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International Journal of Pharmaceutics 299 (2005) 84–91

international  
journal of  
pharmaceutics

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## Development of a multi particulate extended release formulation for ZK 811 752, a weakly basic drug

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Received 5 December 2004; received in revised form 11 April 2005; accepted 25 April 2005

Available online 20 June 2005

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### Abstract

ZK 811 752, a potent candidate for the treatment of autoimmune diseases, demonstrated pH-dependent solubility. The resulting release from conventional mini matrix tablets decreased with increasing pH-values of the dissolution medium. The aim of this study was to overcome this problem and to achieve pH-independent drug release. Mini matrix tablets were prepared by direct compression of drug, matrix former (polyvinylacetate/polyvinylpyrrolidone; Kollidon® SR) and excipients (lactose, calcium phosphate or maize starch). To solve the problem of pH-dependent solubility fumaric acid was added to the drug–polymer excipient system. The addition of fumaric acid was found to maintain low pH-values within the mini tablets during release of ZK 811 752 in phosphate buffer pH 6.8. Thus, micro environmental conditions for the dissolution of the weakly basic drug were kept constant and drug release was demonstrated to be pH-independent. Incorporation of water-soluble (lactose) or highly swellable (maize starch) excipients accelerated drug release in a more pronounced manner compared to the water-insoluble excipient calcium phosphate. Stability studies demonstrated no degradation of the drug substance and reproducible drug release patterns for mini matrix tablets stored at 25 °C/60% RH and 30 °C/70% RH for up to 6 months.

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**Keywords:** pH-Independence; Weakly basic drug; Controlled release; Fumaric acid; Mini matrix tablets

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### 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 autoimmune diseases (Bauman et al., 1998). The weak base

ZK 811 752 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 life of ZK 811 752 in humans ( $t_{1/2} \approx 2.3$  h) drug plasma levels dropped rapidly after administration of ZK 811 752. The required constant plasma level over 24 h could not be achieved when using immediate release tablets.

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This led to the decision to develop an extended release dosage form for the molecule. According to pharmacokinetic modelling, the desired in vitro release profile should demonstrate approximately 60–70% drug release after 6 h.

With controlled release oral dosage forms, a possible pH-dependent release often results in in vivo variability and bioavailability problems (Shah, 1988; Agoram et al., 2001). This has been shown to be an important parameter for weak bases or salts thereof which often demonstrate a pH-dependent solubility in the pH-range of the gastrointestinal tract (Thoma and Ziegler, 1998). Several attempts to overcome the problem of pH-dependent solubility of weakly basic drugs have been published (Narisawa et al., 1997; Doherty and York, 1998; Espinoza et al., 2000).

A matrix composition for sustained drug delivery, which comprises an active agent, a hydrophilic polymer (e.g., HPMC) and an enteric polymer (e.g., Eudragit® L-100-55) has been patented (Oren and Seidler, 1990). In an acidic medium, the enteric polymer is insoluble and acts as a part of the matrix and thus contributes to the retardation of the drug release. At higher pH-values, e.g., intestinal fluids, the enteric polymer dissolves and thus increases the permeability of the dosage form.

pH-independent release of verapamil HCl from pellets was achieved by coating with a combination of the neutral polymer dispersion of polyvinylacetate (Kollicoat® SR) and the enteric polymer dispersion of methacrylic acid and ethyl acrylate copolymer (Kollicoat® MAE) (Kolter et al., 2002; Dashevsky et al., 2004). The two polymers were applied either as separate layers or as polymer blend. A careful balance of the ratios of the polymers allowed pH-independent drug release.

However, 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. These organic acids keep the pH within the drug formulation in the intestinal pH-range low and thus the solubility of the drug high.

Gabr (1992) demonstrated the pH-independent release of papaverine hydrochloride from matrix tablets consisting of cellulose acetate and beeswax as matrix formers in the presence of citric, tartaric and succinic acid. Streubel et al. (2000) achieved pH-independent

release of verapamil hydrochloride from matrix tablets consisting of ethylcellulose or hydroxypropyl methylcellulose (HPMC) by the addition of fumaric, sorbic or adipic acid. They demonstrated that the addition of organic acids to both matrix formers maintained low pH-values within the tablets during drug release in phosphate buffer pH 6.8 leading to pH-independent drug release.

The objective of this study was to achieve pH-independent release of ZK 811 752 from multiple unit extended release mini matrix tablets based on polymeric matrix former and organic acid. Due to its high compressibility and excellent flow properties, the directly compressible physical mixture of eight parts of polyvinylacetate and two parts of polyvinylpyrrolidone (Kollidon SR®, BASF AG, 1999) was chosen as matrix former for manufacturing of ZK 811 752 containing mini matrix tablets. This excipient has been demonstrated to effectively retard the release of highly water-soluble drugs such as propranolol hydrochloride or diphenhydramine hydrochloride (Draganoiu et al., 2001; Shao et al., 2001). In a first series of experiments, several formulation parameters were evaluated in order to establish an extended release dosage form with the desired in vitro release profile of 60–70% drug release within 6 h. In a second series, different process parameters were evaluated to establish a reproducible tabletting process.

## 2. Experimental

### 2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: ZK 811 752 (3-(5-chloro-2-{2-[2(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-2-oxoethoxy}phenyl)uronium hydrogen sulfate, Schering AG, Berlin, Germany), polyvinylacetate/polyvinylpyrrolidone (Kollidon SR®; BASF AG, Ludwigshafen, Germany), lactose ( $\alpha$ -lactose monohydrate, Meggle GmbH, Wasserburg, Germany), calcium phosphate (Fluka, Buchs, Switzerland), maize starch, hydroxypropyl- $\beta$ -cyclodextrine (HP- $\beta$ -CD; Roquette Services Techniques Laboratories, Lestrem, France), magnesium stearate, colloidal silicon dioxide (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany), acetonitrile, adipic

Table 1

Compositions of the investigated tablets (%), based on the total tablet weight)

Formulation no.	PVA/PVP	Lactose	Calcium phosphate	Maize starch	ZK 811 752	Fumaric acid
1	64.2	–	–	–	33.3	–
2	47.5	–	–	–	33.3	16.7
3	30.8	–	–	–	33.3	33.4
4	36.4	11.1	–	–	33.3	16.7
5	20.0	27.5	–	–	33.3	16.7
6	36.4	–	11.1	–	33.3	16.7
7	36.4	–	–	11.1	33.3	16.7

In addition 1% silica and 1.5% magnesium stearate.

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

Mini matrix tablets containing 1.5% (w/w) magnesium stearate as lubricant and 1% colloidal silicon dioxide as flow promoter were prepared by direct compression. 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 2.0 mm punches. The tablet weight was kept constant at 7 mg and the hardness of the mini matrix tablets was kept constant at 25 N if not otherwise mentioned (Schleuniger hardness tester 6 D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For curing experiments mini matrix tablets were stored in an oven (Venticell 222, Medcenter Einrichtungen, Gräfeling, Germany) at 60 °C for 15 h.

### 2.2.2. Stability investigations

Size no. 1 gelatin capsules, containing 300 mg of mini matrix tablets each, 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 3 and 6 months ( $n=6$ ).

### 2.2.3. Drug release studies

In vitro drug release was determined using the USP XXVI rotating basket method [1000 ml 0.1N HCl, Pharm. Eur. artificial gastric juice or USP phosphate buffer pH 6.8; 37 °C; 100 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  $\mu$ l 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.

### 2.2.4. Drug content studies

The total amount of drug within the tablets was analyzed after dissolution of the tablets in a mixture of acetonitrile/methanol/water (6 ml/1 ml/3 ml) and appropriate dilution by using the HPLC method as described above [ $n=10$ ]. The drug extracted from the tablets was intact, no degradation products were detected in the extraction solution with the stability sensitive HPLC method.

### 2.2.5. Solubility of the drug

Excess amount of ZK 811 752 was placed in contact with 0.1N HCl, artificial gastric juice (Pharm. Eur.) and

phosphate buffer pH 6.8 (USP XXVI), respectively, in order to determine its solubility in these media. The samples were shaken for 48 h at 37 °C in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). The final pH of the saturated solutions in HCl or phosphate buffer was adjusted to pH 1, 2 or 6.8, respectively. 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 polyvinylacetate/polyvinylpyrrolidone mini matrix tablets (Table 1, formulation no. 1) was observed in 0.1N HCl or artificial gastric juice when compared to the drug release in phosphate buffer pH 6.8 (Fig. 1). After 1 h, 32.1 and 28.3% drug was released in 0.1 HCl and artificial gastric juice, whereas only 2.9% drug was released in phosphate buffer pH 6.8. After 6 h, 71.0 and 65.2% of the drug was released in 0.1N HCl and artificial gastric juice versus only 14.9% in buffer medium pH 6.8. This can be explained as follows. Upon contact with the release medium, the water-soluble polyvinylpyrrolidone leaches out of the mini matrix tablets thereby creating pores for the active to diffuse out. In contrast, the compressed polyvinylacetate component maintains

the tablet core structure intact during the dissolution run. With decreasing drug solubility within the water-filled pores of the tablet the resulting drug concentration gradient and thus the driving force for the diffusion decreases. For ZK 811 752, the following solubilities were determined: 3.24 mg/ml in 0.1N HCl, 3.01 mg/ml in artificial gastric juice pH 2 and 0.01 mg/ml in phosphate buffer at pH 6.8, thus being an explanation for the rank order of drug release rate: 0.1N HCl > artificial gastric juice pH 2 > pH 6.8.

In order to maintain sink conditions during dissolution testing at higher pH-values, HP-β-CD was added to phosphate buffer pH 6.8 (solubility of ZK 811 752 in phosphate buffer after addition of 10% HP-β-CD: 5.94 mg/ml). Nevertheless, even after addition of 10% HP-β-CD to buffer medium pH 6.8, the release of ZK 811 752 was slower compared to the drug release at pH 1 (71.0% drug release versus 33.1% drug release after 6 h), but the solubility of ZK 811 752 was 1.83 times higher.

This can be explained as follows: HP-β-CD is known to increase the solubility of compounds by the formation of inclusion complexes. For the concentration gradients, being the driving forces for drug diffusion, the drug concentration within the tablet and within the release medium are important. The solubility of ZK 811 752 in the release medium was increased by the addition of HP-β-CD to buffer medium pH 6.8. However, much lower quantities of HP-β-CD can be expected within the tablets (at least at early time points), compared to bulk fluid, resulting in less pronounced increases in drug solubility. Therefore, even after addition of 10% HP-β-CD to buffer medium pH 6.8, the release of ZK 811 752 was slower compared to the drug release at pH 1.

To obtain sink conditions and primarily control the drug release by the dosage form, 5% HP-β-CD was added to the release medium at pH 6.8 at further dissolution testing (solubility of ZK 811 752 at pH 6.8 after addition of 5% HP-β-CD: 2.40 mg/ml). These in vitro dissolution conditions might not exactly reflect the in vivo conditions (in the absence of HP-β-CD). Nevertheless, it is an in vitro model to mimic the open compartment in vivo conditions, where released compound is systemically absorbed. For all the investigated formulations that were containing fumaric acid, the addition of 5% HP-β-CD to the release medium led to complete drug release within 24 h. A detailed

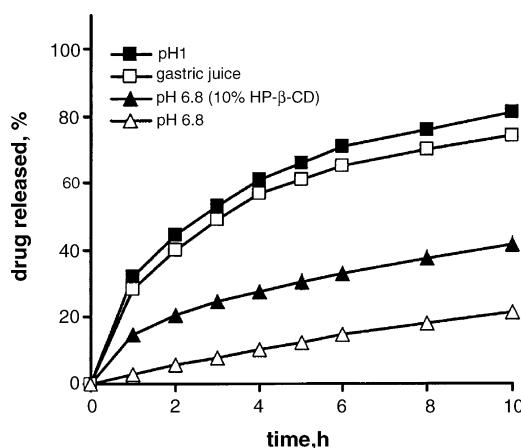


Fig. 1. pH-dependent release of ZK 811 752 from polyvinylacetate/polyvinylpyrrolidone mini matrix tablets.

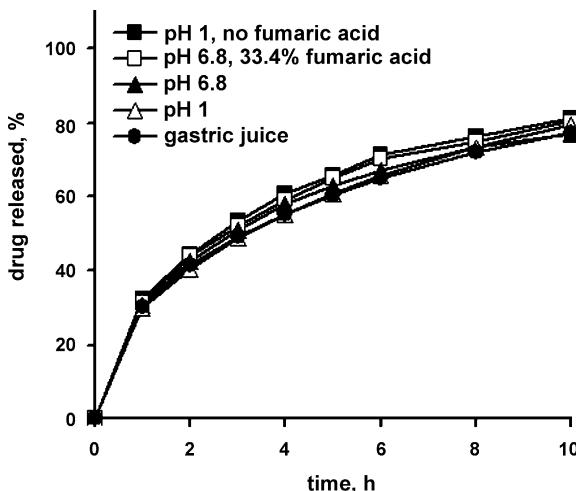


Fig. 2. Effect of the addition of fumaric acid on the release of ZK 811 752 from polyvinylacetate/polyvinylpyrrolidone mini matrix tablets containing 16.7% (w/w, based on total tablet weight) fumaric acid if not otherwise mentioned.

investigation of the in vitro/in vivo correlation was beyond the scope of the paper.

To adjust the release profile of the weakly basic drug ZK 811 752 to that in 0.1N HCl, fumaric acid was added to the mini matrix tablets. Independent of the pH of the dissolution medium, the pH inside the tablet matrix was expected to be acidic and thus the solubility of the weakly basic drug to be high. Therefore, drug release should be pH-independent. Fumaric acid was chosen because it is a substance with high acidic strength ( $pK_{a1}$  3.03 and  $pK_{a2}$  4.54) and relatively low aqueous solubility (0.63 mg/ml) (all values from reference Merck & Co. Inc., 1996).

The addition of fumaric acid (Table 1, formulation nos. 2 and 3) significantly increased the drug release in phosphate buffer pH 6.8 for polyvinylacetate/polyvinylpyrrolidone-based mini matrix tablets (Fig. 2). Irrespective of the amount of organic acid added (16.7 or 33.4% w/w fumaric acid based on the total tablet weight), the resulting release profiles almost overlapped with the ones of fumaric acid free mini matrix tablets (Table 1, formulation no. 1) in 0.1N HCl. Due to the addition of fumaric acid, the drug release was independent of the pH of the bulk fluid in the range of pH 1–6.8. This is in good agreement with the above described hypothesis of a constant micro-environmental pH within the dosage forms.

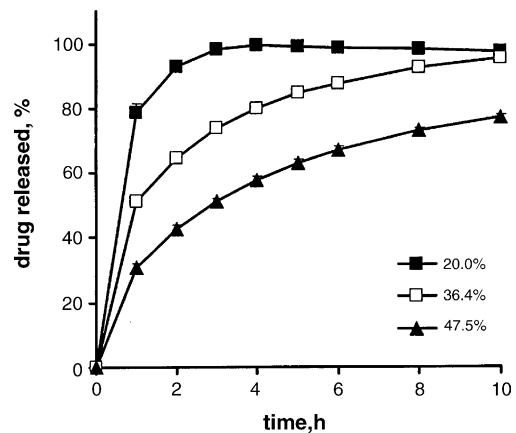


Fig. 3. Effect of the amount of polyvinylacetate/polyvinylpyrrolidone on the release of ZK 811 752 in phosphate buffer pH 6.8 from tablets containing 16.7% (w/w, based on total tablet weight) fumaric acid.

The micro-environmental pH inside the mini matrix tablets was monitored during drug release by the addition of the pH indicator methyl red (0.10% w/w) to the polyvinylacetate/polyvinylpyrrolidone matrix. The indicator is red at acidic pH and yellow at pH-values  $>5.8$ . Drug release was studied in phosphate buffer pH 6.8. Results indicated that the tablet core remained red. Thus, the pH within the core remained acidic during drug release. In addition, the pH-value of the release medium was checked during dissolution testing. It remained constant at pH 6.8.

Next, the influence of the amount of matrix former on the release of ZK 811 752 from mini matrix tablets was investigated in phosphate buffer pH 6.8 (Fig. 3). Therefore, polyvinylacetate/polyvinylpyrrolidone was partially replaced by lactose (Table 1, formulation nos. 2, 4 and 5). As expected, increasing the amount of lactose (keeping the entire tablet weight constant), led to a significant acceleration in 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. These findings are in good agreement to results obtained with diphenhydramine HCl, lactose, polyvinylacetate/polyvinylpyrrolidone matrix tablets (Shao et al., 2001).

The influence of the nature of excipient on the release of ZK 811 752 from mini matrix tablets was investigated in phosphate buffer pH 6.8 (Fig. 4).

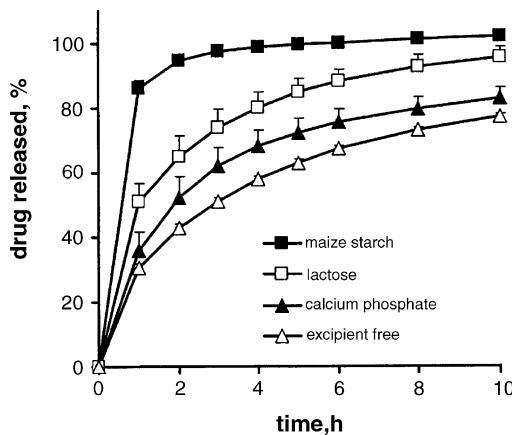


Fig. 4. Effect of the addition of different excipients on the release of ZK 811 752 in phosphate buffer pH 6.8 from polyvinylacetate/polyvinylpyrrolidone tablets containing 16.7% (w/w, based on total tablet weight) fumaric acid.

formulation nos. 1, 4, 6 and 7). After 2 h, almost 100% drug have been released from tablets containing maize starch which can be explained with the disintegrating effect of maize starch, thus leading to rapid tablet dissolution. Addition of the water-soluble lactose led to a significant acceleration in drug release compared to excipient free tablets due to the formation of a porous polymer network. In contrast, drug release from mini matrix tablets containing calcium phosphate only slightly increased compared to excipient free tablets due to the water-insoluble nature of calcium phosphate. These findings are in good agreement to the literature (Shao et al., 2001). Tablet disintegration was only observed for tablets containing maize starch and increased levels of lactose. In addition, all the investigated mini tablets did not stick together during dissolution testing.

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 and fumaric acid (Table 1, formulation no. 2).

The compression force during tabletting of ZK 811 752 was varied in a range of 7–9 kN leading to a mini tablet hardness of 20–30 N (standard hardness: 25 N). Drug release from mini matrix tablets was independent of the tablet hardness within the investigated range as shown in Fig. 5. However, further investigations indicated that the drug release decreased when increas-

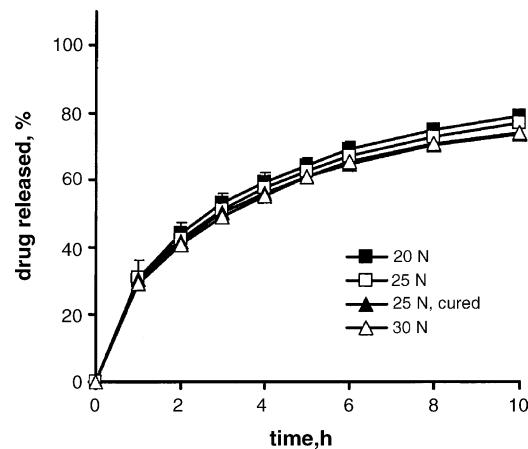


Fig. 5. Effect of the tablet hardness and curing on the release of ZK 811 752 in phosphate buffer pH 6.8 from polyvinylacetate/polyvinylpyrrolidone tablets containing 16.7% (w/w, based on total tablet weight) fumaric acid. Tablets were uncured if not otherwise mentioned.

ing the tablet hardness above 35 N (data not shown). Polyvinylacetate/polyvinylpyrrolidone is a very plastic material that produces a coherent matrix even under low compression force (Draganouiu et al., 2001). Therefore, it can be used as matrix former for the preparation of ZK 811 752 containing mini matrix tablets. 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 (Shao et al., 2001). However, for ZK 811 752 containing mini matrix tablets even storage at 60 °C for 15 h did not influence the initial in vitro dissolution (Fig. 5). Hence, post compression curing of ZK 811 752 containing mini matrix tablets 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. Drug release in phosphate buffer pH 6.8 was investigated upon storage for 3 and 6 months (Fig. 6A 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 mini matrix tablets stored at 40 °C/75%

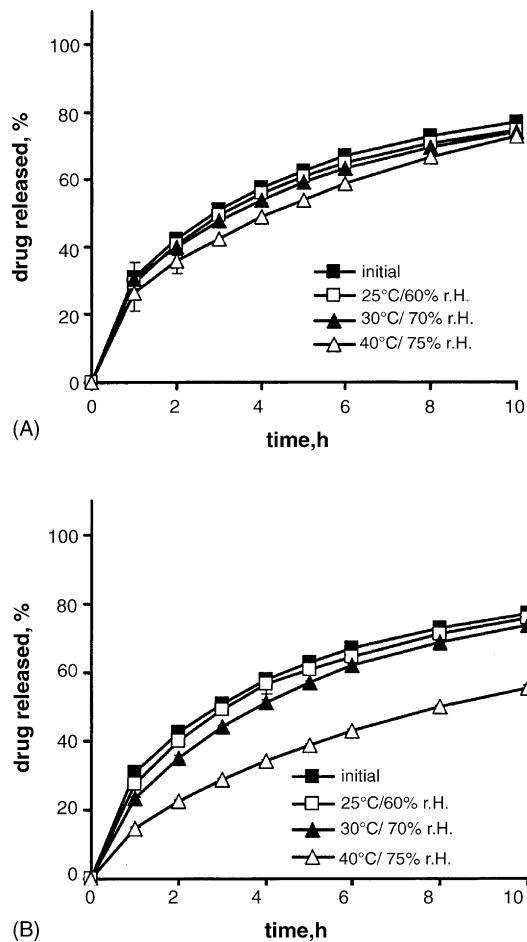


Fig. 6. Release profiles of ZK 811 752 from polyvinylacetate/polyvinylpyrrolidone tablets containing 16.7% (w/w, based on total tablet weight) fumaric acid placed on stability for (A) 3 months and (B) 6 months.

RH decreased significantly. After 6 h, initially 67.1% drug have been released versus only 59.1 and 43.0% 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 mini matrix tablets were stored above the glass transition temperature ( $T_g$ ) of polyvinylacetate/polyvinylpyrrolidone ( $T_g = 35$  °C). The polymer structure changes from the glassy to the rubbery state. Before dissolution testing, mini matrix tablets were than stored at room temperature below the glass transition temperature leading to further hardening of the tablets. For tablets stored at 40 °C/75 RH for 3 and

6 months the tablet hardness increased from 25 to 40 and 50 N thus being an explanation of the decreasing drug dissolution.

Extended release mini matrix tablet 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 addition of fumaric acid to the polyvinylacetate/polyvinylpyrrolidone tablet matrix maintained low pH-values within tablets during drug release in phosphate buffer pH 6.8 leading to pH-independent drug release.

### Acknowledgements

We would like to thank T. Kränow, P. Rothenburg, C. Wiecha and A. Ziemer for their technical assistance.

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