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Research paper

Comparison of the effect of chitosan and polyvinylpyrrolidone on dissolution properties and analgesic effect of naproxen

Naima Zerrouk[a], Natascia Mennini[b], Francesca Maestrelli[b], Chantal Chemtob[a], Paola Mura[b,*]

[a]*Laboratoire de Pharmacie Galénique, Faculté de Sciences Pharmaceutiques et Biologiques, Université de Paris V, Paris, France*
[b]*Dipartimento di Scienze Farmaceutiche, Facoltà di Farmacia, Università di Firenze, Florence, Italy*

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Abstract

The solubilizing and absorption enhancer properties towards naproxen of chitosan and polyvinylpyrrolidone (PVP) have been investigated. Solid binary systems prepared at various drug–polymer ratios by mixing, cogrinding or kneading, were characterized by differential scanning calorimetry, X-ray diffractometry, Fourier transform infrared spectroscopy, and scanning electron microscopy, and tested for dissolution behavior. Both carriers improved drug dissolution and their performance depended on the drug–polymer ratio and the system preparation method. Chitosan was more effective than PVP, despite the greater amorphizing power of PVP as revealed by solid state analyses. The 3/7 (w/w) drug–carrier coground systems with chitosan and PVP were the best products enabling, respectively, an improvement of 4.8 and 3.6 times of drug dissolution efficiency. In vivo experiments in mice demonstrated that administration of 45 mg/kg of drug coground with PVP or chitosan resulted, respectively, in a 25 and 60% reduction of acetic acid-induced writhings in comparison to pure drug, which, instead, was statistically ineffective as compared to the control group. Moreover, the 3/7 (w/w) drug-chitosan coground product demonstrated an antiwrithing potency 2.4 times higher than the coground with PVP. Thus, the direct-compression properties and antiulcerogenic activity, combined with the demonstrated solubilizing power and analgesic effect enhancer ability towards the drug, make chitosan particularly suitable for developing a reduced-dose fast-release solid oral dosage form of naproxen.

Keywords: Naproxen; Chitosan; Polyvinylpyrrolidone; Dissolution; Analgesic effect; Cogrinding

1. Introduction

Chitosan is a linear polycationic copolymer of β(1–4) linked 2-acetamido-2-deoxy-β-D-glucopyranose and 2-amino-2-deoxy-β-D-glucopyranose obtained from deacetylation of chitin, a structural polysaccharide which is very abundantly distributed in nature.

In recent years chitosan has gained increasing interest in the pharmaceutical field due to its favorable biological properties such as biocompatibility, biodegradability, and lack of toxicity, together with its wide availability, low cost and high versatility of use [1–4]. Previously chitosan was largely used as an excipient for oral drug solid dosage forms, due to its binder, anti-adherent and disintegrant properties [5–7]. More recently, it has been widely investigated for its potential in the development of various kinds of drug delivery systems, due to its film-forming and gelation abilities, along with its cationic character, bioadhesiveness and absorption enhancer properties [4,8–12]. Moreover, its ability in improving the dissolution properties and bioavailability of poorly-soluble drugs has been proved [13–16]. Finally, its antiacid and antiulcer activities [17] can be exploited to prevent or reduce gastric irritation induced by some active compounds, such as anti-inflammatory drugs [18,19].

We recently demonstrated the effectiveness of chitosan in enhancing the dissolution properties of naproxen, a very poorly water-soluble nonsteroidal anti-inflammatory drug [20]. The favorable effect of polyvinylpyrrolidone (PVP) on naproxen solubility and dissolution rate has also been previously demonstrated [21]. Therefore, it seemed worthy of interest to extend our investigations and compare in detail the performance of such polymers in improving naproxen dissolution behavior. Solid binary systems, prepared at

* Corresponding author. Dipartimento di Scienze Farmaceutiche, Facoltà di Farmacia, Università di Firenze, Via Gino Capponi 9, 50121 Florence, Italy. Tel.: +39-055-275-7292; fax: +39-055-240776.
E-mail address: mura@unifi.it (P. Mura).

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various drug-to-polymer ratios and using different techniques (mixing, cogrinding, kneading) were thoroughly characterized for physicochemical properties by differential scanning calorimetry, X-ray powder diffractometry, Fourier transform infrared (FT-IR) spectroscopy, and scanning electron microscopy (SEM), and tested for dissolution behavior. The most effective products were then selected to carry out in vivo experiments in mice, in order to evaluate and compare the enhancer activities of the examined polymers on the analgesic effect of naproxen after its oral administration.

2. Materials and methods

2.1. Materials

Naproxen (NAP), polyvinylpyrrolidone K15 (PVP, average molecular weight 10 000 Da) and chitosan (CS, average molecular weight 150 000 Da); were supplied by Sigma (St. Louis, MO, USA). According to the supplier's specifications the degree of deacetylation of CS was 75–85%, and the viscosity of 1% solution in 1% acetic acid at 20 °C was 100 mPas. All other reagents and solvent were of analytical grade.

2.2. Preparation of solid systems

NAP–polymer binary systems in different (w/w) ratios (1:9; 3:7; 5:5) were prepared from the individual components by: (a) tumble mixing with a turbula mixer for 15 min at 50 rpm (physical mixtures, P.M.); (b) ball-milling in a high energy vibrational micromill (Retsch GmbH, Düsseldorf, Germany) for 60 min at 24 Hz (ground systems, GR); (c) wetting in a mortar with the minimum volume of an ethanol-water 6:1 (v/v) mixture and ground thoroughly with a pestle to obtain a paste which was then dried under vacuum at room temperature up to constant weight (kneaded systems, KN).

Sieved products (75–150 μm) were used for all subsequent studies.

2.3. Differential scanning calorimetry (DSC)

DSC analyses were performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell on 5–10 mg samples (Mettler M3 microbalance) scanned in pierced Al pans at 10 °C min^{-1} between 30 and 200 °C under static air.

2.4. X-ray powder diffractometry

X-ray powder diffraction patterns were collected with a Philips PW 1130 powder diffractometer (Cu Kα radiation), in the 10–50 2θ range at 1° min^{-1}.

2.5. FT-IR spectroscopy

FT-IR spectra were obtained with KBr disks using a Perkin Elmer Model 1600 apparatus.

2.6. Scanning electron microscopy

SEM analysis was carried out using a Hitachi Mod. S250 scanning electron microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive (fine coat ion sputter JFC-1100, JEOL). The magnification selected was 1000× since it was enough to appreciate in detail the general morphology of the powders under study.

2.7. Dissolution rate studies

In vitro dissolution rate studies of the pure drug and the different drug–polymer combinations were performed according to the solid dispersed amount method [22]. Previously sieved (75–150 μm) solid systems equivalent to 60 mg of drug were added to 75 ml of water at 37 ± 0.5 °C and stirred at 100 rpm (non sink conditions). At fixed time intervals, samples were withdrawn with a syringe filter (pore size 0.45 μm) and spectrometrically assayed (Perkin Elmer Model 552S) for drug content according to a second derivative ultraviolet absorption method [21]. A correction was calculated for the cumulative dilution caused by replacement of the sample with an equal volume of original medium. Each test was repeated four times (coefficient of variation (CV) $< 1.5\%$). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [23].

2.8. Protocol for in vivo experiments

Adult male Swiss–Webster mice (Janvier Laboratories), weighing 18–20 g at the time of experiments, were used. The animals were housed in air-conditioned rooms and allowed food and water ad libitum. The analgesic effect of NAP, alone or in combinations with CS or PVP, was tested by evaluating the drug's ability to inhibit the acetic acid-induced writhing response [24], a technique widely used for the study of analgesic drugs. The experiments were carried out under approval of the local ethics committee and the protocol followed complied with the European Community Guidelines. The mice were randomly divided into ten groups of nine animals; each group was administered p.o. by gavage with an aqueous suspension of each tested compound, at a dose of 10, 20 or 45 mg as NAP equivalent/kg, or with pure water (control group). Afterwards, the mice were put in individual cages and, 60 min after drug administration, 10 μl/g of a 0.6% acetic acid solution was injected intraperitoneally to each one.

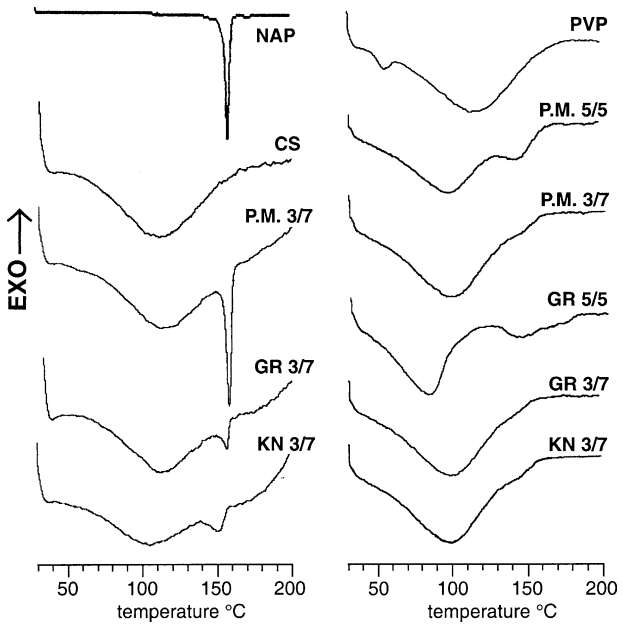

Fig. 1. DSC curves of pure naproxen (NAP), chitosan (CS), PVP, and of some 5/5 and 3/7 (w/w) drug–carrier physical mixtures (P.M.), coground (GR) and kneaded (KN) products.

The induced writhings were then counted for 15 min after acetic acid injection. A mouse was considered to be affected by the treatment with the drug when the number of writhings was less than the value of the mean minus one standard deviation of the control group. Student's *t*-test (Minitab Release 10xtra statistical software) was used to evaluate the significance of the observed differences.

3. Results and discussion

3.1. Solid state studies

The thermal curves of pure components and of some selected drug–carrier physical, kneaded and coground mixtures are shown in Fig. 1. A sharp endothermal effect (T_{peak} 156.7 ± 0.3 °C, fusion enthalpy 140 ± 6 J g^{-1}, four runs) indicated the crystalline anhydrous state of NAP. In contrast, the large endotherms over the 70–130 °C temperature range, associated with water loss, shown by both the examined carriers were typical of amorphous hydrated substances. The comparison of the thermal behavior of NAP–CS and NAP–PVP systems evinced the presence of more intense solid-state interactions between NAP with PVP than with CS. In fact, the fusion endotherm of NAP strongly broadened, shifted to lower values and reduced in intensity in its 5/5 (w/w) combinations with PVP, including simple physical mixture, until fully disappearing in the 3/7 mixtures, revealing total drug amorphization. This phenomenon was clearly less marked in systems with CS, where the decrease in drug fusion enthalpy, directly related to the increase in NAP amorphicity, occurred only for combinations with large carrier contents and as a consequence of the mechanical treatment of the sample.

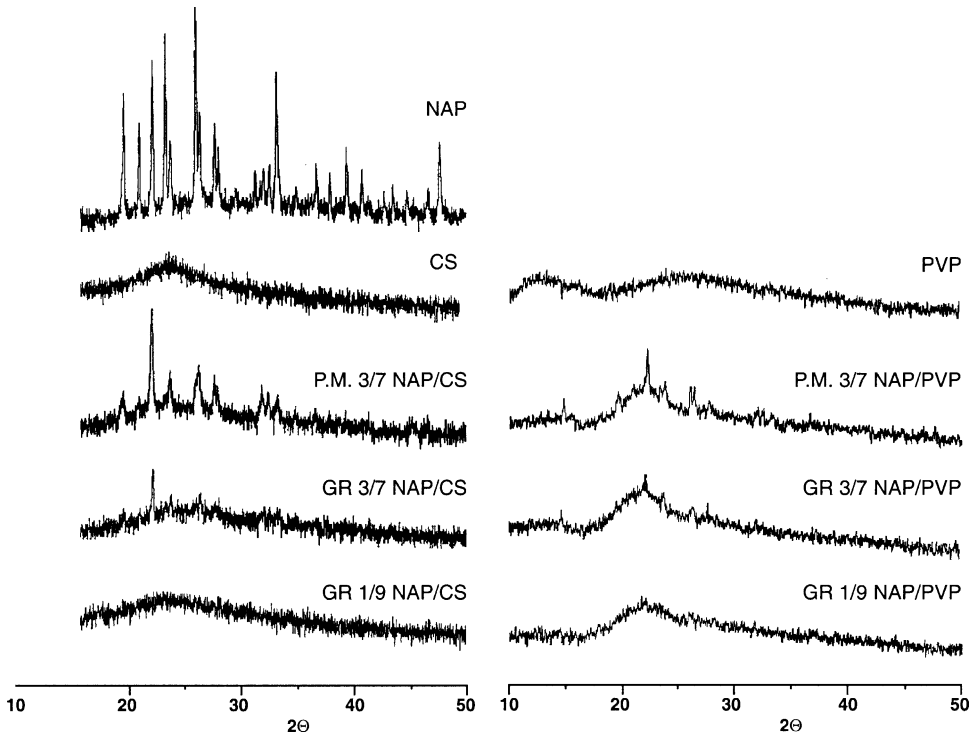

Fig. 2. X-ray powder diffraction patterns of pure naproxen (NAP), chitosan (CS), PVP, and 3/7 or 1/9 (w/w) drug–carrier physical (P.M.) and coground (GR) mixtures.

The greater amorphizing power of PVP towards the drug was confirmed also from the results of X-ray powder diffraction analysis (Fig. 2). In fact, the drug crystallinity peaks were still evident in its physical mixtures with CS, whereas the simple blending with PVP caused a strong decrease of NAP crystallinity, probably as a consequence of a loosening of crystal forces of NAP finely dispersed within the amorphous PVP [25]. However, some characteristic peaks, indicative of the presence of residual NAP crystals, were detectable in the 3/7 (w/w) physical mixture, in contrast with the results of DSC analysis which indicated total loss of drug crystallinity in this system (see Fig. 1).

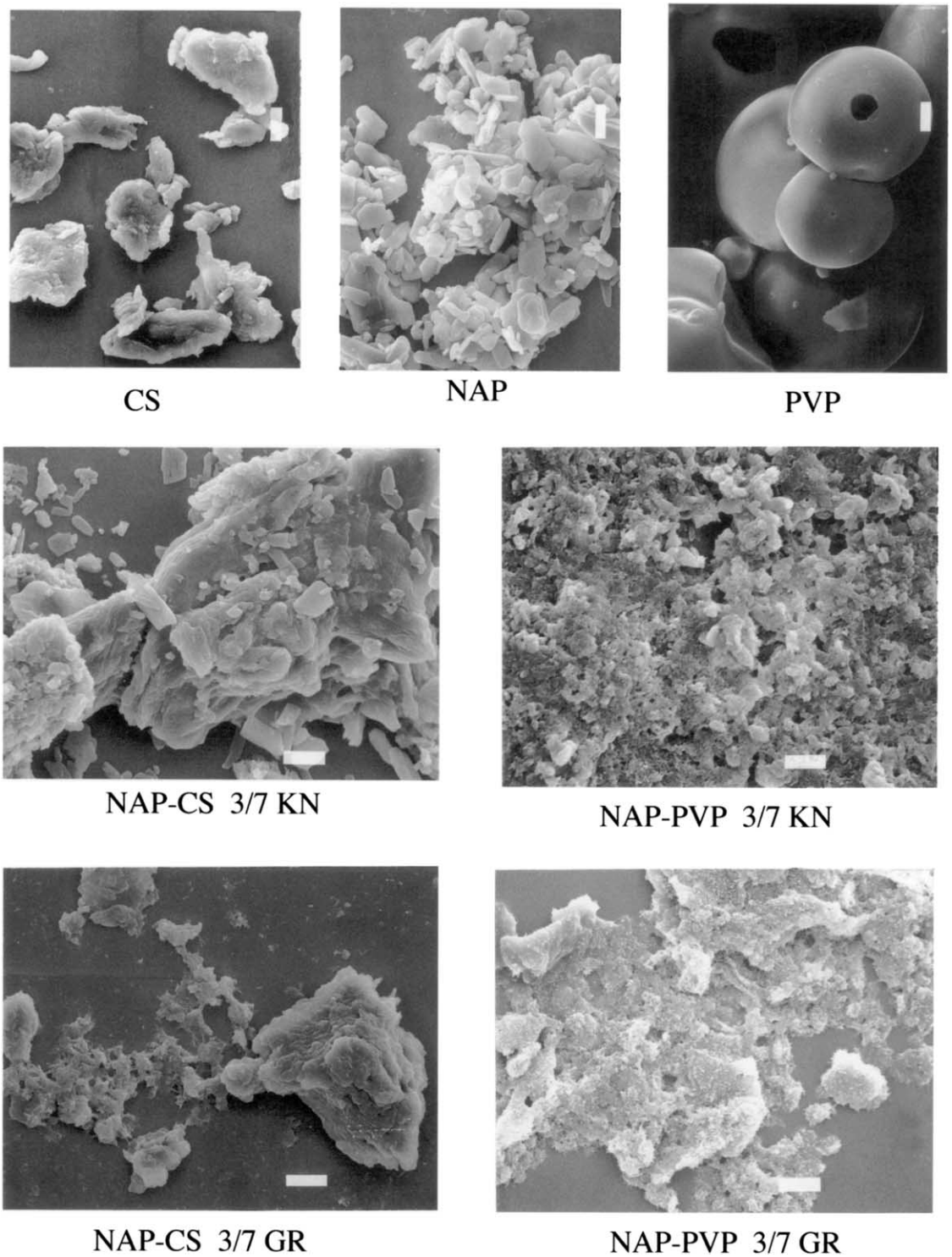

Fig. 3. SEM micrographs of pure naproxen (NAP), chitosan (CS), PVP and 3/7 (w/w) drug–carrier kneaded (KN) and coground (GR) products. The 10 μm calibration bars are shown.

Evidently, the thermal energy supplied during the DSC scan was responsible for complete amorphization of NAP, which was brought to a highly dispersed (but not totally amorphous) state by simple physical mixing. According to the DSC findings, the loss of NAP crystallinity became more evident at increasing carrier contents and as a consequence of mechanical treatment of the sample, owing to the more intimate contact between the components, as well as the finer dispersion of the drug into the amorphous matrix of the polymer.

The morphological features of the NAP–CS and NAP–PVP systems prepared by the different methods were investigated by means of SEM analysis (Fig. 3). NAP particles appeared as small plate-like crystals (5–10 μm) with smooth surfaces of homogeneous morphology. CS consisted of amorphous particles of rather irregular size and shape with a rough surface, whereas PVP was seen as typical amorphous spherical particles. NAP–carrier combinations showed a progressive reduction of drug crystallinity when passing from the physical mixture to the kneaded and even more to the coground systems. Crystals of drug mixed with CS particles were clearly evident in the 3/7 (w/w) drug–polymer physical mixture. The corresponding kneaded system appeared as a substantially amorphous product where only some small NAP crystals finely dispersed or adhered on the surface of the larger CS particles were still detectable. Both drug amorphization degree and particle size reduction, produced by the shear and impact stresses during the high-energy cogrinding treatment, became more marked in the coground product. Morphological changes were much more pronounced for NAP–PVP combinations, where the original appearance of drug and carrier disappeared in both kneaded and coground products, making it no longer possible to differentiate the two components.

Drug–polymer solid state interaction was further investigated through FT-IR spectroscopy. Some representative FT-IR spectra of NAP–CS and NAP–PVP combinations in the C═O stretching region of NAP (1800–1600 cm^{-1}) are shown in Fig. 4. Spectra of the physical mixtures were the weighted average of those of the single components. No appreciable modifications in the characteristic quartet of NAP frequency bands was observed by comparing the spectra of the physical mixtures with CS with those of corresponding kneaded and coground systems. On the contrary a reduction of intensity together with a shift towards lower frequencies for the NAP carbonyl band was observed in coground systems with PVP, attributable to a variation in the hydrogen bond pattern due to a NAP–PVP interaction [26].

3.2. Dissolution studies

The results of dissolution studies are presented in Fig. 5 and summarized in Table 1 in terms of dissolution efficiency after 60 min (DE_{60}), percent dissolved after 10 min (PD_{10})

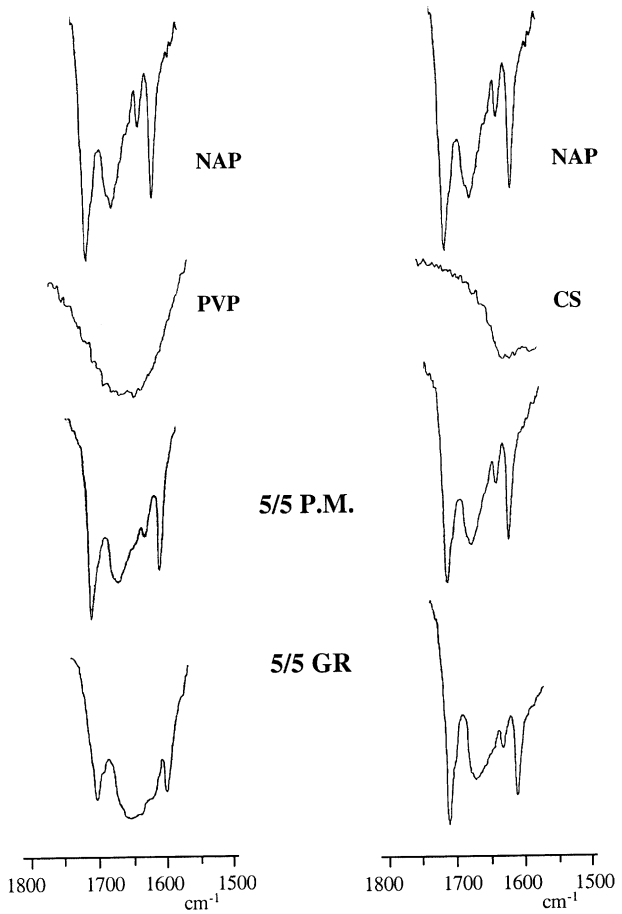

Fig. 4. FT-IR spectra of pure naproxen (NAP), chitosan (CS), PVP and 5/5 (w/w) drug–carrier physical (P.M.) and coground (GR) mixtures.

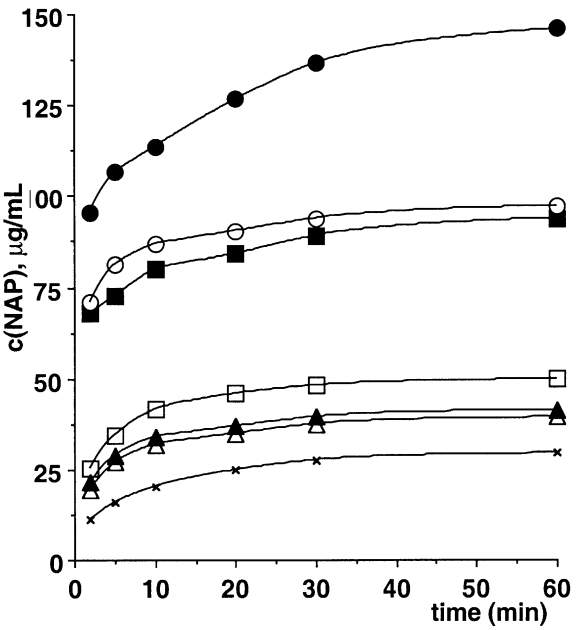

Fig. 5. Dissolution curves of naproxen (NAP) alone (×) and from 3/7 (w/w) physical mixtures (▲,△), kneaded (■,□) and coground (●,○) products with chitosan (black symbols) or PVP (white symbols).

Table 1
Dissolution efficiency at 60 min (DE_{60}), percent drug dissolved at 10 min (PD_{10}) and relative dissolution rate (rdr) at 5 min

Polymer	NAP/polymer w/w ratio	Preparation technique	DE_{60}	PD_{10}	rdr
–	10:0	–	6.2	5.0	–
CS	5:5	Mixing	8.9	8.7	1.6
PVP	5:5	Mixing	8.0	7.3	1.5
CS	5:5	Cogrinding	19.3	18.2	3.6
PVP	5:5	Cogrinding	13.8	13.5	3.2
CS	5:5	Kneading	15.7	15.0	3.4
PVP	5:5	Kneading	10.0	9.3	2.0
CS	3:7	Mixing	9.2	8.5	1.8
PVP	3:7	Mixing	8.7	8.0	1.7
CS	3:7	Cogrinding	30.2	28.4	6.7
PVP	3:7	Cogrinding	22.5	21.7	5.1
CS	3:7	Kneading	21.3	20.0	4.6
PVP	3:7	Kneading	11.2	10.4	2.2

and relative dissolution rate in comparison with the pure drug. As can be seen, both polymers were effective in enhancing the drug dissolution performance, and their efficacy depended on both their content in the mixture and the system preparation method, cogrinding being the best technique. In particular, the 3/7 (w/w) coground products with PVP and CS allowed, respectively, an improvement of drug dissolution rate after 5 min of about 5- and 7-fold, with a 4.8- and 3.6-fold increase in dissolution efficiency. Particle size reduction, improved wettability and loss of crystallinity occurring during the mechanical treatment are considered the principal factors responsible for the enhanced dissolution behavior [27]. However, even though amorphous drug would be expected to dissolve faster than crystalline material, due to its 'high energy state', the effectiveness of the carrier was not directly related to its amorphizing power towards the drug. In fact, PVP was always less effective than CS in promoting NAP dissolution properties, independent of the solid system preparation method, in spite of its better amorphizing properties, as revealed by solid state analyses. Moreover, the higher efficacy of CS cannot be attributed to an initial better wettability of the NAP–CS systems, since it concerned not only the initial drug dissolution rate but also the final dissolution efficiency. Therefore, a specific solubilizing effect of CS, due to formation of soluble drug–carrier complexes, can be reasonably hypothesized. The presence of electrostatic interactions favoring and stabilizing complexation can be supposed, due to the anionic nature of the drug and the strong positive charge of this polymer at pHs of < 6.5 [4].

3.3. In vivo experiments

Drug–carrier coground products (3/7 (w/w)) were selected for in vivo experiments in mice. The results of the writhing test (Fig. 6) demonstrated that both carriers significantly potentiated the analgesic effect of NAP. In fact

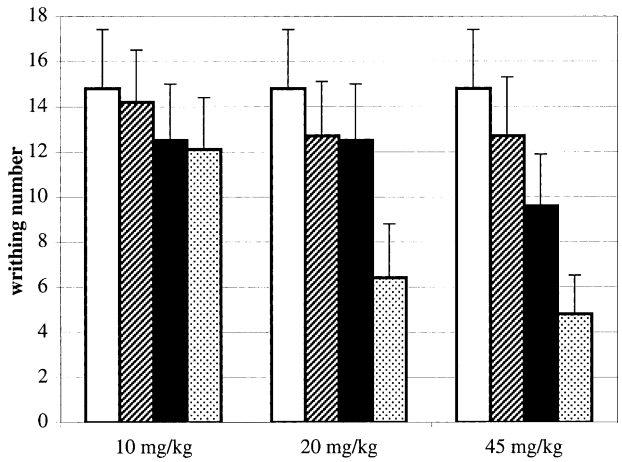

Fig. 6. Reduction of the number of acetic-acid induced writhings in mice after a single oral treatment with 10, 20 or 45 mg/kg of naproxen, alone (oblique shading) or as coground with PVP (black) or CS (stippled) in comparison with the untreated control group (white).

all the doses of NAP, when administered alone, including the highest tested dose (45 mg/kg), were statistically ineffective ($P \geq 0.1$) in reducing the number of writhes, as compared to the control group. Such results were in agreement with the findings of Price et al. [28], who indicated 60 mg/kg as the minimum effective NAP dose to produce analgesic effect. In contrast, administration of the drug as coground product with PVP or CS at a dose of 45 mg/kg, resulted, respectively, in a 25% ($P < 0.05$) and 60% ($P < 0.0001$) reduction of the mean number of writhes in comparison to pure drug at the same dose. Moreover, NAP–CS coground system was efficacious also at the lower drug dose of 20 mg/kg, allowing a 50% ($P = 0.0001$) and 30% ($P < 0.05$) reduction of the mean number of writhes in comparison, respectively, to NAP alone and its coground product with PVP, both at a drug dose of 45 mg/kg.

4. Conclusions

Both polymers favorably affected the NAP dissolution properties. Their effectiveness was influenced by the binary system preparation method and increased with increasing the polymer content but it was not directly related to the drug amorphization process. In fact, CS was more effective than PVP, despite the greater amorphizing power of the latter. The best results were given by the 3/7 (w/w) drug–carrier coground products which allowed a 390 and 260% improvement of the drug dissolution efficiency (DE_{60}) for NAP combinations with CS and PVP, respectively. In vivo experiments demonstrated a significant improvement of NAP analgesic activity when administered as coground product with PVP or CS, allowing a reduction of the dose required to obtain analgesic effect, with a consequent reduction of the incidence of undesired adverse effects. Also in this case CS was more effective than PVP; however, the different performance shown by the two carriers was even

more marked than that observed in dissolution studies. In fact, the 3/7(w/w) NAP–CS coground product demonstrated an antiwrithing potency approximately 2.4 times higher than the corresponding product with PVP, the dose being equal, whereas its solubilizing power was only 1.4 times higher. Thus, the greater efficacy of CS in promoting drug analgesic activity suggested a specific absorption enhancer effect of this polymer, probably due to its excellent bioadhesive properties [1,2], in addition to its higher drug solubilizing effect.

Therefore, from these studies, chitosan appears to be an excipient of choice for the development of a fast-release solid dosage form for oral NAP administration, allowing also a reduction of drug dose necessary to obtain the analgesic effect. Moreover, the possibility of preparing tablets by direct compression, due to the suitable binder, anti-adherent and disintegrant characteristics of chitosan, together with its antiulcer and antiacid properties, which further reduce the most common side effects given by non-steroidal anti-inflammatory drugs, make the use of this polymer particularly attractive. Furthermore, the ease of scale-up and industrial applications of the cogrinding technique, which does not require the addition of solvents, should be taken into account.

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