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Research Paper

Effects of formulation and process variables on the release of a weakly basic drug from single unit extended release formulations

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Abstract

A new commercially available extended release matrix material, Kollidon® SR, composed of polyvinylacetate (PVA) and polyvinylpyrrolidone (PVP), was evaluated with respect to its ability to modulate the in vitro release of the weakly basic drug ZK 811 752. The effect of different formulation and process parameters on the release kinetics of ZK 811 752 from PVA/PVP based matrix tablets was investigated as a function of the (i) nature of excipient added to the drug-polymer mixtures, (ii) method of manufacturing (direct compression versus wet granulation), and (iii) effect of a post-compression curing step. ZK 811 752 containing extended release matrix tablets were successfully prepared by using Kollidon® SR. The drug release from the matrix tablets increased by the addition of excipients such as maize starch, lactose and calcium phosphate. Addition of the highly swellable maize starch and the water-soluble lactose accelerated the drug release in a more pronounced manner compared to the water-insoluble calcium phosphate. Compound release from matrix tablets prepared by wet granulation was faster compared to the drug release from tablets prepared by direct compression. Post compression curing did not influence the drug release rate from drug-lactose-Kollidon® SR formulations. Stability studies demonstrated no degradation of the drug substance and reproducible drug release patterns for matrix tablets stored at 25 °C/60% RH and 30 °C/70% RH for up to 6 months.

Keywords: Weakly basic drug; Controlled release; Polyvinylacetate/polyvinylpyrrolidone; Matrix tablets; Fumaric acid

1. Introduction

ZK 811 752, a low molecular weight (M_w 533) antagonist of the human chemokine receptor *CCR 1,* has been developed for the oral treatment of inflammatory diseases [1]. The weak base ZK 811 752 (Fig. 1) was shown to be selectively active for *CCR 1* in pharmacodynamic in vitro models. Based on pharmacodynamic models a certain constant plasma level of ZK 811 752 seems to be required in order to demonstrate efficacy of the molecule. However, due to the relatively short biological half live of ZK 811 752 in humans drug plasma levels dropped rapidly after administration of ZK 811 752. A desired constant plasma level over 24 h could not be achieved when using immediate release tablets. This led to the development of an extended release dosage form for the active agent.

With controlled release oral dosage forms, a possible pH-dependent release often results in in vivo variability and bioavailability problems [2,3]. This has been shown to be an important parameter for weak bases or salts thereof, which often demonstrate pH-dependent solubility in the pH-range of the gastrointestinal tract [4]. Based on the pK_a of these drugs, they deprotonate in the intestinal fluids, resulting in the formation of less soluble nonionized forms. Due to the low solubility of the nonionized form, slow and incomplete drug release from sustained release formulations can result [5].

Several attempts to overcome the problem of pH-dependent solubility of weakly basic drugs have been published [6–9]. Most approaches for pH-independent drug delivery of weakly basic drugs are based on the presence of acidic excipients such as organic acids within the drug formulation [10,11]. These organic acids keep the pH within

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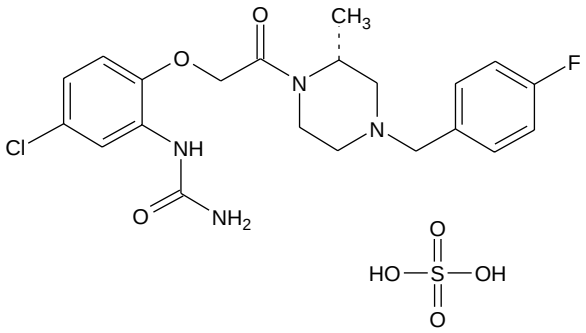

Fig. 1. Structure of ZK 811 752.

the drug formulation in the intestinal pH-range low and thus the solubility of the drug high.

Similar observations have been made for the weakly basic drug ZK 811 752 [12]. The drug release from conventional matrix tablets decreased with increasing pH-values of the dissolution medium. The problem of the pH-dependent drug release was solved by the addition of different organic acids such as fumaric, tartaric, adipic, and glutaric acid to the drug-polymer system. Ethylcellulose, hydroxypropyl methylcellulose, and PVA/PVP were used as matrix former.

The objective of this study was to further investigate the use of PVA/PVP in order to prepare ZK 811 752 extended release matrix tablets that demonstrate pH-independent drug release. Matrix tablets are based on drug substance, matrix former, and fumaric acid. The directly compressible physical mixture of eight parts of PVA and two parts of PVP [13] was chosen as matrix former due to its high compressibility and excellent flow properties. This excipient has been demonstrated to effectively retard the release of highly water-soluble drugs such as propranolol hydrochloride or diphenhydramine hydrochloride [14,15]. In a first series of experiments, several formulation parameters were evaluated in order to establish an extended release dosage form with a desired in vitro release profile of 50–60% drug release within 6 h. In a second series, different process parameters were evaluated to establish a reproducible tabletting process.

2. Experimental section

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: ZK 811 752 (3-(5-chloro-2-{2-[(2R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)uronium hydrogen sulfate, Schering AG, Berlin, Germany), PVA/PVP (Kollidon SR®; BASF AG, Ludwigshafen, Germany), lactose (α-lactose monohydrate, Meggle GmbH, Wasserburg, Germany), calcium phosphate (Fluka, Buchs, Switzerland), hydroxypropyl methylcellulose type E5 (HPMC; Methocel E5, Colorcon, Nordmann Rassmann GmbH & Co., Hamburg, Germany), maize starch, hydroxypropyl-ß-cyclodextrine (HP-ß-CD; Roquette Services Techniques Laboratories, Lestrem, France), colloidal silicon dioxide, ferric oxide pigment, magnesium stearate, talcum, titanium dioxide (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany), acetonitrile, adipic acid, ammonium dihydrogen phosphate, fumaric acid, potassium dihydrogen phosphate, sodium hydroxide, and triethylamine (Merck KGaA, Darmstadt, Germany). All chemicals were reagent grade or higher.

2.2. Methods

2.2.1. Tablet preparation

Matrix tablets containing 1.5% (w/w, based on the core tablet) magnesium stearate as lubricant were prepared by direct compression if not otherwise mentioned. The respective powders (drug, polymer, and additives, for compositions see Table 1) were passed through a 0.8 mm sieve (Haver and Böcker, Celle, Germany) and blended with a turbula mixer (W. A. Bachofen AG, Basel, Switzerland). The tablets were prepared by using a single punch tabletting machine (EK 0, Korsch, Berlin, Germany) equipped with 9.0 mm punches. The tablet weight was kept constant at 300 mg and the hardness of the matrix tablets was kept constant at 100 N if not otherwise mentioned (Schleuniger hardness tester 6 D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For curing experiments matrix tablets were stored in an oven (Venticell 222, Medcenter Einrichtungen,

Table 1
Compositions of the investigated tablets (all quantities given in mg).

Formulation No.	PVA/PVP	Maize starch	Calcium phosphate	Lactose	ZK 811 752	Fumaric acid	Magnesium stearate
1	75	–	–	73.5	100	50	1.5
2	75	73.5	–	–	100	50	1.5
3	75	–	73.5	–	100	50	1.5
4	75	–	–	74	100	50	1
5	75	–	–	73.75	100	50	1.25
6	75	–	–	73.25	100	50	1.75
7	75	–	–	73	100	50	2

Gräfeling, Germany) at 60 °C for 8, 24 or 48 h. For wet granulation the blend (Table 1, formulation No. 1) was granulated in a planetary mixer (MTI, MTI-Mischtechnik Industrieanlagen GmbH, Lage, Germany) by using distilled water.

2.2.2. Coating of the matrix tablets

Matrix tablets (Table 1, formulation No. 1) were coated with 1.12% (w/w, based on the core tablet) hydroxypropyl methylcellulose in a pan coater (Glatt GPC 300, Glatt Maschinen u. Apparatebau AG, Pratteln, Switzerland). Talcum (0.22%) was added as anti-tacking agent, titanium dioxide (0.87%) and ferric oxide pigment (0.004%) were used as coloring agents (% w/w, based on the core tablet). Coating conditions were: batch size = 1000 g, inlet temperature = 60 °C, air flow = 120 m^3/h, nozzle diameter = 0.8 mm, spray pressure = 1.6 bar, and spray rate = 6.5 g/min.

2.2.3. Stability investigations

Matrix tablets were packaged in glass bottles covered with a pierced aluminum sheet. Stability studies were conducted according to the ICH guidelines at 25 °C/60% RH, 30 °C/70% RH and 40 °C/75% RH. Samples were evaluated for drug content and dissolution after storage for three and six months ($n = 6$).

2.2.4. Drug release studies

In vitro drug release was determined using the USP XXVI rotating paddle method (1000 ml 0.1 N HCl or Pharm. Eur. acetate buffer pH 4.5 or USP phosphate buffer pH 6.8; 37 °C; 50 rpm; $n = 6$) (Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, USA). At predetermined time intervals, 10 ml samples were withdrawn (not replaced), filtered and assayed. The amount of ZK 811 752 released was measured with a computer connected Waters-HPLC system (600 E Controller, 600 F pump, 717 plus Autosampler, 2487 Dual Absorbance Detector, Waters Corp., Milford, USA). A 10 µl volume was injected onto a Symmetry C 18 column (Knauer GmbH, Berlin, Germany) using as the mobile phase a mixture of 55 ml 0.05 M triethylammoniumacetate buffer and 45 ml acetonitrile; flow rate: 1.0 ml/min; UV-detection at 244 nm. ZK 811 752 solutions of known concentration were used to calculate the amount of drug released. The ZK 811 752 was stable in the release medium at 37 °C for at least 48 h as indicated with the stability sensitive HPLC method.

2.2.5. Solubility of the drug

Excess amount of ZK 811 752 was placed in contact with 0.1 N HCl, acetate buffer pH 4.5 (Pharm. Eur.) and phosphate buffer pH 6.8 (USP XXVI), respectively, in order to determine its solubility. The samples were shaken for 48 h at 37 °C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). The supernatant was filtered through a 0.2 µm filter; 0.5 ml of the filtrate were immediately diluted with the appropriate dissolution medium and assayed by HPLC as described above. All experiments were conducted in triplicate.

3. Results and discussion

A significant difference in the resulting release of ZK 811 752 from PVA/PVP matrix tablets was observed in 0.1 N HCl when compared to the drug release in buffer medium pH 4.5 and 6.8 [12]. The rank order of drug release rate 0.1 N HCl > pH 4.5 > pH 6.8 can be explained with the solubility of ZK 811 752 within the different dissolution media: 3.24 mg/ml in 0.1 N HCl, 0.24 mg/ml at pH 4.5 and 0.01 mg/ml at pH 6.8. To adjust the release profile of the weakly basic drug ZK 811 752 to that in 0.1 N HCl fumaric acid was added to the matrix tablets (Table 1, formulation No. 1). Independent of the pH of the dissolution medium the pH inside the tablet matrix is expected to be acidic and thus the solubility of the weakly basic drug to be high. Therefore, drug release is shown to be pH-independent (Fig. 2). In order to obtain sink conditions and primarily control the drug release by the dosage form 5% HP-ß-CD were added to the release media at pH 4.5 and 6.8 (solubility of ZK 811 752 at pH 4.5 and 6.8 after addition of 5% HP-ß-CD: 8.00 and 2.40 mg/ml, respectively). Detailed investigations on the addition of HP-ß-CD to the release media and the influence of different organic acids on the drug release of ZK 811 752 from matrix tablets are given elsewhere [12]. The aim of this study was to further investigate several formulation and process variables on the in vitro release of matrix tablets containing ZK 811 752 and fumaric acid. According to pharmacokinetic modeling the desired in vitro release profile should demonstrate approximately 50–60% drug release after 6 h.

The influence of the nature of excipients on the release of ZK 811 752 from matrix tablets (Table 1, formulations No. 1, 2 and 3) was investigated in phosphate buffer pH 6.8

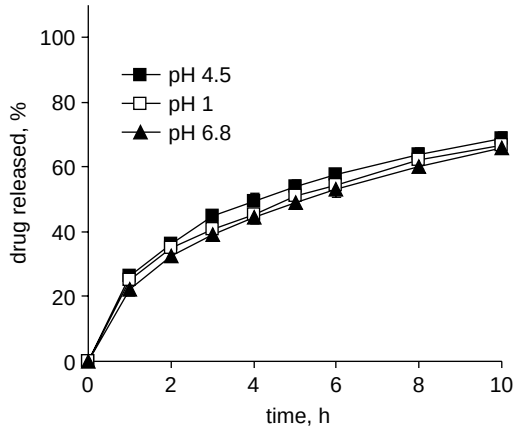

Fig. 2. Effect of the addition of 50 mg fumaric acid on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

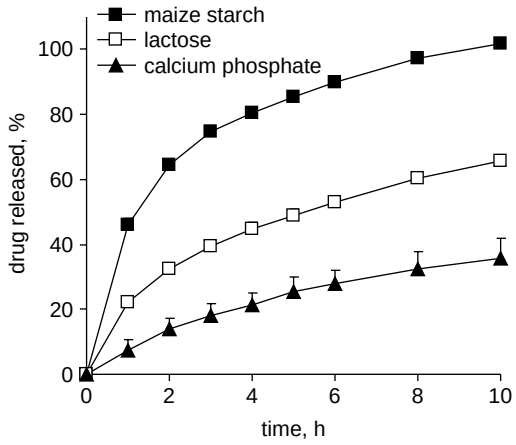

Fig. 3. Effect of the addition of different excipients on the release of ZK 811 752 from PVA/PVP matrix tablets.

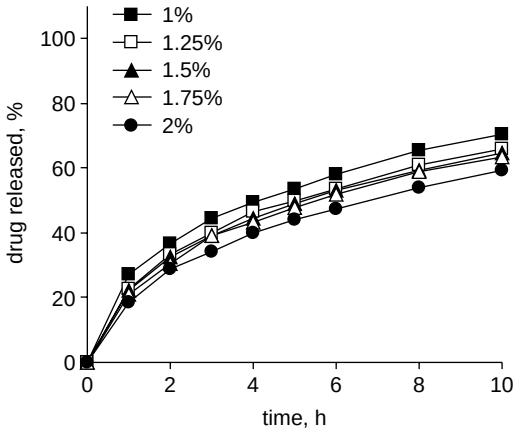

Fig. 4. Effect of different concentrations (w/w, based on total tablet weight) of magnesium stearate on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

(Fig. 3). After 6 h, almost 90% of the drug has been released from matrix tablets containing maize starch. This can be explained by the disintegrating effect of maize starch, thus leading to faster tablet disintegration. Addition of lactose led to a significant acceleration in drug release compared to calcium phosphate (after 6 h 53 versus 28% drug release). This can be attributed to the good water solubility of lactose. Upon contact with the release medium, lactose diffuses out of the device, thereby increasing the porosity of the resulting polymer network. In contrast, drug release from matrix tablets containing calcium phosphate only slightly increased due to the water insoluble nature of calcium phosphate. These findings are in good agreement to the literature [15].

In order to establish a robust tabletting process the impact of the addition of different concentrations of lubricant to the drug/polymer/lactose/fumaric acid powder mixtures was investigated. Addition of 1–2% (w/w, based on the total tablet weight) magnesium stearate (Table 1, formulations No. 1, 4, 5, 6 and 7) led to good compressibility of the mixtures. The influence of the addition of magnesium stearate on the in vitro dissolution was investigated in phosphate buffer pH 6.8 (Fig. 4). As expected the drug release decreased with increasing concentrations of magnesium stearate. After addition of 1.25–1.75% (w/w, based on the total tablet weight) magnesium stearate only slight differences in the resulting in vitro dissolution profiles were observed. However, addition of 2% magnesium stearate decreased the dissolution profile significantly. Decreasing dissolution rates of formulations containing increased concentrations of magnesium stearate can be explained with the hydrophobic nature of the magnesium stearate. With increasing magnesium stearate concentrations the wetting of the matrix tablets decreased, thus leading to decreasing in vitro drug release rates.

In order to investigate the influence of the drug particle size on the in vitro drug release ZK 811 752 was classified into different particle size fractions by sieving. These drug substance fractions were incorporated into formulations containing polymer/lactose/fumaric acid and magnesium stearate (Table 1, formulation No. 1). The in vitro drug release was investigated in phosphate buffer pH 6.8 (Fig. 5). According to the Noyes–Whitney relation:

$$\mathrm{d}M : \mathrm{d}t = AD(c_s - c_t) : h$$

where $\mathrm{d}M$:$\mathrm{d}t$ is the dissolution rate, A the specific surface area of the drug particle, D the diffusion coefficient, h the diffusion layer thickness, c_s the saturation solubility and c_t the instantaneous drug concentration it was expected that the drug release rate increases with decreasing particle size of the drug particles. However, similar in vitro release profiles were obtained when using drug substance particles in the range of 40–300 μm. Obviously for matrix tablets containing ZK 811 752 and fumaric acid, dissolution of the drug substance particles was not the limiting step for drug release during in vitro dissolution. Therefore, the impact of the specific surface area of the drug particles on dissolution is negligible. In this case diffusion of water in the tablet matrix, dissolution of the water soluble matrix components such as PVP and lactose and/or diffusion of dissolved active

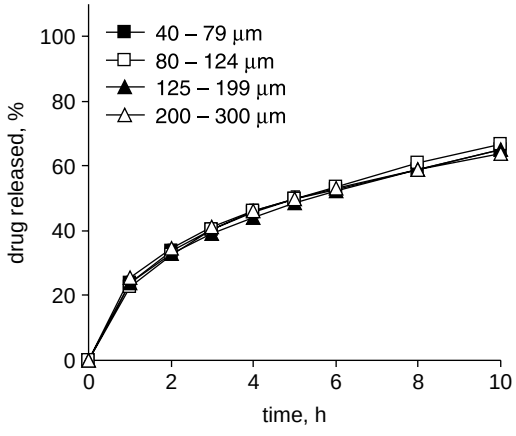

Fig. 5. Influence of the drug substance particle size on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

agent through the polymer and water filled pores into the release medium seem to be release limiting factors. Further theoretical explanation could be that smaller drug substance particles led to denser polymer matrices thus overcompensating the effect of the higher specific surface area. It has to be pointed out that particle size does not influence drug release under these acidic conditions (in the presence of fumaric acid). For matrix tablets without pH-control that are dissolved in higher pH media particle size may remarkably influence drug dissolution.

For taste masking purposes matrix tablets (Table 1, formulation No. 1) were coated with a fast dissolving hydroxypropyl methylcellulose shell. The in vitro drug release of uncoated tablets was compared with the release of coated tablets in phosphate buffer pH 6.8 (Fig. 6). After 1 h 22 versus only 15% of active compound were released from uncoated and coated tablets, respectively. No differences in the dissolution rates were observed at further time points. Different dissolution rates for uncoated and coated tablets at the first sampling point can be explained with the additional dissolution step of the taste-masking coat. Once the fast dissolving tablet shell is dissolved, no differences in dissolution rates were observed for both tablets.

Most of the research reported in the literature utilizes PVA/PVP as a directly compressible excipient for sustained release matrices [14]. The scope of this work was also to study the effect of this excipient on formulating the tablets (Table 1, formulation 1) by wet granulation technique using distilled water as granulating medium. The in vitro release profiles of tablets manufactured by direct compression or after wet granulation were investigated in phosphate buffer pH 6.8 (Fig. 7). Significant differences were observed for both release profiles. After 1 h 79 versus 22% of the active compound was released for formulations prepared by wet granulation or direct compression methods, respectively. A possible explanation could be that the water soluble PVP was deposited on the PVA particles during granulation, thus localizing as discrete granules between PVA particles. This might lead to faster tablet hydration and formation of a more

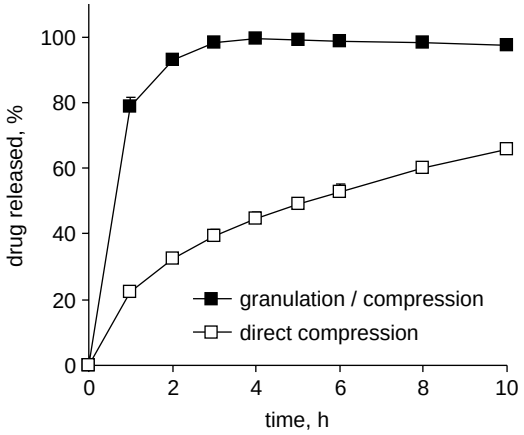

Fig. 7. Effect of the manufacturing method on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

porous matrix tablet structure. Faster hydration and dissolution of matrix tablets prepared after wet granulation was also confirmed visually. Whereas matrix tablets that were prepared by direct compression were visually intact after 24 h, tablets prepared by wet granulation method were completely dissolved after 4 h.

Further investigations on parameters such as effect of tablet hardness or tablet curing on the in vitro dissolution rate as well as stability investigations were carried out on formulations containing drug, polymer, lactose and fumaric acid which were manufactured by direct compression (Table 1, formulation No. 1). This formulation was chosen because it demonstrated the desired in vitro drug release profile of 50–60% drug release within 6 h.

In order to establish a robust tabletting process the drug release from tablets should be relatively independent of the applied compression force and thus of the hardness of the tablets. The compression force during tabletting of ZK 811 752 was varied in a range of 10–15 kN leading to a tablet hardness of 80–120 N (standard hardness: 100 N). Drug release from matrix tablets was independent of the tablet hardness within the investigated range as shown in Fig. 8.

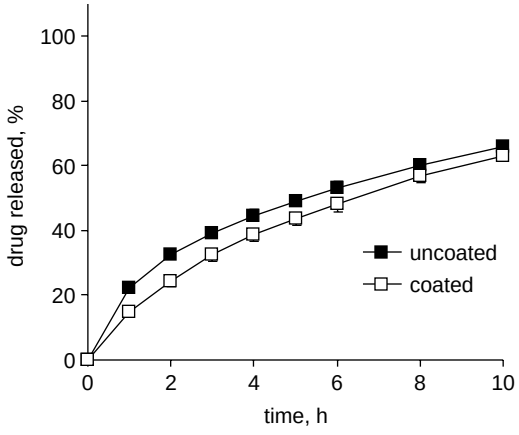

Fig. 6. Effect of a fast dissolving tablet coat (hydroxypropyl methylcellulose) on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

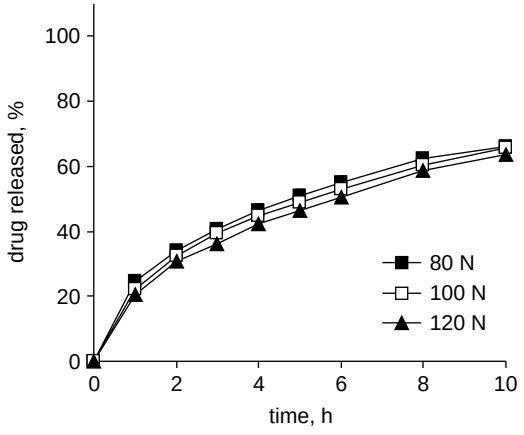

Fig. 8. Effect of the tablet hardness on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

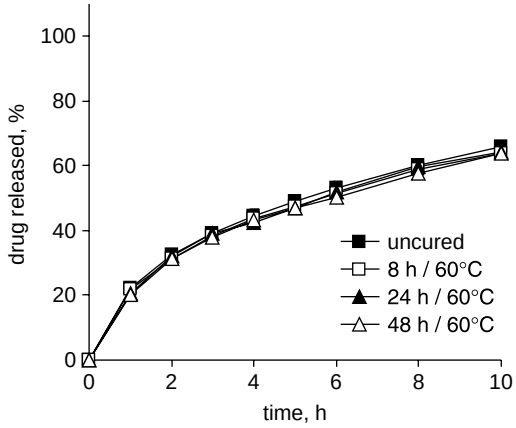

Fig. 9. Effect of post compression curing on the release of ZK 811 752 from PVA/PVP-lactose matrix tablets.

PVA/PVP is a very plastic material that produces a coherent matrix even under low compression force [14]. Therefore, it can be used as matrix former for the preparation of ZK 811 752 containing matrix tablets. However, further investigation indicated that the drug release decreased when increasing the compression force to 20 and 25 kN thus leading to a tablet hardness of 140 and 160 N, respectively (data not shown).

For diphenhydramine containing matrix tablets, post compression curing at 60 °C for 1 h decreased the initial drug release and stabilized the in vitro dissolution profile upon storage due to polymer structural relaxation [15]. However, for ZK 811 752 containing matrix tablets even storage at 60 °C for 48 h did not influence the initial in vitro dissolution (Fig. 9). Hence, post compression curing of matrix tablets containing ZK 811 752 seems not to be required to stabilize the dissolution profile. Differences between both studies might be explained by the nature of the dosage form and drug substance as well as by the level of matrix former within the dosage form.

Uncured tablets were put on stability at 25 °C/60% RH, 30 °C/70% RH and 40 °C/75% RH according to the ICH guidelines. The stability studies demonstrated no degradation of the drug substance upon storage for 6 months. Drug release in phosphate buffer pH 6.8 was investigated after 3 and 6 months (Fig. 10(A) and (B)). Drug release profiles from tablets stored at 25 °C/60% RH and 30 °C/70% RH for 6 months remained almost unchanged when compared to the initial release profiles. However, drug release from matrix tablets stored at 40 °C/75% RH decreased slightly. After 6 h initially 53% drug has been released versus only 47 and 43% drug release after storage for 3 and 6 months, respectively. Changes in the in vitro dissolution for tablets stored at 40 °C/75% RH can be explained as follows: at 40 °C/75% RH the matrix tablets were stored above the glass transition temperature (T_g) of PVA/PVP ($T_g = 35$ °C). The polymer structure changes from the glassy to the rubbery state. Before dissolution testing matrix tablets were then stored at room temperature below the glass transition temperature leading to further

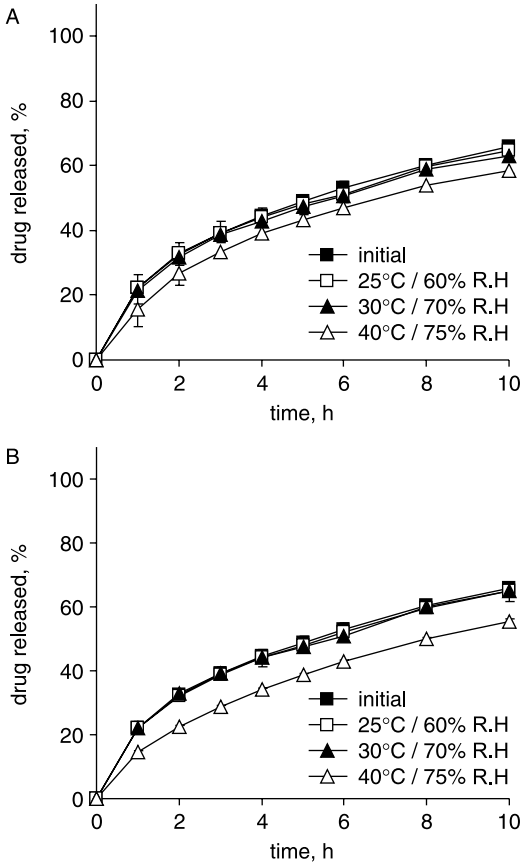

Fig. 10. Release profiles of ZK 811 752 from PVA/PVP-lactose tablets placed on stability for (A) 3 months and (B) 6 months.

hardening of the tablets. For tablets stored at 40 °C/75% RH for 3 and 6 months the tablet hardness increased from 100 to 140 N and 160 N thus being an explanation for the decreasing drug dissolution rate.

Extended release matrix tablets for ZK 811 752, a potent candidate for the oral treatment of autoimmune diseases, have been developed which provided the desired in vitro drug release profile. Various formulation parameters have been identified as potent tools to modify the resulting release patterns. The desired in vitro release profiles of 50–60% drug release after 6 h were obtained by direct compression of powder mixtures of drug substance/polymer/lactose and fumaric acid.

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