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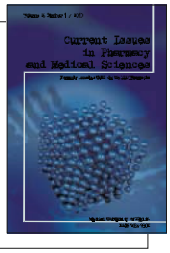

Influence of the dissolution medium type on the release of diclofenac sodium and papaverine hydrochloride from granules and tablets

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ABSTRACT

The release studies of diclofenac sodium (DIC) and papaverine hydrochloride (PAP) from composed granules and tablets into the dissolution media at different pH using the flow-through cell apparatus were carried out. The solubilities of these active substances vary and depend on the pH of a dissolution medium which confirmed the outcomes of the release studies on granules and tablets containing only one substance DIC or PAP. The most effective dissolution medium for the carried out release study of DIC and PAP from composed solid dosage form as granules or tablets was citrate buffer at pH 6.5.

Keywords: Diclofenac sodium, papaverine hydrochloride, release study, dissolution media

INTRODUCTION

Diclofenac sodium {sodium 2-[(2,6-dichlorophenyl)amino]phenyl-acetate} is a potent non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic and antipyretic properties [13,18,19,20]. For improvement of the therapeutic effect and decrease the adverse effects of diclofenac sodium, the composed pharmaceutical preparations containing misoprostol, lidocaine hydrochloride, escin, tribenosine and gentamicin sulphate were produced [18,19]. For increased analgesic effect, the granules and tablets designed for oral administration and containing diclofenac sodium and papaverine hydrochloride in one preparation were manufactured and patented [6,8]. However, choosing the dissolution medium for testing in the release study on these preparations was a problem, because the solubilities of these active substances vary [10,13,14, 23,26]. In vitro studies, such as the release study, can be used to predict in vivo release profiles and indicate the expected in vivo behaviour [23].

The solubility of diclofenac sodium depends on pH, ionic strength and composition of the aqueous medium [10]. A salt of a weak acid, diclofenac sodium is almost insoluble in acidic pH of the stomach [3,10, 23,29], sparingly soluble in water [13], and soluble in phosphate buffer at pH 6.8 [4,10,16]. Those properties are confirmed by tests on the release of diclofenac sodium in the aqueous media with various ionic strengths, ionic compositions and pH in the range of 1-10 [10,29]. The solubility of papaverine hydrochloride depends on the pH of the medium and increases proportionally to the decrease of the pH of the medium in the range from 2.2 to 3.9 [14,26].

For the release studies Polish Pharmacopeia IX [20] recommended various dissolution media such as hydrochloric acid at pH 1 or with the addition of sodium chloride at pH 1.2 and 1.5, phosphate and acetate buffers at pH 4.5, 5.5, 5.8, phosphate buffers at pH 6.8, 7.2, 7.5 and artificial gastric and intestine juices.

In literature, there are reports describing the release studies of diclofenac sodium from different solid dosage forms carried out in various dissolution media, for example from tablets of prolonged release in an artificial gastric juice without pepsine at pH 1.2, phosphate buffer at pH 4.5 and 8, water, an artificial intestine juice without pancreatine at pH 6.8 [1,2], from coated tablets in water and phosphate buffer at pH 6.8 [12], from polymeric matrix to media at pH from the range of 1 to 6.8 [24] or 1 to 10 [10], in phosphate buffer at pH 6.5 with addition of 0.2% polysorbate [11], 0.1 mol/l HCl and phosphate buffer at pH 7.5 [25] at pH 6.8 [16], at pH 7.4 [22], at pH 5.4 and at pH 7.4

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[21], from polymeric beads crosslinked glutaraldehyde in media at pH 1.2; 6.8; 7.4 [27], nanoparticles based on Eudragit L-100 i L-100-PLGA in phosphate buffer at pH 6.8 [4].

The US Pharmacopoeia [28] recommended water as a dissolution medium for the release study of papaverine hydrochloride in tablets. Although there are reports describing this case, for the release studies of papaverine hydrochloride in matrix tablets phosphate buffer at pH 6.8 [5] or water [15] as dissolution media were used.

There is no solid dosage form containing diclofenac sodium and papaverine hydrochloride in one preparation for oral administration, therefore there are no data on the release study of these two active substances from a composed preparation. The aim of this study was to choose the best dissolution medium which would be let us carry out the release studies of diclofenac sodium and papaverine hydrochloride from composed dosage forms such as granules and tablets.

MATERIALS AND METHODS

Substances and reagents. Diclofenac sodium (DIC) produced by Caesar and Loretz, GmbH, Hilden, Germany, papaverine hydrochloride (PAP) obtained from Galfarm PPH, Cefarm Lublin, Poland, the solution of HCL (1 mol/L), citric acid monohydrate, citrate sodium dihydrogen, potassium dihydrogen orthophosphate and sodium hydroxide (1 mol/L) were all purchased from POCh Gliwice, Poland. Also, distilled water was used. All other reagents were of an analytical grade.

Solid dosage forms. Composition and preparation of the granules (G) and tablets (T) containing DIC and PAP were described in the patents [6,8]. Granules containing only one substance DIC (G-DIC) or PAP only (G-PAP), were obtained in the same manner as described in the patents [6,8], but composition contained only one active substance.

Composition: One dose of granules (G) or tablets (T) consists of 50 mg DIC, 20 mg PAP and excipients to obtain 300 mg of weight. One dose of granules (G-DIC) or tablets (T-DIC) consists of 50 mg DIC and excipients to obtain 280 mg of weight. One dose of granules (G-PAP) or tablets (T-PAP) consists of 20 mg PAP and excipients to obtain 250 mg of weight. Granules and tablets have different excipients.

Preparation. Granules (G, G-DIC, G-PAP) were prepared by wet granulation process (granulator Erweka, Germany with a 1.0 mm sieve). Tablets (T, T-DIC, T-PAP) were prepared by the tabletting of granules (a tablet press machine Erweka, Germany), which were previously obtained by wet granulation process.

Physical properties of the prepared granules and tablets are in compliance with pharmacopeial requirements [20]. The content of active substances are 50 mg DIC (± 5%) and 20 mg PAP (± 5%) in one tablet at 300 mg of weight of (T) or one dose of granules (G) and 50 mg DIC (± 5%) in one tablet at 280 mg of weight of (T-DIC) or one dose of granules (T-DIC) and 20 mg PAP (± 5%) in one tablet at 250 mg of weight of (T-PAP).

Dissolution media. The dissolution media such as hydrochloric acid 0.1 mol/L, citrate buffers at pH 4.5, 6.5, 6.8 and phosphate buffers at pH 4.5, 6.5, 6.8 were used.

Release study. The release test of active substances from granules and tablets was carried out at the flow-through cell apparatus similar to pharmacopeial apparatus 4, previously used at the release test [7], equipped with the dissolution cell with the internal diameter of 2 cm and internal height of 2.5 cm made of a transparent plastic, in which there were two glass filters at pore size 15-40 μm placed on the upper and lower parts of the cell. The tablet was set horizontally on the lower glass filter in the dissolution cell. The dissolution medium was pumped at a 4.26 mL/min flow rate by the peristaltic pump (Cole Parmer, Masterflex, USA). The apparatus was maintained at 37° ± 0.5°C by water heated from the thermostat (MLW, Mechanik, Medingen, Germany). The accurately weighed tablet or one dose of the granules was placed into the dissolution cell, the dissolution medium flew at an appropriate rate and 20 mL portions of effluents were collected and filtered using Whatmann filters. Five milliliters of each effluent was instantly diluted in 10 mL of methanol. Experiments were performed for six tablets and six doses of granules.

Spectrophotometric analysis. The contents of active substances and the quantity of the released DIC and PAP in the dissolution media were determined by spectrophotometric method based on simultaneous equation method published earlier [9]. The absorbances of the solutions were measured in a spectrophotometer (Spectromom 195, Hungary).

RESULTS

As shown Fig. 1a, within 70 min, 98.18% (80% within 8 min) of DIC from (G-DIC) and 31.15% of PAP from (G-PAP) were released in water. Also, 92.02% of DIC (80% within 11.7 min) and 62.65% of PAP were released from composed granules (G).

Within 70 min, only 7.36% of DIC from single granules (G-DIC) were released in acidic medium (0.1 mol/l HCl) (Fig. 1b), but the release of PAP (80% in 6 min) from (G-PAP) amounted to 92.05%. Similarly, within 70 min, 3.86% DIC and 91 % PAP (80% after 17 min) were released from composed granules (G) .

DIC was completely released (100%) in phosphate buffer at pH 6.8 (Fig. 1c) within 70 min from single granules (G-DIC) (80% in 8 min) and from (G) the value reached 84.1% (80% in 48 min). The release of PAP from

(G-PAP) amounted to 9.75% and from (G) to 51.05% PAP.

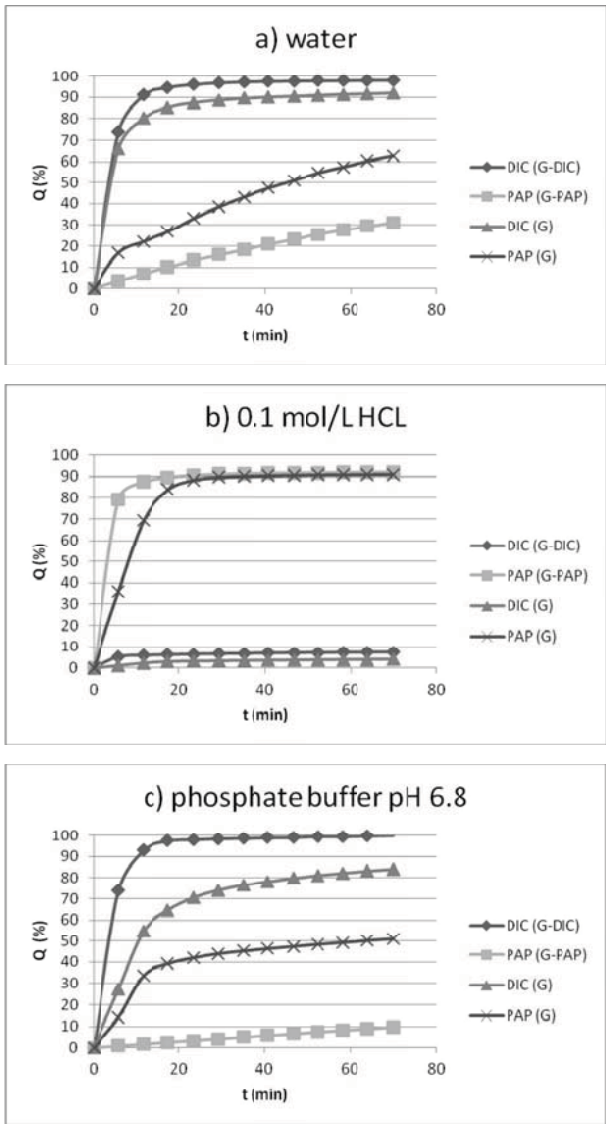
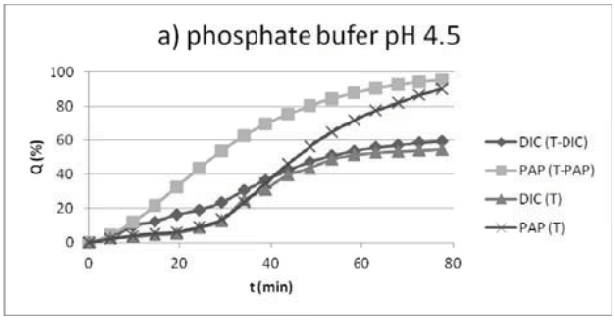


Fig. 1. Mean dissolution profiles of DIC and PAP from single and composed granules (G-DIC, G-PAP, G) at different media: a) water, b) 0.1 mol/L HCL, c) phosphate buffer pH 6.8.

As shown in Fig. 2a, within 78 min, 59.64% DIC and 95.5% PAP were released in phosphate buffer at pH 4.5 from single tablets (T-DIC; T-PAP) and from composed tablets (T) 54.66% DIC and 90.25% PAP were released.

As shown in Fig. 2b, in phosphate buffer at pH 6.5, 93.62% DIC from single tablets (T-DIC) and 53.09% PAP from (T-PAP) were released, whereas the values for composed tablets amounted to 89.64% DIC and 65.24% PAP.



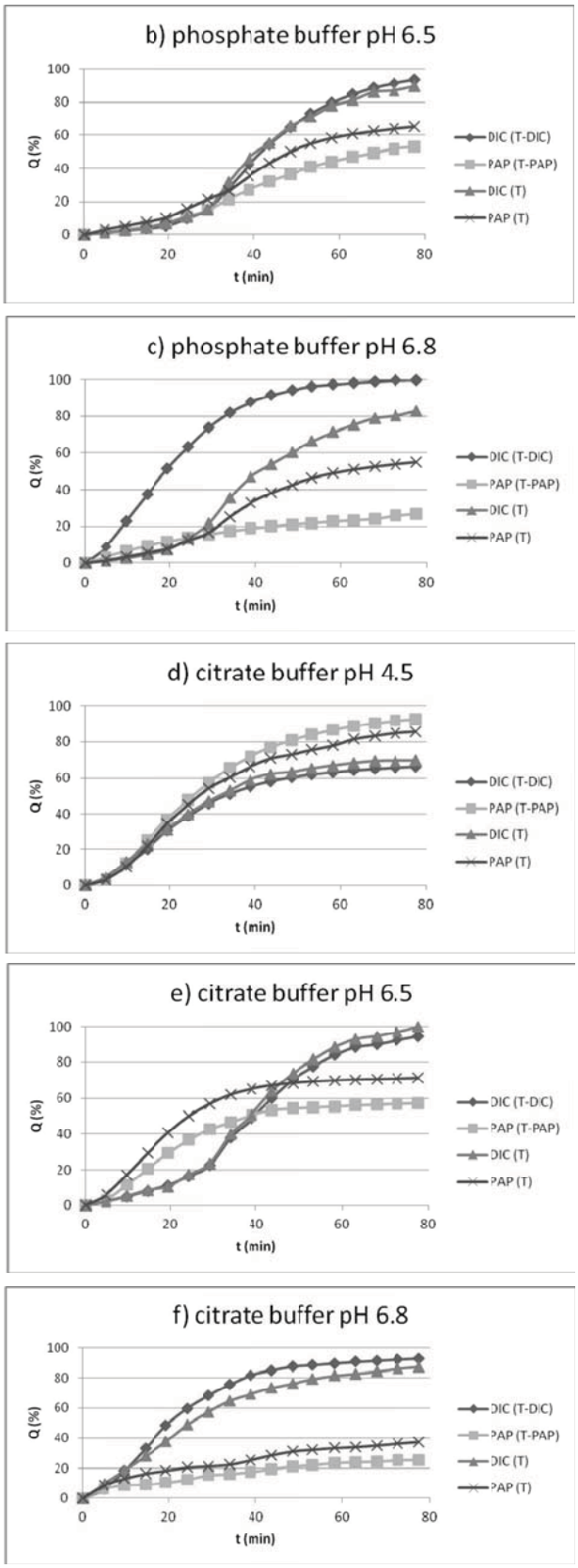


Fig. 2. Mean dissolution profiles of DIC and PAP from single and composed tablets (T-DIC, T-PAP, T) at different media: a) phosphate buffer pH 4.5, b) phosphate buffer pH 6.5, c) phosphate buffer pH 6.8, d) citrate buffer pH 4.5, e) citrate buffer pH 6.5, f) citrate buffer pH 6.8.

In phosphate buffer at pH 6.8 (Fig. 2c), 100% and 83% DIC were released from (T-DIC) and (T) whereas for (T-PAP) and (T) the values amounted to 26.7% and 55% PAP, respectively.

In citrate buffer at pH 4.5, (Fig. 2d) 66.27% and 69.7% DIC and 92.8% and 85.76% PAP were released from single and composed tablets, respectively.

With the increase of pH of citrate buffers the quantity of the released DIC and PAP were changing as follows: at pH 6.5 (Fig. 2e) 94.5% and 99.87% DIC from (T-DIC) and (T) and 65.86% and 71.32% PAP from (T-PAP) and (T); whereas at pH 6.8 (Fig. 2f) 93.1% and 87.56% DIC, and 25.4% and 37.56% PAP from single and composed tablets were released respectively.

DISCUSSION

The results of the release study of active substances from granules in the three dissolution media such as water, 0.1 mol/L HCl and phosphate buffer at pH 6.8 show that the quantity of the substances released from single granules (G-DIC, G-PAP) are different than from composed granules (G). In acidic medium within 70 min about 4% DIC from (G-DIC), 98% in water and 100% in phosphate buffer at pH 6.8 were released, what confirms that diclofenac sodium is practically insoluble in hydrochloric acid at pH 1.1, and fairly soluble in water and in phosphate buffer at pH 6.8 [10,29]. The solubility of PAP is higher when pH of dissolution medium is decreased [26], which is shown by the data of PAP quantity released to 0.1 mol/l HCl (92.05%), water (31.15%) and phosphate buffer at pH 6.8 (9.75%).

In acidic medium the presence of PAP in the composed granules (G) did not affect the improvement of the release of DIC, whereas the presence of DIC delayed PAP release for about 11 min, because 80% PAP was released after 6 min and 17 min from (G-PAP) and (G), respectively. The presence of DIC in water in (G) caused a double increase in quantity of PAP released (31.15% from G-PAP to 62.65% from G), and in phosphate buffer at pH 6.8 the presence of DIC in (G) caused the increase of PAP release over four times (9.75% from G-PAP to 51.05% from G). Taking all the outcomes into account, the impact of one of the substances on solubility of the other substance in the dissolution medium can be observed.

Bertocchi et al. [2] reported that about 30% DIC from tablets with prolonged release containing DIC in phosphate buffer at pH 4.5 was released. In an artificial gastric juice at pH 1.2 about 1% DIC and in an artificial intestine juice at pH 6.8, 80-100% DIC were released. These data confirm that solubility of DIC depends on the pH of a dissolution medium.

The release studies of DIC and PAP from single granules (G-DIC; G-PAP) confirmed that DIC is practically insoluble in hydrochloric acid 0.1 mol/L and showed that addition of PAP in composed granules (G) does not change the solubility of DIC in tested acidic medium. Nowadays water is not recommended by Polish Pharmacopea [20] to be used as a dissolution medium therefore for dissolution study of active substances from tablets phosphate and citrate buffers at different pH were used. In phosphate buffer at pH 4.5 within 78 min about 80% PAP were released while from T-PAP it took 48 min and 68 min from (T). The data show that presence of DIC in (T) caused a prolonged release time of PAP for about 20 min. In tablets (T) it could observed that the quantity of the released DIC decreased in about 5%, which was probably caused by the presence of PAP. Within 78 min more DIC both from T-DIC and from (T) (about 6% and 15%, respectively) in citrate buffer at pH 4.5 were released.

Bartolomei et al. [1] reported that the release of DIC from tablets with prolonged release depended on a dissolution medium as follows: at phosphate buffers at pH 6.8 about 70-90% in 1-2 h, at pH 4.5 about 1.5% in 1 h and 3.5% in 2 h.

The solubility of DIC in dissolution media at pH 3 and below 3 is low, but increased in media at pH 6.5 and higher [10,17].

The results from the release studies in phosphate buffer at 6.8 showed that the quantity of released PAP from composed tablets was higher for about 28% and DIC was lower for about 17% than from single tablets. Bearing in mind the slight release of PAP from single tablets (T-PAP) in phosphate buffer at pH 6.8 (26.7%), the release study in citrate buffer at pH 6.8 was carried out.

The impact of phosphate buffer on citrate buffer at pH 6.8 did not cause the increase in the quantity of released substances from T-DIC and T-PAP, but a little decrease in the release of DIC (about 5%) and a slight increase in the release of PAP (about 8%). Within 78 min, in phosphate buffer at pH 6.5, about 94% DIC and 53% PAP from single tablets and 90% DIC and 65% PAP from composed tablets were released. It showed that the presence of both substances in the solution while the release caused the decrease in the quantity of the released DIC in about 4% and increased PAP in about 12%. When the phosphate buffer was changed to citrate buffer at pH 6.5, 95% DIC and 57% PAP from T-DIC and 100% DIC and 71% PAP T-PAP and from (T) were released, respectively. It shows that the release process carried out in citrate buffer at pH 6.5 was the best and runs in parallel to time for both substances. The citrate buffer at pH 6.5 is the best dissolution medium for the carried out release study of DIC and PAP from composed solid dosage forms such as tablets.

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