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Research paper

Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer

Ghada Ahmed Abdelbary, Mina Ibrahim Tadros *

Department of Pharmaceutics and Industrial Pharmacy, Cairo University, Cairo, Egypt

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Abstract

The purpose of this work was to develop an extended release matrix tablet of nicorandil; a freely water soluble drug used in cardiovascular diseases. Chitosan (CH)/hyaluronate sodium (HA), pectin (PE) or alginate sodium (AL) interpolymer complexes (IPCs) were prepared. The optimum IPCs (CH:HA, 40:60), (CH:PE, 30:70) and (CH:AL, 20:80) were characterized by Fourier transform infrared spectroscopy. The IPCs were based on electrostatic interactions between protonated amine groups of CH and carboxylate groups of HA, PE or AL. Nicorandil matrix tablets were prepared using the optimum IPCs, alone or in combination with Imwitor® 900 K. Evaluations such as weight variation, thickness, content uniformity, friability, disintegration and in vitro release studies were performed. The tablets showed acceptable pharmacotechnical properties and complied with compendial requirements. Results of the dissolution studies revealed that formula F11 (CH:AL, 20:80) IPC:Imwitor® 900 K, 3:1) could extend drug release >8 h. Most formulae exhibited non-Fickian diffusion drug release profiles. When compared to the immediate release Ikorel® tablet, the duration of effective nicorandil therapeutic concentration from formula F11, in healthy human volunteers, was significantly ($P < 0.05$) extended from 4 to 8 h with expected lowering in side effects potential.

Keywords: Nicorandil; Chitosan; Hyaluronic acid sodium salt; Pectin; Alginate; Interpolymer complex; Imwitor® 900 K; Matrix tablet

1. Introduction

Nicorandil is a nitrate derivative of nicotinamide that is used in the treatment of hypertension and angina pectoris. It is a potassium-channel opener providing vasodilatation of arterioles and large coronary arteries. Its nitrate component produces venous vasodilatation [1]. Successful treatment of cardiovascular diseases means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired [2]. Nicorandil has an elimination half-life of 1 h, and the therapeutic dose is in the range of 5–40 mg taken twice daily [3]. To reduce the frequency of administration and to improve patient compliance, sustained-release formulations of nicorandil are desirable.

The drug is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. One of the most commonly used methods of modulating the drug release is to include it in a matrix system. Hydrophilic gel-forming polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance [4–6]. Indeed, the interpolymer complexes (IPCs) between polycationic chitosan and polyanionic polymers as gelatin type B [7], Carbopol [8], carrageenan [9] and xanthan gum [10] were addressed as better sustained-release drug matrices than the original hydrophilic polymers. However, rapid diffusion of hydrophilic drugs through the hydrophilic gel-like

* Corresponding author. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Kasr El-Aini Street, Cairo 11562, Egypt. Tel.: +2 012 3620458; fax: +2 02 23628426.
E-mail address: mina_ebrahim@yahoo.com (M.I. Tadros).

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networks necessitates the incorporation of hydrophobic polymers as ethylcellulose [11], pH dependent polymers as Eudragit RL 100-55 [12] or waxy retardant polymers as Compritol 888 ATO [13] along with a hydrophilic polymer for developing sustained-release matrix tablets.

Imwitor® 900 K is a glyceryl monostearate containing 40–50% monoglycerides, it has been used as a waxy retardant polymer to form sustained-release matrices, including the formulation of pellets for tablets [14] or suppositories [15], and the preparation of implantable, biodegradable, controlled-release matrices [16].

In the present work, preliminary experiments were carried out to develop nicorandil matrix tablets using certain natural, non-toxic, biodegradable and biocompatible, hydrophilic, gel-forming polymers; chitosan (CH), sodium hyaluronate (HA), sodium alginate (AL) and pectin (PE). To investigate the suitability of other extended release drug matrices, CH–HA, CH–PE and CH–AL (IPCs) were developed. The optimum IPCs were formulated as matrix tablets, alone and in combination with Imwitor® 900 K. The prepared matrix tablets were evaluated in vitro using different techniques. Finally, the in vivo oral absorption of the drug from the optimum formula as well as the commercially available immediate release Ikorel® tablet (Sanofi-Aventis, France) was investigated in six healthy human volunteers.

2. Materials and methods

2.1. Materials

Nicorandil was kindly provided by Eva Pharma, Cairo, Egypt. Low viscosity chitosan (CH) (viscosity of 1% w/v acetic acid solution at 25 °C = 45 mPa s) with a degree of deacetylation 85% was purchased from Sigma–Aldrich Chemical Co., St. Louis, MO, USA. High molecular weight hyaluronic acid sodium salt from Streptococcus equi (HA) (1.5–1.8 × 10^6 Da) (viscosity of 0.5% w/v aqueous solution at 25 °C = 30 mPa s), Glyceryl monostearate (Imwitor® 900 K) and low viscosity pectin (PE) (viscosity of 1% w/v aqueous solution at 25 °C = 30 mPa s) were procured from Fluka Biochemika, St. Louis, MO, USA. Low viscosity sodium alginate (AL) (viscosity of 1% w/v aqueous solution at 25 °C = 35 mPa s) was purchased from SD Fine Chemicals Ltd., Mumbai, India. Acetonitrile, Glacial acetic acid, potassium dihydrogen phosphate and disodium hydrogen phosphate were provided by Merck, Darmstadt, Germany. Spray dried lactose was purchased from Meggle GmbH, Wasserburg, Germany. Aerosil® 200 was from Degussa Corporation, NJ, USA. Magnesium stearate was from CG Chemikalien, Germany. All other chemicals were of analytical grade and used as received.

2.2. Determination of the optimum ratio between CH–HA, CH–PE and CH–AL

Polymer solutions were prepared as described hereunder:

CH: 0.5 g of the polymer was dispersed in 100 ml 0.5% v/v acetic acid solution. The dispersion was then stirred until a uniform solution was obtained.
HA: 0.5 g of the polymer was hydrated in 100 ml water over 12 h.
AL or PE: 0.5 g of the polymer was dispersed in 100 ml water. The dispersion was then stirred until a uniform solution was obtained.

CH–HA, CH–PE and CH–AL solutions were mixed in different proportions to make 20 ml. The mixtures were incubated at 37 °C for 48 h, followed by centrifugation at 15,000 rpm for 20 min (Megafuge 1.0 R, Heraeus, Germany). Finally, the viscosity of the supernatant solution was measured at 25 °C (Brookfield DV-II + PRO, Brookfield Engineering Labs, Inc., Middleboro, MA, USA). Plots representing the influence of varying CH–HA, CH–PE and CH–AL ratios on the supernatant viscosity were drawn. The optimal ratios between CH and HA, PE or AL were obtained when the supernatant viscosity was close to the solvent viscosity.

2.3. Preparation and characterization of (CH–HA), (CH–PE) and (CH–AL) IPCs using Fourier transform infrared (FT-IR) spectroscopy

The obtained precipitates (IPCs) upon mixing of the optimal ratios of CH–HA, CH–PE and CH–AL were washed with distilled water and dried in a desiccator jar (H-4960, Humboldt Mfg. Co., Norridge, USA) over anhydrous calcium chloride for 24 h. The dried complexes were ground in a mortar. The powders were sieved for 15 min using a sieve shaker (Setaccio Di Prova, Milano, Italy) through a test sieve with an aperture width of 200 μm which was placed over a test sieve with an aperture width of 63 μm. The powder fraction that was retained on the latter sieve was used for further studies.

FT-IR spectra were obtained on a FT-IR spectrophotometer (Genesis II, Mattson, USA). Samples of CH, HA, PE, AL and the prepared IPCs were prepared in KBr discs (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm^{-1} and the resolution was 1 cm^{-1}.

2.4. Preparation of nicorandil tablets

Tablets containing 20 mg nicorandil were prepared by direct compression. The investigated formulations are shown in Table 1. The respective powders (drug, polymers or IPCs, Imwitor® 900 K, spray dried lactose, Aerosil® 200 and magnesium stearate) were passed through a 200 mesh sieve. The powders were blended thoroughly using a pestle and mortar. Then, 120 mg of each mixture was weighed and fed manually into the die of a single punch tabletting machine equipped with flat faced punches (7.0 mm) to produce the desired tablets. The hardness of the tablets was kept constant at approx. 80 N (HDT-300, Logan Instruments Corp., NJ, USA).

Table 1
The composition of the investigated nicorandil tablets[a]

Form. No.	Drug	CH	HA	PE	AL	(CH–HA) IPC	(CH–PE) IPC	(CH–AL) IPC	Imwitor® 900 K	Spray dried lactose	Aerosil® 200	Mg stearate
F1	20	20								74	5	1
F2	20		20							74	5	1
F3	20			20						74	5	1
F4	20				20					74	5	1
F5	20					20				74	5	1
F6	20						20			74	5	1
F7	20							20		74	5	1
F8	20						60			34	5	1
F9	20							60		34	5	1
F10	20						60		20	14	5	1
F11	20							60	20	14	5	1

[a] Values in the table are weights in mg.

2.5. Evaluation of the prepared tablets

2.5.1. Tablet weight variation

Twenty matrix tablets were randomly selected and accurately weighed using an electronic balance (Sartorius GmbH, Gottingen, Germany). The results are expressed as mean values of 20 determinations.

2.5.2. Tablet thickness

The thickness of ten randomly selected matrix tablets was determined using a vernier caliper (For-bro Engineers, Mumbai, India). The results are expressed as mean values of 10 determinations.

2.5.3. Drug content uniformity

Ten tablets were weighed individually, crushed and the drug was extracted in water. The solution was filtered through a cellulose acetate membrane (0.45 μm) and the drug content was determined by UV spectroscopy (1601-PC Double beam spectrometer, Shimadzu, Kyoto, Japan) at a wavelength of 262 nm after a suitable dilution.

2.5.4. Tablet friability

According to the BP [17] specifications, a sample of whole tablets corresponding to 6.5 g was placed in the drum of a tablet friability test apparatus (FAB-2, Logan Instruments Corp., NJ, USA). The drum was adjusted to rotate 100 times in 4 min then the tablets were removed from the drum, dedusted and accurately weighed. The percent weight loss was calculated. The test was run twice for each tablet formulation.

2.5.5. Tablet disintegration

The standard BP test [17] was employed to assess the disintegration times; the time necessary for complete disintegration of the tablets, using a Disintegration tester (DST-3, Logan Instruments Corp., NJ, USA). Tests were carried out in 800 ml of distilled water at 37 ± 0.5 °C. Six tablets were tested in each run.

2.5.6. In vitro drug release studies

Dissolution tests were performed in a USP Dissolution Tester Apparatus I (Basket method) (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ, USA) at 37 ± 0.5 °C. The baskets were rotated at a speed of 50 rpm. The prepared tablets, in addition to commercially available Ikorel® tablets (Sanofi-Aventis, France), were placed in the baskets and then submerged into 900 ml of 0.1 N HCl solution (pH 1.2) for 2 h. These were then transferred to 900 ml of Sorensen's phosphate buffer (pH 6.8) and left in this media for additional 8 h. Aliquots of 5 ml were withdrawn at different time intervals, filtered through cellulose acetate membrane (0.45 μm) and the content of nicorandil was determined spectrophotometrically at a wavelength of 262 nm, as mentioned before. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. The release studies were conducted in triplicates and the mean values were plotted versus time.

The target release profile parameters of a sustained-release product [18] were reported as follows: After 2 h: $35 \pm 15\%$; After 4 h: $60 \pm 15\%$; After 8 h: $90 \pm 15\%$;

The resulting data were analyzed by using the software SPSS 14.0 (SPSS Inc., Chicago, USA) applying one-way ANOVA followed by Post Hoc multiple comparisons using the least square difference (LSD) test. Differences between formulations were considered to be significant at $P < 0.05$.

2.5.7. Kinetic analysis of the release data

The mechanism of drug release from the prepared matrix tablets during dissolution tests in 0.1 N HCl and phosphate buffer pH 6.8 was determined using zero order, first order, Higuchi and Korsmeyer–Peppas equation (Eq. (1)) [19]:

$$\left(\frac{M_t}{M_\infty}\right) = kt^n, \tag{1}$$

where k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism and (M_t/M_∞) represents the drug dissolved fraction at time t.

To clarify the release exponent for different formulations, the log value of the percentage drug released was plotted against log time according to Eq. (2).

$$\log\left(\frac{M_t}{M_\infty}\right) = \log k + n \log t. \quad (2)$$

In case of Fickian release (diffusion controlled release), n has the limiting values of 0.45 for release from cylinders. The n value is 0.89 in case of Case II transport (relaxation controlled release) from cylinders. The non-Fickian release (anomalous transport of drug) occurs when the n values fall between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation.

2.6. In vivo absorption studies

2.6.1. Study design

The study was carried out to compare the pharmacokinetics of nicorandil from a prepared matrix tablet formulation (F11) to a conventional commercially available immediate release tablet formulation (Ikorel®, Sanofi-Aventis, France) following administration of single doses of 20 mg each using a non-blind, two-treatment, two-period, randomized, crossover design.

Six healthy male volunteers participated in the study after giving informed written consent and were randomly assigned to one of two groups of equal size. The subjects ranged in age from 30 to 37 (mean 34), in height from 169 to 185 cm (mean 172 cm) and in weight from 67 to 80 kg (mean 69 kg). The study was approved by the Cairo University Protection of Human Subjects Committee and the protocol complies with the declarations of Helsinki and Tokyo for humans. All subjects were prohibited from taking medicines and smoking for 1 week before the beginning of the studies to the end of the test. All subjects fasted for at least 10 h before the study day (FDA, 2002). At 8:00 a.m. the assigned treatment was given. The study was performed on two phases.

Phase I, half the number of volunteers received a matrix tablet (F11, treatment A) and the remainder received the immediate release commercial tablet (Ikorel®, treatment B) which is considered as a standard. Both treatments were ingested with 200 ml of water. No food was allowed for 4 h after dosing. A washout period of one week separated the phases. On the second phase, the reverse of randomization took place.

Each group was supervised by a physician who was also responsible for their safety and collection of samples during the trial. Venous blood samples (5 ml) were collected into heparinized tubes at the following set points: 0 min (pre-dose), 30 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 16 and 24 h after administration of each treatment. Plasma was obtained by centrifugation at 2000g for 10 min (Centurion Scientific Ltd., West Sussex, UK). The plasma was pipetted into glass tubes and then frozen at −20 °C until ready to be analyzed.

2.6.2. Chromatographic conditions

Plasma concentrations of nicorandil were determined using an HPLC procedure described by Ojha and Pargal [20]. Reversed phase chromatography was conducted using a mobile phase consisting of acetonitrile:phosphate buffer (40:60, v/v) with UV detection at 230 nm. Metformin was adopted as an internal standard. The column was a reverse-phase micro-particulate Bondapack C18, particle size 10 m, 25 cm × 4.6 mm (Waters Corp., Milford, MA, USA). The flow rate was 0.8 ml/min. Peak areas were determined with a C-R6A chromatopac Shimadzu integrator.

2.6.3. Standard solutions

Primary standard solutions (100 μg/ml) of nicorandil and metformin were prepared in methanol. Blank plasma samples were spiked with the nicorandil stock solution to contain 5–300 ng/ml. To each tube, 1 ml of metformin stock solution was added. Aliquots of 100 μl of spiked plasma samples were mixed with 250 μl of acetonitrile and the mixtures were vortexed for 30 s and centrifuged at 3000g for 10 min. A portion of the supernatants were transferred to HPLC tubes and 50 μl was injected onto the HPLC column.

Under the described conditions, the retention time of nicorandil and metformin was 4.8 and 7.2 min, respectively. A plasma sample, without the addition of nicorandil, also was treated in the same way. A standard curve was constructed by plotting the peak area ratio of nicorandil to metformin against nicorandil concentrations in plasma. All assays were performed in triplicate. The lower limit of quantification was 5 ng/ml. A linear response ($R^2 = 0.998$) across the full range of concentrations from 5 to 300 ng/ml was obtained.

2.6.4. Plasma analysis and quantitation

The plasma samples derived from the six subjects after receiving treatment A (F11) and treatment B (Ikorel®) were assayed as described above without the addition of nicorandil. The unknown sample concentration was calculated from the following formula:

$$Q = \left[\frac{R \pm B}{A}\right] \times \text{Dilution Factor}, \quad (3)$$

where Q is Nicorandil concentration, R is the peak area ratio (drug/internal standard), A is the slope of the standard curve and B is the Y-intercept.

2.6.5. Pharmacokinetic analysis

The pharmacokinetic parameters of the two treatments were estimated for each subject by using a computer program; WinNonlin® (version 1.5, Scientific consulting, Inc., Cary, NC, USA), adopting non-compartmental analysis. The maximum drug concentration (C_{max}, ng/ml) and the time to reach C_{max} (T_{max}, h) were obtained from the individual plasma concentration–time curves. The mean residence time (MRT, h), as well as the area under the

curve from zero to infinity, $AUC_{(0-\infty)}$, ng h/ml), was calculated using the trapezoidal rule method.

2.6.6. Statistical analysis

Results are expressed as mean values of 6 volunteers ±SD. A two-way analysis of variance (ANOVA) was performed for the untransformed data derived from the pharmacokinetic parameters; C_{max}, T_{max}, $AUC_{(0-\infty)}$ and MRT using the software SPSS 14.0 (SPSS Inc., Chicago, USA), in order to investigate the statistical significance among groups. The level of significance was $\alpha = 0.05$. A P-value < 0.05 was considered statistically significant.

3. Results and discussion

3.1. The optimum ratio between CH–HA, CH–PE and CH–AL

Fig. 1 represents a plot illustrating the influence of varying the CH–HA, CH–PE and CH–AL ratios on the supernatant viscosity of the corresponding mixture.

When the CH concentration was 0%, the viscosities, representing HA, PE and AL solutions, were 28, 13 and 16 mPa s, respectively. As the CH concentration was increased, the supernatant viscosity was decreased indicating that the protonated amine groups of CH were undergoing complexation with the carboxylate groups of the anionic polymers to variable extents. This relation was held true till a certain CH concentration (40%, 30% and 20% for CH–HA, CH–PE and CH–AL mixtures, respectively) where the supernatant viscosity was approximately 1. This could indicate that the interaction sites of chitosan and these anionic polymers were almost saturated. Therefore, the reacting polymers formed an insoluble complex and the supernatant viscosity would represent that of the solvent. Above this optimum ratio, as the CH concentration was increased, the supernatant viscosity was increased till reaching 20 mPa s at 100% CH solution.

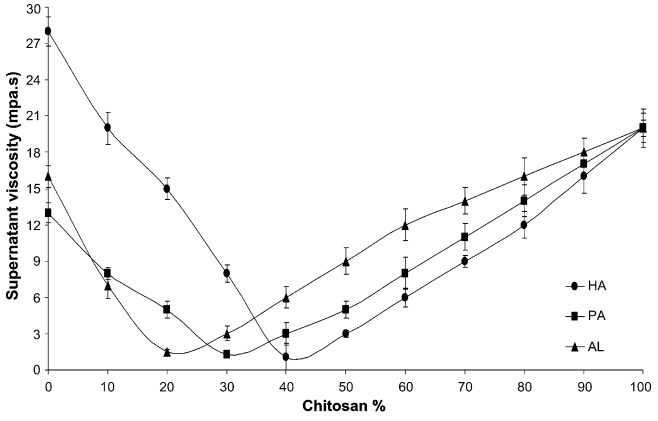

Fig. 1. The influence of varying the CH–HA, CH–PE and CH–AL ratios on the supernatant viscosity of the corresponding mixture (mean ± SD, $n = 3$).

In view of the aforementioned, the results of the viscosity studies clearly showed that the optimum complexation ratios between CH and HA, PE and AL were 40%, 30% and 20%, respectively. Therefore, these ratios were used to characterize the IPCs, which were in turn used to formulate tablets for which the release profiles were evaluated.

As shown in Figs. 2–4, the FT-IR spectrum of chitosan showed an intense absorption band at 1655.1 cm^{-1} assigned to the $-NH_3^+$ groups. On the other hand, the FT-IR spectra of HA, PE and AL showed broad absorption bands at 1446.4 cm^{-1} assigned to $-COO^-$ groups. It could be observed that the FT-IR spectra of (CH:HA, 40:60), (CH:PE, 30:70) and (CH:AL, 20:80) IPCs showed new absorption bands. Indeed, these bands are absent in the individual spectrum of CH, HA, PE or AL. Furthermore, the intensity of the absorption bands assigned to the $-NH_3^+$ and $-COO^-$ groups were markedly changed and/or displaced. These results confirm the formation of IPCs between CH and these anionic polymers.

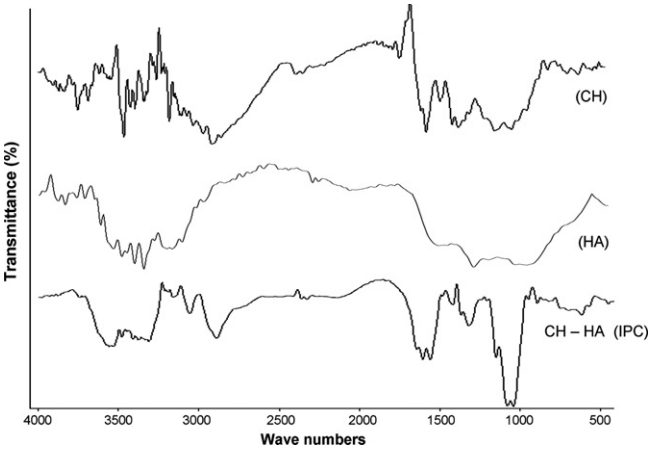

Fig. 2. FT-IR spectra of CH, HA and CH–HA (IPC).

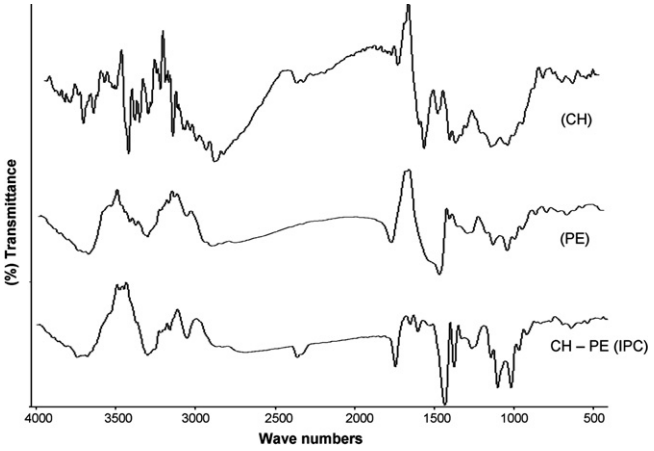

Fig. 3. FT-IR spectra of CH, PE and CH–PE (IPC).

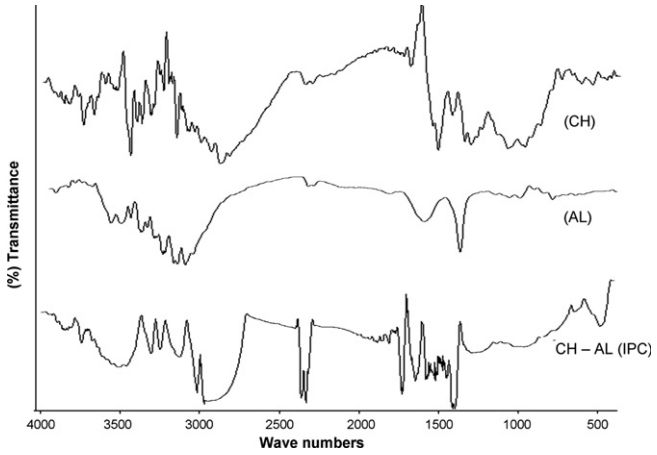

Fig. 4. FT-IR spectra of CH, AL and CH–AL (IPC).

3.2. Physical properties of the tablets

The comparison of physical properties of the matrix tablets is shown in Table 2. The weight and thickness of the formulations ranged from 118.24 to 122.43 mg and from 1.18 to 1.23 mm, respectively. All tablets prepared in this study meet the USP 27 requirements for weight variation tolerance; coefficient of variation of all formulae was less than 2%.

Drug uniformity results were found to be good among different batches of tablets, and the percentage of drug content was more than 97%.

Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the compendial limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability.

Concerning the disintegration testing, tablets prepared with a drug-to-CH or HA ratio of 1:1 (Formulae F1 and F2) disintegrated rapidly within 30 min in distilled water. Marked variations were observed in the disintegration time of other formulae; the disintegration time for the tablets having a drug-to-PE or AL ratio of 1:1 (F3–F4) and those containing 1:1 physical mixtures of the drug and CH–HA (40–60), CH–PE (30–70) or CH–AL (20–80) IPCs (Formulae F5–F7) ranged from 40.50 to 95.60 min.

Indeed, formulae F8, F9 containing 1:3 physical mixtures of the drug and CH–PE (30–70) or CH–AL (20–80) IPCs and formulae F10, F11 containing 1:3:1 physical mixtures of the drug: CH–PE (30–70) or CH–AL (20–80) IPCs:Imwitor 900 K did not disintegrate even after 120 min. This behavior suggested that these polymers could be used, with the previously evaluated ratios, as compressed non-disintegrating porous, swellable matrices for sustained-release tablets.

3.3. In vitro release of nicorandil from the prepared tablets

As shown in Fig. 5, 100% of the drug was released from Ikorel® tablets within 30 min. On the other hand, the tablets that were prepared with a drug-to-polymer ratio of 1:1 released 100% of the drug within 3 h.

The rapid release of the drug from CH- (formula F1) and HA- (formula F2) based tablets could be related to the solubility of CH and HA in the acidic medium. Indeed, the dissolution of CH-based tablets in 0.1 N HCl is suggested to be related to the transformation of the amine groups of the glucosamine units of CH into the positively charged water soluble form [21].

In order to compare the drug release profile from the prepared tablets, the percentage drug released after 2 h, Q_{2h}, was measured and statistically analyzed using one-way ANOVA followed by Post Hoc multiple comparisons using LSD test.

Previous reports [22,23] have shown that, in the acidic media, the carboxylate anions of PE or AL readily undergo inter-conversion to the free carboxyl groups. Thereby, forming pectinic or alginic acid, respectively, that are practically insoluble at pH 1.2. Therefore, it is perhaps reasonable to expect a slower drug release in acidic medium from PE- (formula F3) and AL- (formula F4) based tablets. However, the Q_{2h} values, in this study, were 98.98% and 92.32%, respectively.

Table 2
Physical properties of the prepared tablets

Form. No.	Tablet weight (mg)	Tablet thickness (mm)	Drug content (%)	Tablet friability (%)	Disintegration time (min)
F1	118.29 ± 0.34	1.21 ± 0.04	98.34 ± 0.22	0.52 ± 0.12	15.50 ± 1.10
F2	119.78 ± 0.45	1.19 ± 0.03	99.21 ± 0.11	0.67 ± 0.23	10.20 ± 0.50
F3	118.98 ± 0.55	1.18 ± 0.02	98.10 ± 0.18	0.34 ± 0.22	57.30 ± 3.50
F4	121.19 ± 0.36	1.19 ± 0.03	98.20 ± 0.39	0.74 ± 0.21	70.10 ± 5.20
F5	122.43 ± 0.12	1.23 ± 0.02	101.31 ± 0.21	0.56 ± 0.24	40.50 ± 2.20
F6	118.56 ± 0.24	1.18 ± 0.01	98.55 ± 0.67	0.41 ± 0.11	75.30 ± 5.10
F7	121.78 ± 0.13	1.19 ± 0.02	100.56 ± 0.89	0.61 ± 0.19	95.60 ± 5.10
F8	120.34 ± 0.23	1.18 ± 0.02	101.34 ± 0.79	0.78 ± 0.16	>120
F9	119.35 ± 0.54	1.19 ± 0.03	97.11 ± 0.12	0.58 ± 0.11	>120
F10	118.24 ± 0.76	1.21 ± 0.02	98.34 ± 0.45	0.31 ± 0.12	>120
F11	118.37 ± 0.38	1.18 ± 0.03	98.15 ± 0.28	0.41 ± 0.18	>120

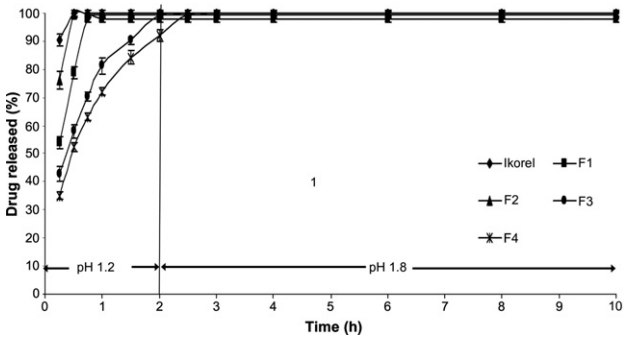

Fig. 5. In vitro drug release from the tablets prepared with a drug:polymer ratio of 1:1 in 0.1 N HCl (pH 1.2) for 2 h and Sorensen's phosphate buffer (pH 6.8) for additional 8 h at 37 ± 0.5 °C (mean ± SD, $n = 3$).

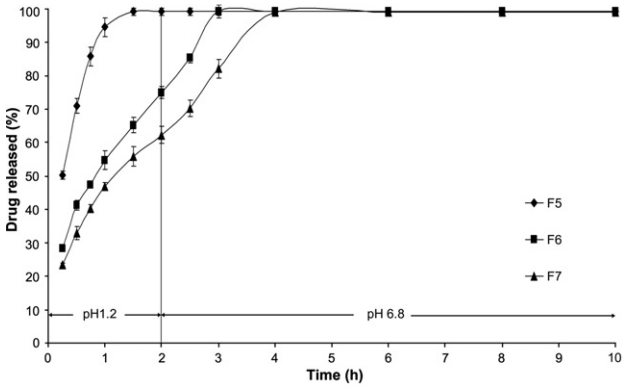

Fig. 6. In vitro drug release from the matrix tablets prepared with a drug:IPC ratio of 1:1 in 0.1 N HCl (pH 1.2) for 2 h and Sorensen's phosphate buffer (pH 6.8) for additional 8 h at 37 ± 0.5 °C (mean ± SD, $n = 3$).

This unexpected rapid drug release from PE- and AL-based tablets has been reported by Sriamornsak et al. [23,24]. A possible explanation to this behavior could be related to the use of low viscosity grades of PE or AL. It was suggested that these tablets, upon hydration in acidic medium, were not viscous or adhesive in nature like other tablets formulated using high viscosity grades of PE or AL, but acquired a tough and rubbery texture. Thereby, they formed very weak gels that were not rigid enough to retard the rate of drug release for a sufficient period of time.

In addition, the formation of pectinic or alginic acids is expected to stimulate tablet disintegration. These acids, being water insoluble, are swellable in acidic medium and have been traditionally used as tablet disintegrants in compressed tablets designed for immediate drug release [25,26].

Statistical analysis of the results revealed that the Q_{2h} values of formulae F3 and F4 are significantly ($P < 0.05$) higher than those obtained with formulae F1 and F2. Post Hoc multiple comparisons using LSD test revealed that Q_{2h} value of formula F4 is slightly but not significantly ($P > 0.05$) higher than that obtained with formula F3.

The retarding influence of the IPCs of CH–HA, CH–PE and CH–AL on the drug release from the tablets prepared with a drug:IPC ratios of 1:1 (formulae F5–F7) and 1:3 (formulae F8–F9) was evaluated.

As shown in Fig. 6, the drug release from the tablets was influenced by pH of the release media. Drug release from formula F5, containing the drug and CH–HA (IPC), was essentially complete within a short period of time; 1.5 h. However, this period is markedly longer than that obtained with CH- (0.75 h) and HA- (0.5 h) based tablets. It is worthy to note that the complete drug release from formula F5 within 90 min could indicate that the CH–HA (IPC) is soluble in the acid medium.

On the other hand, the drug release from formulae F6 and F7 was longer than that achieved with formula F5 and extended for 3 and 4 h, respectively. Unlike the complete drug release from formulae F1 and F3 within 2 h, the Q_{2h} value of formula F6 (74.98%) was significantly ($P < 0.01$) lower. In a similar way, it was proved statistically that the Q_{2h} value of formula F7 (62.23%) was significantly ($P < 0.01$) lower than that obtained with formulae F1 (100%) and F4 (92.1%).

Physical examination of the tablets (formulae F6 and F7) after immersion in 0.1 N HCl revealed the presence of excessive patterns of deformation (like the presence of some cracks, grooves) in the former formula than in the latter one. It is likely that, in acidic medium, the pressure built-up within the matrix could not be released by the matrix swelling and thus the ruptured surface was generated [23]. This explains why the Q_{2h} value of formula F6 was significantly ($P < 0.05$) higher than that of formula F7. Among the investigated IPCs, CH–PE and CH–AL-based tablets retarded the drug release for a longer period of time. Hence they were selected for further formulation developments.

Fig. 7 shows the influence of using a drug:IPC ratio of 1:3 on the in vitro drug release profiles from the selected IPC-based matrix tablets.

The Q_{2h} values of the formulae F8 and F9 (66.32% and 56.98%, respectively) were significantly ($P < 0.05$) lower than their corresponding values obtained with the formulae F6 and F7 (74.98% and 62.23%, respectively). Also, it could be observed that 100% of the drug was released from the formulae F8 and F9 within 6 h, while the same drug concentration was released from formulae F6 and F7 within 3 and 4 h, respectively.

Conclusively, the use of a higher drug:IPC ratio of 1:3 (formulae F8 and F9) enabled the designing of better sustained-release drug matrices than those prepared with a drug:IPC ratio of 1:1.

As mentioned before, a suitable sustained-release formulation is suggested to release 35 ± 15% of drug in the first 2 h, followed by slow release to reach 90 ± 15% by the end of 8 h. Hence, the initial burst release (Q_{2h} value > 50% of drug) and deviations in the release profile from the theoretical target release pattern demonstrated the need for further development in order to attain a suitable formulation that mimics the theoretical pattern.

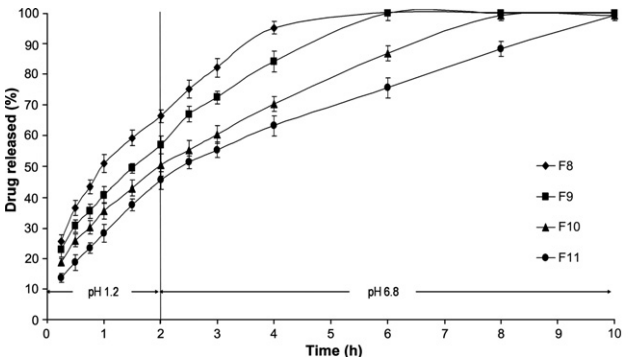

Fig. 7. In vitro drug release from the matrix tablets prepared with a drug:IPC ratio of 1:3 (formulae F8 and F9) and the matrix tablets prepared with a drug:IPC:Imwitor® 900 K ratio of 1:3:1 (formulae F10 and F11) in 0.1 N HCl (pH 1.2) for 2 h and Sorensen's phosphate buffer (pH 6.8) for additional 8 h at 37 ± 0.5 °C (mean ± SD, $n = 3$).

Therefore, formulae F8 and F9, which exhibited the slowest dissolution profiles of the evaluated formulae, were modified by the incorporation of Imwitor 900 K in order to control the drug release in the initial hours, in addition to achieving a higher cumulative drug release at the end of 8 h.

As illustrated in Fig. 7, the Q_{2h} values of the formulae F10 and F11 were 50.32% and 45.38% of the drug, respectively. These values were significantly lower ($P < 0.05$) than the corresponding values of the formulae F8 and F9, respectively. Moreover, the drug release profiles of the latter formulae were extended for longer periods; 8 h (formula F10) and 10 h (formula F11). A possible explanation to these results could be related to the incorporation of Imwitor 900 K which is a well-known waxy retardant polymer.

As evident by Peh et al. [27,28], the incorporation of Imwitor 900 K caused an increase in the matrix lipophilicity, leading to a decrease in the effective interfacial area between the drug and the dissolution medium. This results in a reduction of the matrix wettability (the rate of dissolution medium penetration into the matrix) and consequently leading to a decrease in drug diffusion from the matrix.

Statistical analysis of the data revealed that the Q_{2h} value of formula F11 was significantly ($P < 0.05$) lower than that of formula F10.

3.4. Kinetic analysis of the release data

The mechanism of drug release from matrices containing swellable polymers is complex. Some systems may be classified as either purely diffusion or erosion controlled, while other systems exhibit a combination of these mechanisms [29]. Higuchi model is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix. A good fit to Korsmeyer–Peppas equation could indicate combined effects of diffusion and erosion mechanisms for drug release.

As illustrated in Table 3, the nicorandil release from the prepared tablets showed good fit into Korsmeyer–Peppas equation. The correlation coefficient (R^2) and the diffusional exponent (n), obtained in all formulae, were greater than 0.9938 and 0.45, respectively. The exception is for the formulae F1, F2 and F5, showing rapid disintegration (within 40 min) in the acidic medium. Therefore, the correlation coefficients and the diffusional exponents for these formulations could not be calculated as a result of insufficient data points, up to 60%, on the drug release profiles to provide accurate values.

The relative complexity of the prepared formulae may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion. The drug release mechanism could be best described as non-Fickian or anomalous diffusion.

3.5. In vivo absorption study

The in vitro drug release studies, carried out in this work, have revealed that the release rate of nicorandil could be efficiently extended for more than 8 h upon incorporation in matrix tablets based on a hydrophobic waxy retardant polymer, Imwitor® 900 K and hydrophilic (CH:PE, 30:70) or (CH:AL, 20:80) IPCs. Indeed, formula

Table 3
Mathematical modeling and release kinetics of nicorandil from the prepared formulations, F1–F11

Form. No.	Zero order plots	First order plots	Higuchi's plots	Korsmeyer–Peppas plots		
	Correlation coeff. (R^2)	Correlation coeff. (R^2)	Correlation coeff. (R^2)	Correlation coeff. (R^2)	Diffusional exponent (n)	Order of release
F1	0.9947	0.9190	0.9999	n/a	n/a	n/a
F2	n/a	n/a	n/a	n/a	n/a	n/a
F3	0.9401	0.8892	0.9874	0.9994	0.4811	Non-Fickian
F4	0.9233	0.8875	0.9824	0.9968	0.4993	Non-Fickian
F5	0.9909	0.9935	0.9996	n/a	n/a	n/a
F6	0.9814	0.9850	0.989	0.9938	0.4744	Non-Fickian
F7	0.9836	0.9962	0.9974	0.9982	0.4765	Non-Fickian
F8	0.9829	0.9982	0.9990	0.9992	0.4705	Non-Fickian
F9	0.9895	0.9971	0.9981	0.9984	0.4732	Non-Fickian
F10	0.9777	0.9967	0.9990	0.9996	0.4842	Non-Fickian
F11	0.9652	0.9936	0.9950	0.9957	0.5823	Non-Fickian

n/a, not applicable.

F11, containing (CH:AL, 20:80) IPC and Imwitor® 900 K, was considered to be superior to formula F10, containing (CH:PE, 30:70) and Imwitor® 900 K. The drug release from the former formula showed comparatively less deviation from the theoretical target profile; 88% of the drug was released within 8 h (Fig. 7) [18]. On the other hand, a nearly similar drug percentage was released from Ikorel® tablets within 15 min (Fig. 5).

Therefore, the in vivo oral absorption of nicorandil (20 mg) from an extended release matrix tablet, formula F11, as well as an immediate release Ikorel® tablet, was evaluated in 6 healthy human volunteers under the fasted condition. As illustrated in Fig. 8, the plasma concentration–time profiles of nicorandil explicitly indicate that the matrix tablets, formula F11, successfully sustained the oral absorption of nicorandil. Remarkable differences in the shape of the plasma concentration–time courses between the two treatments were found, expressed by lower C_{max} and delayed T_{max} (by 2 h) values for the matrix tablet. The mean C_{max} estimates from matrix tablets and Ikorel® tablets were 176.5 ± 10.1 and 346.6 ± 16.8 ng/ml, respectively (Table 4). The differences between the two treatments for C_{max} and T_{max} were statistically significant ($P < 0.05$). Furthermore, the MRT was prolonged from 3.8 h, with Ikorel® tablets, to 5.1 h, with formula F11. This difference was proved to be statistically significant ($P < 0.05$). On the other hand, the $AUC_{(0-\infty)}$ of nicorandil for F11 was slightly lower than that for Ikorel® tablets. However, this difference was not statistically significant ($P > 0.05$). Therefore, it could be considered that matrix tablet, F11, successfully maintained the AUC of nicorandil [30]. Compared with immediate release nicorandil tablets, the relative bioavailability judged from the $AUC_{(0-\infty)}$ was found to be 96.3%.

Previous reports [31,32] have shown that the minimum effective therapeutic concentration of nicorandil ranges from 40 to 60 ng/ml. The intensity of the side effects like flushing, palpitation, weakness, headache, mouth ulcers, nausea and vomiting, has been proved to be strongly associated with nicorandil plasma level.

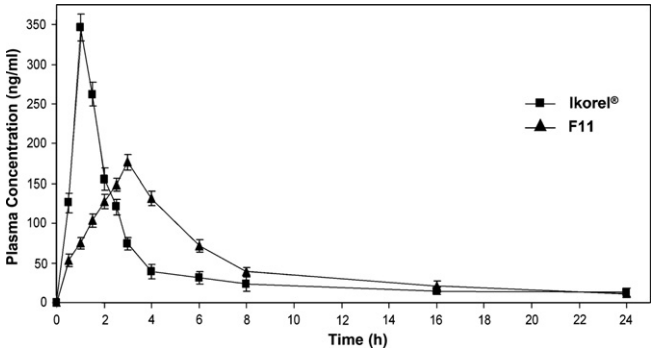

Fig. 8. Plasma concentration profiles of nicorandil after oral administration of matrix tablets (F11) and immediate release tablets (Ikorel®) to six healthy human volunteers under fasted conditions (mean ± SD).

Table 4
Pharmacokinetic parameters of nicorandil after oral administration of F11 matrix tablets and Ikorel® immediate release tablets to six healthy human volunteers under fasted condition (mean ± SD)

Formulation	$AUC_{(0-\infty)}$ (ng h/ml)	C_{max} (ng/ml)	T_{max}[a] (h)	MRT (h)
F11	1244.9 ± 84.2	176.5 ± 10.1	3.0	5.1 ± 0.2
Ikorel®	1293.4 ± 143.1	346.6 ± 16.8	1.0	3.8 ± 0.3

[a] Median.

Based on these findings, it could be concluded that following administration of Ikorel® tablets, an effective nicorandil plasma level was maintained for approximately 4 h. On the other hand, upon administration of formula F11 tablets, the drug plasma level was markedly lower but was maintained at a therapeutic level for almost 8 h. This extended lower nicorandil plasma level was expected to reduce the intensity of the previously mentioned side effects commonly associated with the immediate release tablets.

4. Conclusions

This study showed that Imwitor® 900 K is an appropriate hydrophobic waxy retardant polymer that could be utilized as an efficient matrix-forming agent, in combination with certain hydrophilic interpolymer complexes like those formed between CH–AL and CH–PE, to control the release rate of nicorandil. The in vitro drug release studies revealed that formula F11 (CH:AL, 20:80) IPC:Imwitor® 900 K, 3:1) could extend drug release for more than 8 h. The release data of most formulae showed a good fit to the Korsmeyer–Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. When compared to the immediate release Ikorel® tablets, the prepared matrix tablets, formula F11, would provide an extended duration of nicorandil plasma concentration with minimum potential for side effects.

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