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RESEARCH PAPER

Development of Tablets for Controlled Joint Release of Nifedipine and Atenolol

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ABSTRACT

Oral combinations of nifedipine and atenolol are widely used in the treatment of hypertension, proving particularly effective when the atenolol is released immediately and the nifedipine is released in a sustained manner. This work examined the potential of combining nifedipine and atenolol in a tablet, which would be easier to manufacture than currently available combined formulations. The results indicated that a 40:60 (w/w) nifedipine–atenolol mixture forms a eutectic melting at 140°C. Nevertheless, both drugs were stable when incorporated in tablets elaborated using cellulose ethers as base excipients. Tablets prepared from atenolol–lactose granules and solid dispersions of nifedipine–hydroxypropylmethylcellulose (100 cP) had more adequate dissolution profiles than a more complex reference formulation in hard capsules.

INTRODUCTION

Combination therapy of hypertension with calcium antagonists and β-blockers is justified on both physiopathological and pharmacological grounds (1), and in practice affords much better results than monotherapy with drugs of either class (2–4). One of the most useful such combination therapies is that formed by nifedipine and atenolol (5–8), which have been widely used in patients from diverse population groups (9,10). One advantage of nifedipine and atenolol is that they have no known biopharmaceutical or pharmacokinetic interactions (8,

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11). This, together with the fact that patient compliance with dosage schedules is greatly improved when chronic diseases such as hypertension are treated using fixed-dose combinations (12,13), has prompted the development of single-dosage combinations of nifedipine and atenolol (14).

The present paper reports the results of work to formulate a nifedipine–atenolol tablet that would be easier to manufacture than currently available dosage forms. The doses selected were 20 mg of nifedipine and 50 mg of atenolol, which have been reported to afford an optimal balance between clinical response and side effects (7,8,15–17) and are the doses habitually used in antihypertensive therapy (14).

The suitability of combining nifedipine and atenolol in a single dosage form is heavily conditioned by the different solubilities and biopharmaceutical profiles of these drugs. Atenolol is a hydrosoluble drug that is absorbed rapidly but incompletely in the upper sections of the small intestine and is thus usually administered in immediate-release dosage forms (18–20). In contrast, nifedipine is a poorly hydrosoluble drug for which oral administration in sustained-release formulations, either in monotherapy or in combination therapy, is known to improve the pharmacodynamic profile, despite the associated reduction in bioavailability (21,22). In developing the new tablet formulation, special attention was paid to achieving controlled release of the nifedipine, since this has been associated with improved antihypertensive efficacy and reduced incidence of side effects when this drug is used in combination therapy (23,24).

Development of a sustained-release formulation of a lipophilic drug generally involves first improving its hydrosolubility by dispersing it in a hydrophilic polymer, and then controlling its rate of dissolution by an appropriate formulation device (25–27). This study evaluated the potential of four cellulose ethers to fulfill both of these functions, these polymers being of known utility both in the hydrosolubilization of lipophilic drugs and in the sustained-release of drugs with diverse physicochemical properties (25).

EXPERIMENTAL

Drugs, Excipients, and Reagents

Nifedipine USP/BP (Sigma Química, Spain, batch 72H058), and atenolol BP (J. Escuder, Spain, batch 009) were used. Hydroxypropylmethylcellulose (HPMC) USP (Dow Chemical, Orpington, U.K.) products included Methocel® K100LV (nominal viscosity 100 cP, batch 88031321) and Methocel K100M (100,000 cP, batch MM86041602K). Methylcellulose USP (Dow Chemical) products included Methocel A15LV (15 cP, batch MM86100621A) and Methocel A15C (1500 cP, batch MM84022202A). Lactose USP (Claudio Barcia, Spain, batch 872) and magnesium stearate BP (Claudio Barcia, batch 548) were also used.

Compatibility Studies

Testing of compatibility used differential scanning calorimetry (DSC) in a Shimadzu (Kyoto, Japan) DSC-50 instrument. Nifedipine–atenolol mixtures were initially tested in the ratio 1:2.5 (w/w). Subsequently, in order to construct the corresponding phase diagram, they were tested in a series of nine ratios ranging, in equal increments, from 1:9 to 9:1 (w/w). In all other cases, 1:1 (w/w) combinations of the drugs and excipients were tested. In all cases, the DSC thermograms were recorded for 1-mg samples sealed in aluminum pans under an air atmosphere, heating at a rate of 10°C min^{-1} across the temperature range 50–250°C.

Thermogravimetric analyses of atenolol, nifedipine, and 1:1 (w/w) atenolol–nifedipine were also performed in the Shimadzu DSC-50 instrument.

Preparation of Solid Dispersions of Nifedipine in Cellulose Ethers, and of Nifedipine Tablets

The components were oven-dried (30°C, 24 hr), mixed in the combinations and ratios indicated in Table 1, and dissolved in ethanol. This solution was concentrated until a mass of appropriate consistency formed, and then this mass was granulated by wet-sieving (0.5-mm mesh). The resulting granulation was dried (45°C, 24 hr), and the 0.25–0.5 mm particle-size fraction was sifted out.

Tablets incorporating 20 mg of nifedipine were prepared in a Korch (Berlin, Germany) EKO excentric press equipped with flat-faced 6-mm punches and operating at a compression pressure of 265 MPa.

Characterization of the Nifedipine–Polymer Dispersions

Prior to compression, each of the nifedipine–polymer dispersions and their components was characterized by DSC over the range 50–250°C, as described above, by powder x-ray diffraction using Cu-Kα radiation, between 4 and 50 °2θ, performed in a Philips (Eindhoven, The

Table 1

Composition of the Nifedipine Dispersions in the Cellulose Ethers

Formulation	Polymer	Nominal Viscosity (cP)	Variety	Drug-to-Polymer Ratio
N-K100LV$_{1:3}$	HPMC	100	Methocel K100LV	1:3
N-K100M$_{1:3}$	HPMC	100.000	Methocel K100M	1:3
N-A15LV$_{1:3}$	MC	15	Methocel A15LV	1:3
N-A15C$_{1:3}$	MC	1.500	Methocel A15C	1:3
N-K100LV$_{1:2}$	HPMC	100	Methocel K100LV	1:2
N-K100LV$_{1:1}$	HPMC	100	Methocel K100LV	1:1

Netherlands) PW 1710 diffractometer; and by IR spectroscopy (KBr disks) between 400 and 4000 nm, performed in a Perkin-Elmer (Norwalk, CT) 1330 IR spectrophotometer.

Preparation of Atenolol–Lactose Granules

Atenolol and lactose were mixed in the ratios 1:3, 1:6, and 1:9 (w/w) and wet-granulated using standard methodology, binding the powder blends with a 0.25% (w/v) aqueous dispersion of the HPMC Methocel K100LV (final proportion of polymer, 2% w/w), and then sieving the mass to 5 mm. The granulated mass was then dried (45°C, 24 hr) and the 0.25–0.50 mm particle-size fraction was sifted out.

Preparation of Nifedipine–Atenolol Tablets

Tablets containing 20 mg nifedipine and 50 mg atenolol were prepared from the above three atenolol–lactose granulations and selected nifedipine dispersions in HPMC, as follows. The granulated blends were mixed in appropriate proportions for 30 min at 30 rpm in a Túrbula (Basel, Switzerland) T2C mixer, 0.5% (w/w) magnesium stearate was added after 20 min, and then the mixture was compacted at 125 MPa in a Korch EKO excentric press equipped with flat-faced 12-mm punches. Tablet compositions and the nomenclature used to identify each formulation are given in Table 2.

Dissolution Rates Studies

All of the nifedipine and nifedipine–atenolol tablets prepared were subjected to dissolution assays. For comparison, assays were also performed on hard gelatin capsules containing 20 mg of nifedipine, and on a commercial formulation combining atenolol (50 mg) in pellets

Table 2

Composition of the Nifedipine–Atenolol Tablets

Formulation	Nifedipine Dispersion	Atenolol Granulation
N_1A_3	N-K100LV$_{1:1}$	A-Lact$_{1:3}$
N_2A_6	N-K100LV$_{1:2}$	A-Lact$_{1:6}$
N_3A_9	N-K100LV$_{1:3}$	A-Lact$_{1:9}$

and a nifedipine (20 mg) minitablet in a hard gelatin capsule (Niften®, Tarrasa, Spain). Assays were performed on six replicate dosage units enclosed in stainless-steel parallelepiped baskets (2.8 × 2.8 × 11 cm; 1.6 mm DIN), and were carried out in a Turu-Grau (Zeneca, Germany) apparatus (USP 23, Method II) that had been adapted to accommodate a 5-liter vessel for the dissolution medium, which was 4 liters of distilled water, held at 37°C and stirred at 100 rpm, as per Sangalli et al. (28). Nifedipine and/or atenolol were periodically determined by HPLC using the method described by Koenigbauer (29).

Stability Trials

Nifedipine–atenolol tablets were stored at 50°C and 0 or 50% relative humidity. After 3 and 6 months, dissolution profiles were obtained for the active ingredients as described.

Treatment of Results

Dissolution profiles were characterized by fitting them with the equation of Korsmeyer et al. (30) by means of a linear-regression computer program. Statistically significant differences among the resulting rate coefficients

were identified using the Kruskall–Wallis nonparametric test.

RESULTS AND DISCUSSION

The DSC thermograms for nifedipine, atenolol, and a 1:2.5 (w/w) mixture of the two are shown in Fig. 1. Nifedipine and atenolol show endotherms attributable to melting at 174 and 155°C, respectively, whereas the mixture shows an endotherm at 140°C and no sign of the endotherms due to the individual components. Thermogravimetric analysis (Fig. 1) confirmed these endotherms to be due to melting transitions.

Figure 2 shows the DSC traces for nifedipine, atenolol, and nine of the mixtures, together with the phase diagram constructed from them, which shows a simple eutectic for the 40:60 (w/w) nifedipine–atenolol mixture. Thus the shifts observed in the characteristic endotherms of the two drugs upon mixing appear to be unimportant in relation to their compatibility in solid dosage forms, being attributable to eutectic formation (31).

The DSC thermograms for various excipient, atenolol–excipient, and nifedipine–excipient combinations showed no evidence of interactions among these compo-

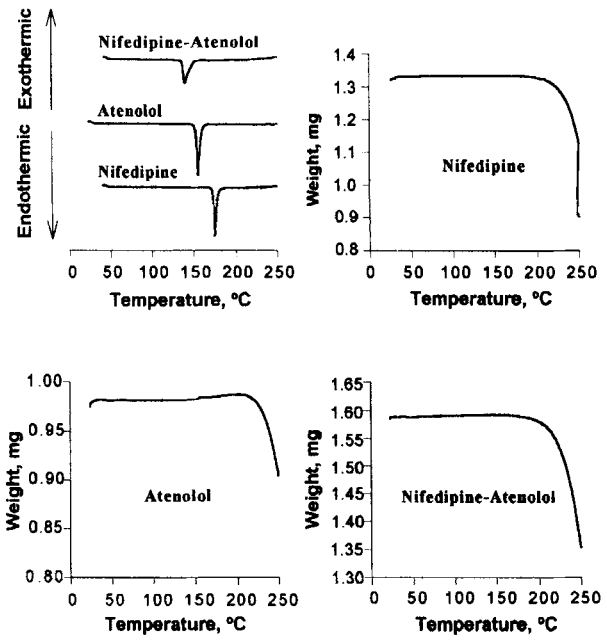

Figure 1. DSC and thermogravimetry traces for nifedipine, atenolol, and a 1:2.5 physical mixture of the two drugs.

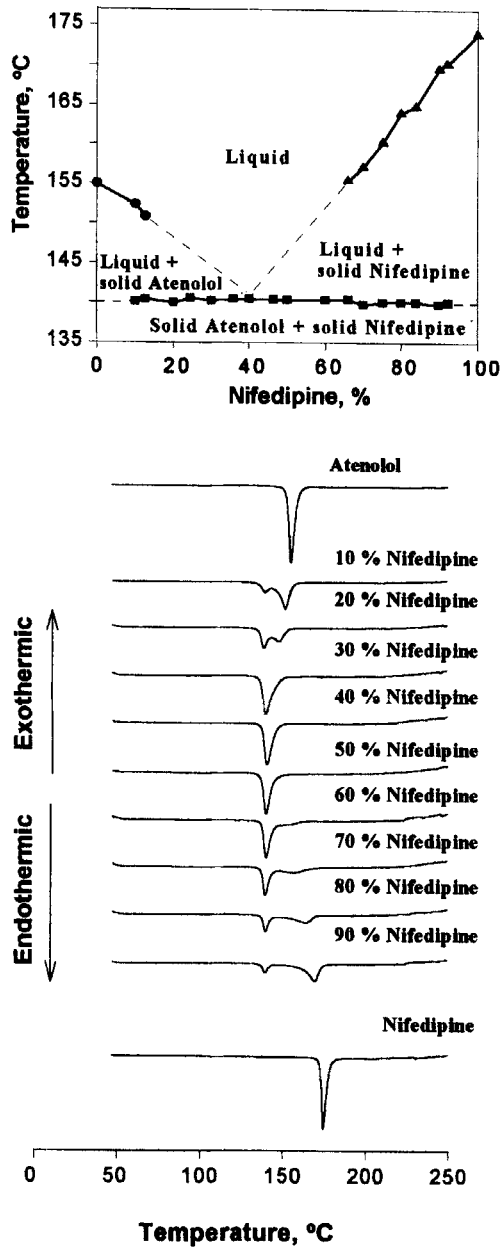

Figure 2. DSC traces for nifedipine, atenolol, and nine nifedipine–atenolol dispersions, and the phase diagram derived from them.

nents. The only exception was the atenolol/lactose physical mixture, for which the characteristic endotherm of lactose at 208°C shows a modification; Botha and Lötter (32) have associated similar shifts with the yellowing process commonly undergone by lactose during pro-

longed contact with amino compounds, such as atenolol. These results suggest that the excipients are suitable for use in the nifedipine–atenolol formulation.

Because cellulose ethers are available with a variety of structures and nominal viscosities, and can form highly stable systems, it seemed feasible that an appropriate cellulose ether might serve to control nifedipine release from the tablets without unduly delaying release of the atenolol.

The DSC thermograms for the dispersions of nifedipine in the various cellulose ethers were very similar to those for the corresponding physical mixtures. Similarly, x-ray diffractograms and IR spectra both suggested that the nifedipine had suffered no significant modifications upon incorporation in the solid dispersions.

Figure 3 shows dissolution profiles for tablets prepared from 1:3 dispersions of nifedipine and each of the cellulose ethers, together with the profile obtained for dissolution of an equivalent dose of nifedipine from a hard gelatin capsule. The cellulose ether that released the nifedipine fastest was the HPMC Methocel K100LV. In view of this result, tablets prepared from 1:1 and 1:2 dispersions of nifedipine in this excipient were also tested, the latter of which released the nifedipine faster. Thus, although the HPMC Methocel K100LV promotes wetting and dissolution of nifedipine from the tablets, its incorporation in excessive amounts can overly delay release. Fits of the equation of Korsmeyer et al. (30) to these dissolution profiles afforded values of the exponent n ranging from 0.59 to 1.09.

The solid dispersions of nifedipine in the HPMC Methocel K100LV, and the atenolol–lactose granules, were used to prepare nifedipine–atenolol tablets. Figure 4 shows the dissolution profiles recorded for these tablets and for the commercial reference formulation. The fits of the equation of Korsmeyer et al. (30) to the dissolution profiles for nifedipine afforded values of the exponent n that ranged from 0.22 to 0.30, and were thus considerably smaller than the n values obtained for tablets containing nifedipine alone. This difference was undoubtedly a result of the presence of lactose in the combined formulation, which would confer increased porosity on the hydrated tablets and thus facilitate their rapid disaggregation. Fixing the value of n at the intermediate value of 0.25 allowed comparison of the rate coefficients for the three formulations (Table 3) using the Kruskall–Wallis test, which showed them to be significantly different ($p \leq 0.05$).

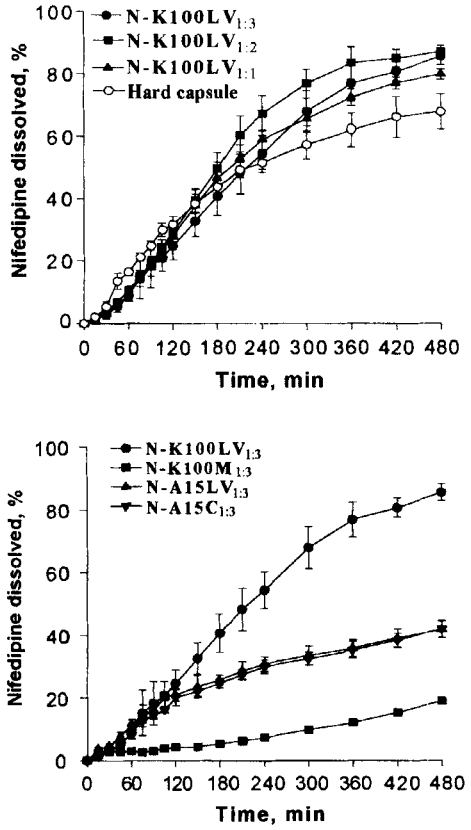

Figure 3. Nifedipine dissolution profiles for the indicated formulations.

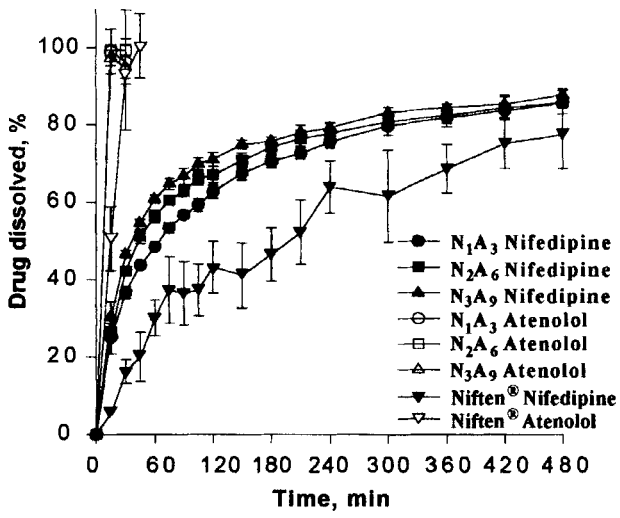

Figure 4. Nifedipine and atenolol dissolution profiles for the indicated formulations.

Table 3

Rate Coefficients for Korsmeyer et al. (30) Equation, with the Exponent (n) Fixed at 0.25, Fitted to the Data for the Nifedipine Dissolution from the Indicated Formulations (See Table 2), Together with the Corresponding Correlation Coefficients R and F values

Formulation	K ($\% \cdot min^{-0.25}$)	*R*	*F*
N_1A_3	18.49 (0.28)	0.975	4238.25[a]
N_2A_6	19.47 (0.30)	0.967	4219.79[a]
N_3A_9	20.24 (0.33)	0.954	3728.16[a]

[a] 1, 15 degrees of freedom; $\alpha < 0.01$.

For atenolol, the dissolution profiles were similar for the three formulations tested, 95% of the dose being released within the first 15 min.

The biopharmaceutical stability studies indicated that the dissolution profiles of both nifedipine and atenolol from the three formulations studied were unaltered after storage for up to 6 months.

In summary, these results suggest the proposed nifedipine–atenolol formulation to be an interesting alternative to the technologically more complex formulations currently available. Indeed, comparison of the dissolution profiles for the tablets and the commercial reference formulation (Fig. 4) suggests that the former may even offer some advantages over the latter.

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