential scanning calorimeter (Mod. TA 4000, equipped with a measuring cell DSC 20 Mettler, UK). Samples were placed in pierced aluminium pans and heated at a scanning rate of 10°C/min from 90 to 180°C.

X-ray diffractometry was carried out using a Siemens wide angle diffractometer, over a range of 2θ angles from 4 to 35 degrees, by exposing the solid to CuKα (1.5418 Å wavelength) radiation.

2.2.4. Solubility studies

Apparent solubility of atenolol from the coprecipitates was determined by rotating an excess amount of coprecipitate in 20 ml of simulated gastro-intestinal fluids in a glass vial at 37 ± 0.5°C for 24 h (previously determined to be an adequate time for equilibration). The solutions were then filtered through a membrane filter (pore size 0.45 μm) and assayed spectrophotometrically at 275 nm. Solubility of atenolol alone, recrystallised from methanol, and atenolol from physical mixtures was similarly determined.

2.2.5. Dissolution studies

The USP XIII rotating paddle apparatus (Mod. DT-1, Erweka, Italy) was used with a stirring rate of 50 rpm and maintained at 37 ± 0.1°C. The composition of the dissolution media was 0.2 M NaCl/0.2 M HCl (pH 1.2) or 0.2 M KH_2PO_4/0.2 M NaOH (pH 7.4) according to USP XXIII. The

coevaporate powder, containing a suitable amount (100 mg) of atenolol for sink condition ($C \ll C_s$) was added over the surface of 900 ml of dissolution medium. The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer, absorbance values were recorded at 275 nm. The polymers did not interfere with the UV analysis. The results were averaged from at least triplicate experiments and the standard deviations were within 5% of mean value.

The same procedure was followed for sample of 100 mg of recrystallised atenolol.

3. Results and discussion

3.1. X-ray diffraction

XRD patterns of solid dispersions are presented in Figs. 1–4 compared to the recrystallised drug and the physical mixtures with the highest polymer content.

The powder XRD of the solid dispersions atenolol: PVP showed several peaks corresponding to the crystalline form of the drug in the 1:1 weight ratio only (Fig. 1B). In samples with a higher amount of the polymer, no diffraction peaks were detected, suggesting that atenolol was in the amorphous state (Fig. 1C–D). On the other hand, the diffraction pattern of 1:5 physical mix-

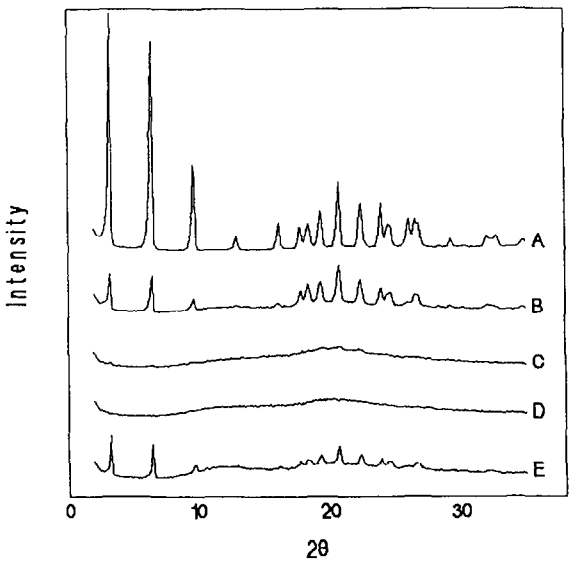

Fig. 1. XRD patterns of atenolol–PVP systems. Atenolol (A), solid disersions 1:1 w/w (B), 1:3 w/w (C), 1:5 w/w (D), physical mixtures 1:5 w/w (E).

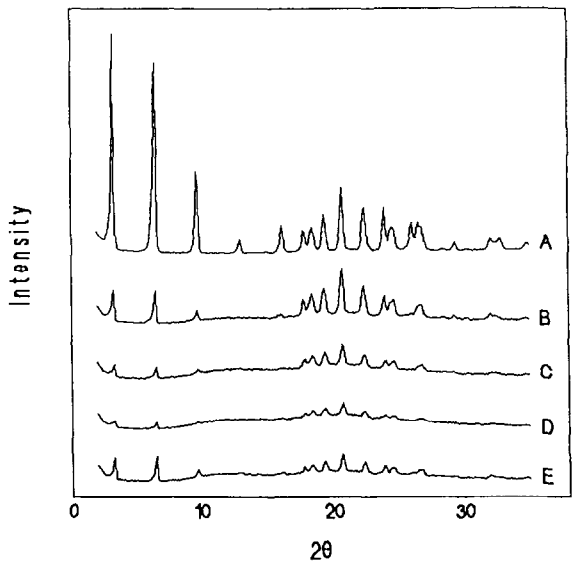

Fig. 2. XRD patterns of atenolol–PVP-CL systems. See Fig. 1.

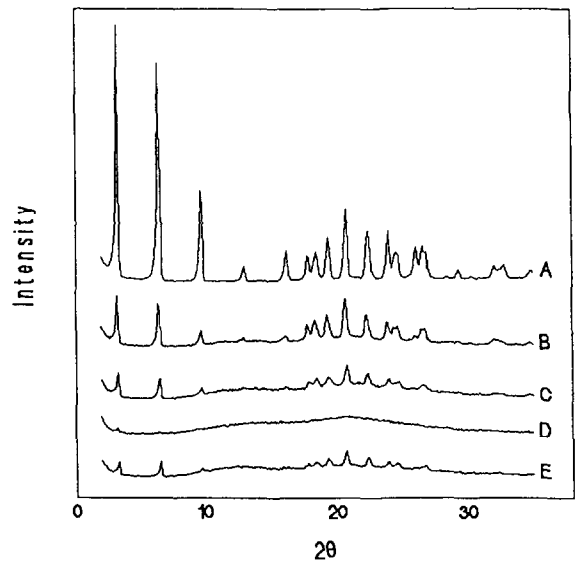

Fig. 3. XRD patterns of atenolol–PVP/VA systems. See Fig. 1.

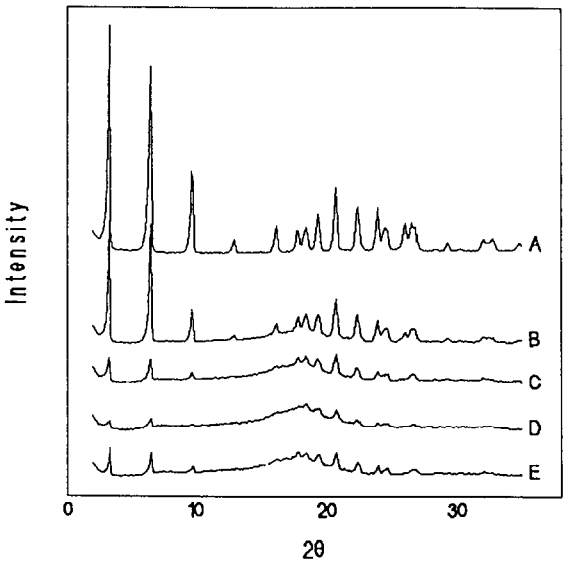

Fig. 4. XRD patterns of atenolol–Eudragit®E systems. See Fig. 1.

ture (Fig. 1E) showed several peaks attributable to the crystalline form of the drug. This fact indicated that disappearance of peaks in solid dispersions was not due to instrument sensitivity, but to the presence of the drug in an amorphous state.

XRD analysis of solid dispersions and physical mixture with PVP-CL showed that crystalline drug was always detectable, as indicated by Figs. 2B–D and 2E, respectively. A decrease of peak intensity by increasing polymer content was detected, and this was probably due to the dilution effect.

XRD patterns of the solid dispersions with PVP/VA showed the same behaviour as the PVP systems, even if it was necessary to reach 1:5 weight ratio to obtain the amorphous state of the drug (Fig. 3B–D). In this case also the physical mixture revealed the drug in a crystalline form (Fig. 3E).

All binary systems with Eudragit®E exhibited the same behaviour as the samples with PVP-CL, thus the drug was always present in a crystalline or microcrystalline form (Fig. 4B–E).

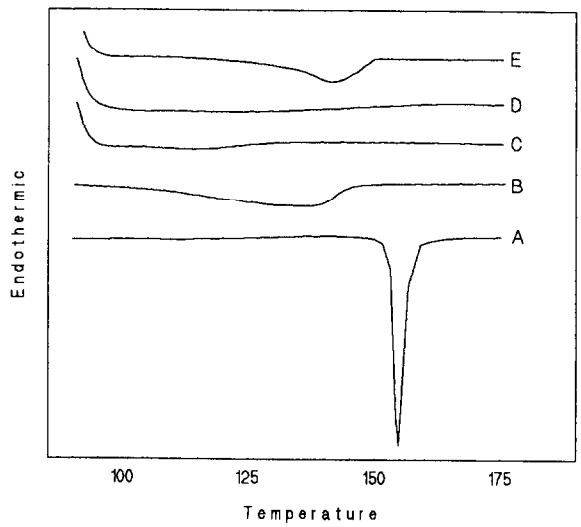

Fig. 5. DSC thermograms of atenolol–PVP systems. Atenolol (A), solid dispersions 1:1 w/w (B), 1:3 w/w (C), 1:5 w/w (D), physical mixtures 1:5 w/w (E).

3.2. Differential scanning calorimetry

DSC thermograms of solid dispersions are presented in Figs. 5–8, compared to the recrystallised drug and the physical mixtures with the highest polymer content.

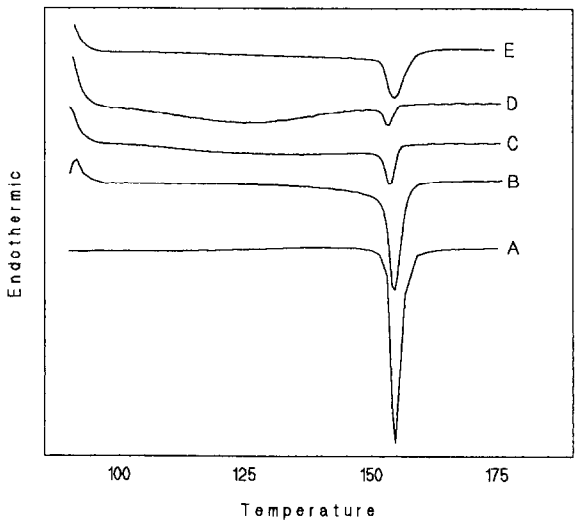

Fig. 6. DSC thermograms of atenolol–PVP-CL systems. See Fig. 5.

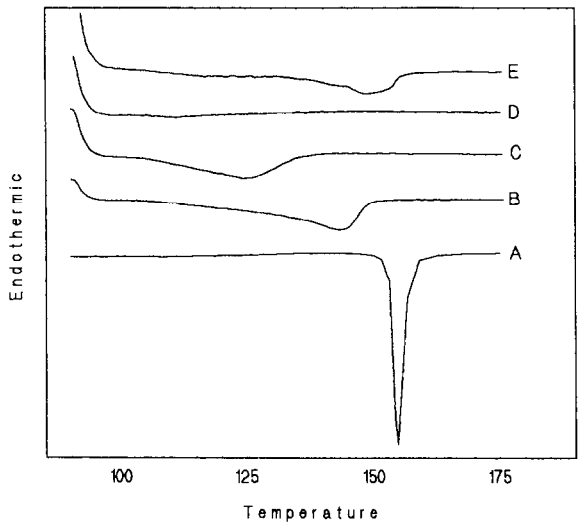

Fig. 7. DSC thermograms of atenolol–PVP/VA systems. See Fig. 5.

The thermogram of the pure drug showed a sharp melting event at 154.6°C, with an enthalpy of fusion of 136.4 J/g.

The solid dispersion with PVP in the 1:1 ratio (Fig. 5B) exhibited a very broad endotherm ranging between 70 and 145°C with a peak at 140°C and an enthalpy of fusion of 29.2 J/g. The samples in the 1:3 and 1:5 weight ratios (Fig. 5C and 5D, respectively) showed no endothermic peaks indicating the drug in the amorphous state. The decrease or disappearance of the thermal features of the drug indicate that some interaction with the polymer occurred, due to the formation of an amorphous solid solution. Interactions of PVP with atenolol has been reported in the literature (Botha and Lötter, 1990).

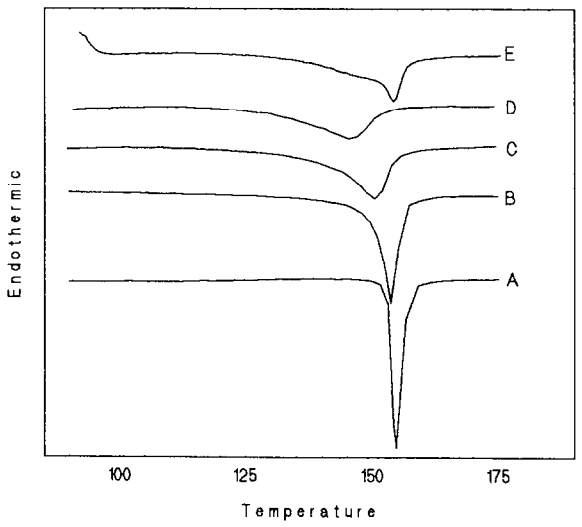

Fig. 8. DSC thermograms of atenolol Eudragit®E systems. See Fig. 5.

In Fig. 6 thermograms of the solid dispersions with PVP-CL have been reported. In all samples the endothermal event attributable to the crystalline form of the drug was evident even if the enthalpy of fusion decreased increasing the polymer content in the formulation.

The solid dispersion thermogram with PVP/VA in the 1:1 weight ratio (Fig. 7B) showed a broad endotherm with peak temperature and enthalpy of fusion less than the pure drug. This endothermal event was attributable to a crystalline form of the drug still present, confirming the results obtained by X-ray analyses. The 1:3 weight ratio sample also exhibited a broad endotherm attributable to the drug (Fig. 7C) while in the thermogram of the sample in the 1:5 weight ratio (Fig. 7D) no endothermal event occurred indicating the drug to be in an amorphous state.

The DSC curves of solid dispersions with Eudragit® E have been reported in Fig. 8. In all samples the thermal characteristic of the pure drug was always present indicating the presence of the drug in a crystalline form. Peak temperature in solid dispersions slightly shifted to lower temperature with respect to the drug alone, while the enthalpy of fusion also decreased. Those phenomena could be attributed to the appearance of an eutectic mixture.

DSC thermograms of physical mixtures 1:5 w/w (Figs. 5E, 6E, 7E and 8E) confirmed the results obtained from X-ray analyses.

3.3. Solubility studies

An improvement of solubility of atenolol in all the prepared solid dispersions, except for systems with Eudragit® E, was demonstrated. This was probably due to less hydrophylicity of this polymer with respect to PVP, PVP-CL, and PVP/VA. Table 1 reports solubility values of atenolol in our

Table 1
Solubility of atenolol in solid dispersions (g/100 ml)

Sample	pH 1.2	pH 7.4
Recrystallised drug	3.13	2.48
PVP 1:1 w/w	4.96	3.27
PVP 1:3 w/w	5.30	3.84
PVP 1:5 w/w	5.30	3.27
PVP-CL 1:1 w/w	4.63	2.50
PVP-CL 1.3 w/w	4.71	2.81
PVP-CL 1:5 w/w	5.05	2.77
PVP/VA 1:1 w/w	5.22	4.21
PVP/VA 1:3 w/w	5.23	4.96
PVP/VA 1:5 w/w	4.77	4.18
Eudragit® E 1:1 w/w	2.77	2.03
Eudragit® E 1:3 w/w	1.37	2.67
Eudragit® E 1:5 w/w	0.99	2.68

systems, compared to the recrystallised drug alone.

3.4. Dissolution studies

Since the analyses of drug content confirmed the theoretical value on the formulations, the release of atenolol from solid dispersions and physical mixtures in gastro-intestinal fluids was analysed and $t_{90\%}$ values have been reported in Table 2 compared to the drug alone.

Dissolution profiles of solid dispersions with PVP showed an increase of dissolution rate with respect to the physical mixtures and the reference drug. This phenomenon could be attributed to the hydrophilic character of the carrier and to the amorphous state of the drug in solid dispersions containing more than 50% of polymer. A faster release of atenolol at pH 1.2 than at pH 7.4 was observed, probably due to the favourable solubility of the drug in the gastric juice.

With respect to the drug alone an improvement of dissolution rate from PVP-CL binary systems was also achieved; however, the release from physical mixtures was slightly faster than the release from coprecipitates. This would be due to the different preparation methods of the two systems. In fact while in the coprecipitates the polymer swelling allows the deep incorporation of the drug into the polymeric network, in the physical mixtures the two components are only mixed in a solid state.

A fast release of atenolol from coprecipitates and physical mixtures with PVP/VA was also obtained. However, in the coprecipitates, a release speed inversely correlated to the amount of polymer was observed. This result could be ascribed to the formation of a viscous hydrophilic layer around the particles of the drug, as already reported (Zingone and Rubessa, 1994).

Table 2
Dissolution parameters ($t_{90\%}$)[a] of prepared formulations

Sample	Coprecipitates		Physical mixtures	
	pH 1.2 (min)	pH 7.4 (min)	pH 1.2 (min)	pH 7.4 (min)
Recrystallised drug	6.00	14.00	6.00	14.00
PVP 1:1 w/w	3.42	7.50	4.00	12.00
PVP 1:3 w/w	2.50	9.00	4.17	9.17
PVP 1:5 w/w	2.08	2.66	3.33	4.66
PVP-CL 1:1 w/w	3.33	12.00	2.58	8.00
PVP-CL 1.3 w/w	2.17	5.33	1.75	1.75
PVP-CL 1:5 w/w	2.00	3.33	1.83	1.75
PVP/VA 1:1 w/w	2.42	3.17	3.59	5.00
PVP/VA 1:3 w/w	2.75	3.59	5.00	4.50
PVP/VA 1:5 w/w	12.00	7.83	4.33	4.83
Eudragit® E 1:1 w/w	7.00	15.00	8.00	17.00
Eudragit® E 1:3 w/w	8.00	12.00	10.00	23.00
Eudragit® E 1:5 w/w	8.33	21.00	11.00	24.00

[a] Time after which 90% of the drug release occurs.

The release of atenolol from the binary systems with Eudragit® E was slower than reference, and this effect was enhanced by an increase in the polymer content. This fact may depend on the same phenomenon recognised for the systems with PVP/VA. Furthermore a faster release of the atenolol from solid dispersion as compared to physical mixtures can be observed. This may be attributed to the partial amorphisation of the drug in solid dispersions, as indicated by DSC and X-ray analyses.

An improvement of dissolution rate of atenolol in systems prepared with PVP was demonstrated. However, from the results of DSC the atenolol was detected in a amorphous state only in solid dispersions with a high polymer content. An increase in the dissolution rate of the drug was also obtained using PVP-CL, although no complete amorphisation of the atenolol was achieved. This phenomenon can be ascribed to the superdisgregant properties of the polymer. Furthermore, from the results of DSC no compatibility problems were recognised.

It can be concluded that PVP and PVP-CL were identified as optimum carriers to enhance the in vitro dissolution rate of atenolol.

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