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Research paper

pH-independent drug release of an extremely poorly soluble weakly acidic drug from multiparticulate extended release formulations

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Abstract

Extended release mini matrix tablets for 8-Prenylnaringenin (8-PN), an extremely poorly soluble weakly acidic drug, were developed by using polyvinylacetate/polyvinylpyrrolidone as matrix former. Mini matrix tablets were manufactured by direct compression or wet granulation technique. With conventional modified release formulations, the drug demonstrated pH-dependent release due to pH-dependent solubility of the drug substance (i.e., increasing solubility at higher pH-values). In order to achieve pH-independent drug release two classes of pH-modifying agents (water-soluble vs. water-insoluble) were studied with respect to their effect on the dissolution of 8-PN. Addition of water-soluble salts of weak acids (sodium carbonate and sodium citrate) failed in order to achieve pH-independent 8-PN release. In contrast, addition of water insoluble salts of a strong base (magnesium hydroxide and magnesium oxide) was found to maintain high pH-values within the mini matrix tablets during release of 8-PN at pH 1 over a period of 10 h. The micro-environmental conditions for the dissolution of the weakly acidic drug were kept almost constant, thus resulting in pH-independent drug release. Compound release from mini matrix tablets prepared by wet granulation was faster compared to the drug release from tablets prepared by direct compression.

Keywords: pH-independence; Weakly acidic drug; Controlled release; Extended release; Basic excipients; Matrix tablets

1. Introduction

The oral route is the most common route of drug application because of its advantages in terms of convenient administration, thus leading to increased patient compliance. Extended release (ER) formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dosing frequency, and a decrease in the incidence and/or intensity of adverse effects by a constant blood concentration level [1]. Matrix tablets are one of the most common ER forms because of two main reasons: they can be made by cost-effective methods (e.g., direct compression) and the risk of dose dumping is low.

Oral tablets can be provided as single-unit or multiparticulate dosage forms. The main advantage of multiple unit dosage forms is related to their in vivo behavior, e.g., increased uniformity of plasma levels and better reproducible bioavailability [2]. Mini matrix tablets combine the advantages of a multiple unit dosage form with the advantages of matrix tablets as their manufacturing technique is well established and includes less constraints than for example extrusion/spheronization [3]. In addition, with mini matrix tablets administered drug doses can be varied easily.

Polyvinylacetate/polyvinylpyrrolidone (PVA/PVP) is a commercially available tableting excipient in the form of a physical mixture of eight parts of PVA and two parts of PVP [4]. PVA/PVP shows excellent flow properties and high compressibility, thus being a good candidate for tableting using the direct compression method [5–7]. Moreover, in mini tableting small particle sizes are necessary for

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reproducible die filling [8]. PVA/PVP has an average particle size of 100 μm indicating its possible suitability for the compression of mini-tablets.

With extended release dosage forms drug release in vitro should preferably be independent of the pH of the release medium in order to achieve as little biopharmaceutical variability as possible [9]. This has been shown to be an important parameter for weakly basic or acidic drugs [1]. Depending on the pH of the release medium or intestinal fluid they exist in their dissociated or non-dissociated form, thus showing pH-dependent solubility. 8-Prenylnaringenin (8-PN) is an extremely poorly soluble, weakly acidic estrogen that has recently been found in plants (Fig. 1). The compound seems to be a potent candidate for the treatment of postmenopausal symptoms, especially when administered in an extended release dosage form.

Several attempts to overcome pH-dependent solubility of weakly basic drugs have been published. Some authors used blends of enteric and extended release polymers as film coating materials [10,11]. 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 [9,12–14]. These organic acids keep the pH within the drug formulation in the intestinal pH-range low and thus the solubility of the drug high.

Only few studies have been carried out in order to achieve pH-independent release of weakly acidic drugs. Doherty and York [15] used a buffer system of disodium hydrogen orthophosphate and citric acid to achieve pH-independent release of the weakly acidic frusemide from PVP solid dispersions. The system was successful by increasing frusemide release in acidic media and decreasing release rates at higher pH. Rao et al. [16] developed controlled release matrix tablets for the weakly acidic drug divalproex sodium by compression of drug substance, hydroxypropyl methylcellulose and Eudragit E or dibasic calcium phosphate. Incorporation of Eudragit E which is soluble at low pH and insoluble at higher pH provided pH-independent drug release. In contrast, dibasic calcium phosphate was less effective in order to achieve pH-independent drug release which was attributed to the relative inability to elevate the pH and shorter residence time of dibasic calcium phosphate in the matrix relative to Eudragit E.

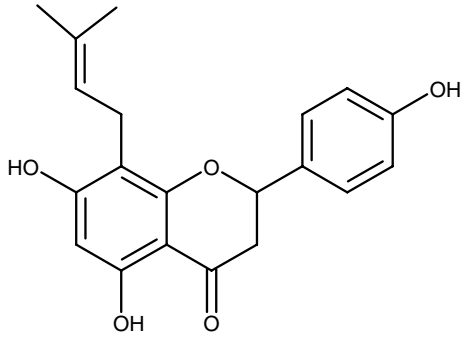

Fig. 1. Structure of 8-PN.

The objective of the present study was to achieve pH-independent release of the extremely poorly soluble but weakly acidic 8-PN from mini matrix tablets. According to pharmacokinetic modeling the desired in vitro drug release profile should demonstrate approximately 50–60% drug release within 6 h (complete drug release within 15–20 h). In a first series of experiments, several buffering excipients were evaluated in order to achieve pH-independent drug release profiles. In a second series, different formulation and process parameters were evaluated to vary the in vitro drug release rates.

2. Experimental section

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: 8-Prenylnaringenin (8-PN; 5,7-Dihydroxy-2-(4-hydroxyphenyl)-8-(3-methyl-but-2-enyl)-chroman-4-on; $pK_a = 6.2$; Schering AG, Berlin, Germany), PVA/PVP (Kollidon® SR; BASF, Ludwigshafen, Germany), magnesium hydroxide, magnesium oxide, magnesium trisilicate (Fluka, Buchs, Switzerland), acetonitrile, ammonium dihydrogen phosphate, calcium phosphate, potassium dihydrogen phosphate, sodium carbonate, sodium citrate, sodium hydroxide, triethylamine (Merck KGaA, Darmstadt, Germany), lactose (Danone GmbH, München, Germany), microcrystalline cellulose (Avicel PH 101; FMC, Philadelphia, USA), maize starch, hydroxypropyl-β-cyclodextrine (HP-β-CD; Roquette Services Techniques Laboratoires, Lestrem, France), colloidal silicon dioxide, and magnesium stearate (Herwe Chemisch-technische Erzeugnisse, Sinsheim-Dühren, Germany). All chemicals were of reagent grade or higher.

2.2. Methods

2.2.1. Mini matrix tablet preparation

Mini matrix tablets containing 1.5% (w/w) magnesium stearate as lubricant and 1% (w/w) colloidal silicon dioxide as flow promoter 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 tableting 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 22–28 N (Schleuniger hardness tester 6 D, Schleuniger Pharmatron AG, Solothurn, Switzerland). For wet granulation the blend (Table 1, formulation No. 5) was granulated in a planetary mixer (MTI, MTI-Mischtechnik Industrieanlagen GmbH, Lage, Germany) by using distilled water.

Table 1
Compositions[a] of the investigated tablets (all quantities given in %)

Formulation no.	PVA/PVP	Lactose	Calcium-phosphate	Maize starch	Microcryst. cellulose	Sodium carbonate	Sodium citrate	Magnesium oxide	Magnesium hydroxide	Magnesium trisilicate
1	14.3	28.5	–	–	21.4	–	–	–	–	–
2	14.3	11.8	–	–	21.4	16.7	–	–	–	–
3	14.3	11.8	–	–	21.4	–	16.7	–	–	–
4	14.3	11.8	–	–	21.4	–	–	16.7	–	–
5	14.3	11.8	–	–	21.4	–	–	–	16.7	–
6	14.3	11.8	–	–	21.4	–	–	–	–	16.7
7	25.0	1.1	–	–	21.4	–	–	–	16.7	–
8	10.0	16.1	–	–	21.4	–	–	–	16.7	–
9	14.3	–	11.8	–	21.4	–	–	–	16.7	–
10	14.3	–	–	11.8	21.4	–	–	–	16.7	–

[a] In addition 33.3% drug substance, 1.0% silicon dioxide, and 1.5% magnesium stearate.

2.2.2. Solubility of the drug

Excess amount of 8-PN was placed in 0.1 N HCl and phosphate buffer, pH 6.8 (USP XXVI) in order to determine its solubility. Further solubility measurements of 8-PN were conducted in the pH range from 8 to 12. An excess of drug was added to deionized water. The pH was modified with 1 N sodium hydroxide. The samples were stirred with a magnetic stirrer until reaching equilibrium solubility. The final pH of the saturated solutions was adjusted, respectively. The supernatant was passed through a 0.22 μm filter; 0.5 ml of the filtrate was immediately diluted with the appropriate dissolution medium and assayed spectrophotometrically at 290 nm. All experiments were conducted in triplicate.

2.2.3. Drug release studies

In vitro drug release was determined by using the USP XXVI rotating basket method (37 ± 0.5 °C, 100 rpm, $n = 3$) (Distek Premiere 5100 Dissolution System, Distek Inc., North Brunswick, USA). Drug release was investigated by placing approx. 100 mg of the mini matrix tablets in 1000 ml USP phosphate buffer, pH 6.8, or 0.1 N HCl. In order to reach sink conditions 10% (w/v) HP-β-CD was added to the dissolution medium, respectively. At predetermined time intervals, 10 ml samples were withdrawn (not replaced), filtered, diluted, and assayed. The amount of 8-PN was measured at 290 nm by means of UV–Vis double beam spectrophotometer against standard solutions.

3. Results and discussion

Solubilities of 8-PN at different pH-values are given in Table 2. The active compound is extremely poorly soluble in aqueous media, particularly at low pH. The pH-dependent solubility can be explained by the weakly acidic nature of 8-PN. At lower pH-values the molecule is uncharged, whereas at higher pH the molecule is negatively charged. Therefore, the solubility of 8-PN increases at increasing pH-values. In order to maintain sink conditions during dissolution testing HP-β-CD was added to 0.1 N HCl and buffer medium, pH 6.8. After addition of HP-β-CD the solubility of 8-PN strongly increased in a pH range of 1–12. This can be explained as follows: HP-β-CD increases the solubility of poorly water-soluble drugs by forming an inclusion complex, because the exterior surface of the cyclodextrine molecule is hydrophilic whereas the internal cavity is more hydrophobic [17,18]. The formation of an inclusion complex of HP-β-CD with hydrophobic molecules has been described by hydrogen bonding and van der Waals interactions [17,18]. The slight tendency of decreasing solubility of 8-PN with increasing pH in the presence of HP-β-CD might be explained with the uncharged nature of the drug at lower pH. However, since the solubility of 8-PN increased over the entire pH-range of 1–12 in the presence of HP-β-CD, interaction of 8-PN with HP-β-CD mainly happens through other regions of the molecule than the part which can be influenced through protonation.

Table 2
Solubility of 8-PN at different pH values

	Solubility at 25 °C (mg/ml)					
	pH 1	pH 6.8	pH 8	pH 9	pH 10	pH 12
No HP-β-CD	<0.0003	0.003	0.008	0.014	0.023	0.025
5% HP-β-CD	0.31	0.24	0.23	0.21	0.20	0.20
10% HP-β-CD	0.56	0.48	0.47	0.45	0.43	0.42

Such in vitro dissolution conditions might not exactly reflect the in vivo conditions (where there is no HP-β-CD present). However, it is an in vitro model to mimic an open in vivo compartment, where the released compound may readily be absorbed systemically (perfect sink). HP-β-CD as a high-molecular weight compound is assumed not to interact with the matrix itself.

However, a significant difference in the resulting release of 8-PN from PVA/PVP mini matrix tablets (Table 1, formulation no. 1) was observed in 0.1 N HCl when compared to the drug release in phosphate buffer, pH 6.8. (Fig. 2). Even after the addition of 10% HP-β-CD to buffer medium, pH 6.8, or 0.1 N HCl the drug release of 8-PN was faster at pH 6.8, whereas the solubility of the active compound was higher at pH 1. This can be explained as follows: Drug dissolution rates are mainly influenced by the concentration gradients between mini matrix tablets and the release medium. The solubility of 8-PN in the release medium was increased by the addition of HP-β-CD. However, much lower quantities of HP-β-CD can be expected within the tablet, compared to the bulk fluid, resulting in less increases in drug solubility. Therefore, even after the addition of 10% HP-β-CD the drug release was faster at pH 6.8.

If the solubility of the drug in the wetted tablet matrix is important, adjustment of the micro-pH within the mini matrix tablets and the surrounding unstirred layer should be an useful approach to increase 8-PN release rates at lower pH, thus resulting in pH-independent drug release. For a weakly acidic drug this may be achieved by adding a basic excipient to maintain high pH-values within the matrix tablet and the unstirred layer during drug release at lower pH-values. Two classes of basic excipients were studied: water-soluble salts of weakly acids and poorly soluble bases.

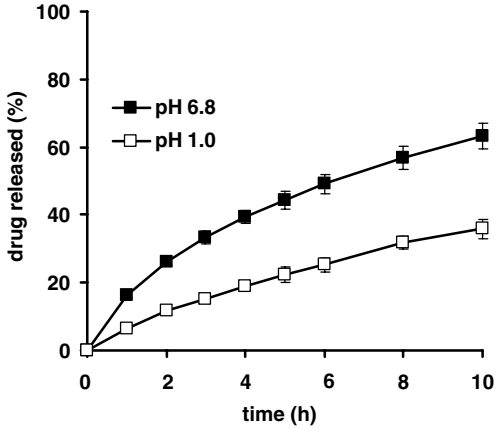

Fig. 2. pH-dependent release of 8-PN from PVA/PVP mini matrix tablets.

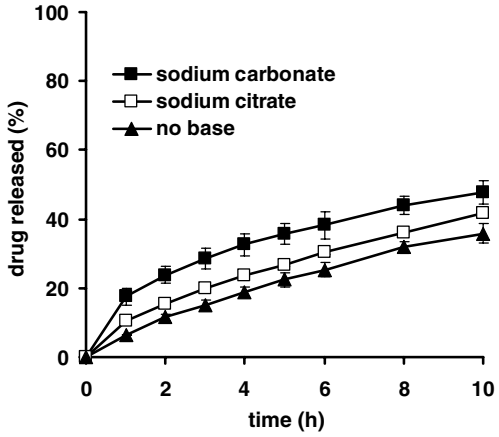

Fig. 3. Effect of the addition of salts of weakly acids on the release of 8-PN at pH 1 from PVA/PVP mini matrix tablets.

The effect of the addition of different basic pH-modifying agents to the tablet matrix on drug release rates was investigated in 0.1 N HCl (Fig. 3). Two salts of weak acids namely sodium carbonate and sodium citrate (Table 1, formulations 2 and 3) were studied first. These salts are known to increase the pH of aqueous solutions as they are able to accept protons. Both salts increased the dissolution rate compared to the formulation without base. The observed differences in dissolution rates between sodium carbonate and sodium citrate containing formulations can be explained with the higher basic strength of sodium carbonate compared to sodium citrate (aqueous solutions yielding pH 11.6 and pH 8, respectively) [19]. Furthermore, sodium carbonate is less water-soluble than sodium citrate (solubilites are 1 part in 3.5 parts of water for sodium carbonate, and 1 part in 1.3 parts of water for sodium citrate at 25 °C, respectively) [19]. Compared to sodium carbonate a faster leaching of sodium citrate from the mini matrix tablets is expected, resulting in lower micro-environmental pH-values and thus leading to slower 8-PN release rates. However, the goal of approximately 50–60% drug release within 6 h was not achieved in any of these cases. In addition, increasing the amount of sodium carbonate and sodium citrate within the mini matrix tablets to 28.5% by decreasing the amount of lactose did not accelerate in vitro dissolution profiles at pH 1 (data not shown).

As a next step, bases of even lower water-solubility were investigated (Table 1, formulations 4–6). Again the drug

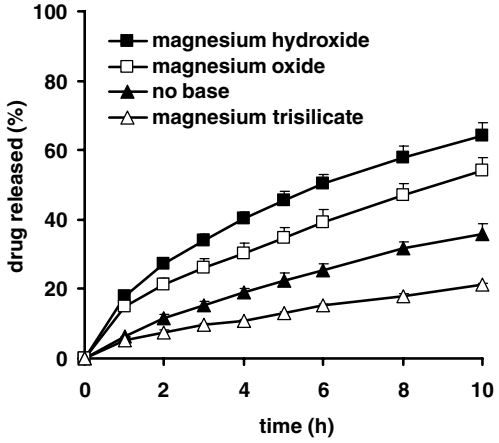

Fig. 4. Effect of the addition of poorly soluble basic pH-modifying agents on the release of 8-PN at pH 1 from PVA/PVP mini matrix tablets.

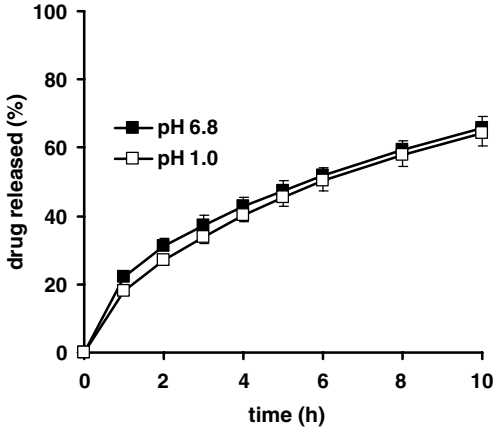

Fig. 5. pH-independent release of 8-PN from PVA/PVP mini matrix tablets containing 16.7% (w/w) magnesium hydroxide.

release was investigated in 0.1 N HCl (Fig. 4). Poorly water-soluble salts of strong bases are expected to remain in the matrix tablet during drug release and therefore to increase the pH within the matrix tablet over the entire dissolution time. Magnesium oxide, magnesium hydroxide, and magnesium trisilicate were chosen because they are known to be practically water-insoluble [19]. The pH-values of aqueous slurries are 9.5–10.5 for magnesium hydroxide, 10.1 for magnesium trisilicate, and 10.3 for magnesium oxide, respectively [19]. For magnesium oxide and magnesium hydroxide addition of pH-modifying agents significantly increased drug release rates, whereas addition of magnesium trisilicate decreased release rates compared to the formulation without additional base. The decreased drug release rate from magnesium trisilicate mini matrix tablets might be explained by drug adsorption of active compounds to magnesium trisilicate. Another possible explanation could be that magnesium trisilicate is hygroscopic and decomposes in aqueous mineral acid media, where a gelatinous mass (silicic acid) is formed, thereby reducing the diffusion coefficient and dissolution rate of the drug substance. Upon contact with water (or acidic solutions), magnesium oxide first forms magnesium hydroxide which finally decreases the pH within the tablet matrix. This step takes additional aqueous fluid (competing with the dissolution of 8-PN), thus explaining slower drug release rates from formulations containing magnesium oxide compared to formulations with magnesium hydroxide.

The addition of magnesium hydroxide significantly increased the 8-PN release in 0.1 N HCl. Therefore, the resulting release profiles of 8-PN at pH 1 almost overlapped with the drug release profiles at pH 6.8 (Fig. 5). This indicates that pH-independent drug dissolution can be expected within the human gastrointestinal tract, thus minimizing potential biopharmaceutical problems. Increasing the amount of magnesium hydroxide to 28.5% by decreasing the amount of lactose did not further accelerate the in vitro drug release at pH 1. In contrast, decreasing the amount of magnesium hydroxide to 8.4% resulted in lower drug release rates at pH 1 (data not shown).

To check the hypothesis of high micro-environmental pH-values for mini matrix tablets containing basic excipients the surface pH of the tablets was measured by using pH-test paper at predetermined intervals. In contrast to mini matrix tablets without basic excipient and formulations containing sodium carbonate or sodium citrate, the surface pH of tablets containing magnesium oxide and magnesium hydroxide remains high (>pH 9) during dissolution testing in pH 1 over a period of 10 h. This indicates that buffering excipients should possess low pK_b-values indicating high basic strength, and low water-solubility in order to remain within the dosage form over the entire dissolution time. Magnesium hydroxide was found to be the most effective excipient to increase 8-PN release rates at lower pH and was therefore used for further studies. Solubility values of 8-PN at pH 1 and pH 6.8 varied by a factor of approximately 10 (Table 1). In cases where pH-modification had been applied to weakly basic drugs (by using acids as modifiers), the approach was successful even for drugs where the pH-dependent solubility varied by a factor of 50 [14]. To investigate if the presented pH-modifying concept for weakly acidic drugs works for other drugs as well was beyond the scope of this paper.

The influence of the amount of matrix former on the release of 8-PN from mini matrix tablets was investigated in 0.1 N HCl (Fig. 6). Therefore, PVA/PVP was partially replaced by lactose (Table 1, formulation nos. 5, 7, and 8). Increasing the amount of lactose led to a significant acceleration in drug release. This can be explained as follows: when PVA/PVP tablets are introduced into aqueous fluids, the water-soluble PVP component leaches from the device and a porous network is formed through which the active component diffuses from the matrix [4]. In contrast, the compressed PVA component, which is water-insoluble, maintains the matrix structure during dissolution experiments. Increasing the amount of water-soluble components within the tablet matrix by

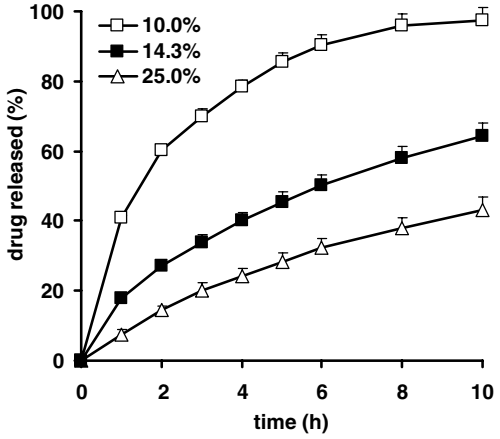

Fig. 6. Effect of the amount of PVA/PVP on the release of 8-PN at pH 1 from mini matrix tablets containing 16.7% (w/w) magnesium hydroxide.

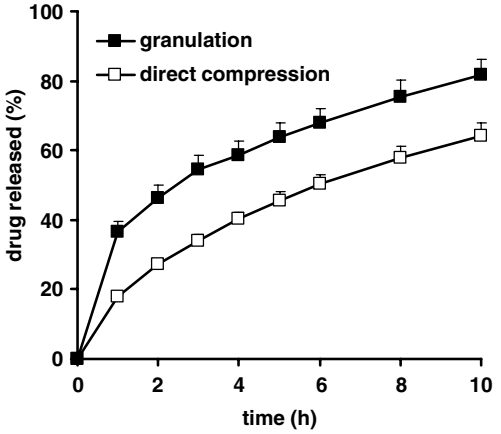

Fig. 8. Effect of the manufacturing method on the release of 8-PN at pH 1 from PVA/PVP mini matrix tablets containing 16.7% (w/w) magnesium hydroxide.

the addition of well water-soluble lactose increased the porosity of the resulting polymer network, thus accelerating drug release rates. These findings are in good agreement to the literature [5].

Next, the influence of the nature of excipient on the release of 8-PN from mini matrix tablets was investigated in 0.1 N HCl (Fig. 7, formulation nos. 5, 9, and 10). Drug release rate was fastest from mini matrix tablets containing maize starch which can be explained with the disintegrating effect of maize starch, thus leading to more pronounced tablet dissolution. Addition of water-soluble lactose led to a significant acceleration in drug release compared to matrix tablets containing calcium phosphate which can be explained with the water-insoluble nature of calcium phosphate.

Most of the research reported in the literature utilizes PVA/PVP as a directly compressible excipient for extended release matrices [5]. The aim of this study was also to investigate the effect of this excipient on formulating the tablets (Table 1, formulation no. 5) by wet granulation technique using distilled water as granulating medium. The in vitro release rate of 8-PN from mini matrix tablets manufactured by direct compression or after wet granulation was investigated in 0.1 N HCl (Fig. 8). Significant differences were observed for both manufacturing methods. After 1 h, 37% versus 18% of the active compound was released from formulations prepared by wet granulation or direct compression method, respectively. A possible explanation can 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 porous mini matrix tablet structure.

Extended release mini matrix tablets for the extremely poorly soluble but weakly acidic 8-PN have been developed which provided the desired in vitro drug release profiles of approximately 50–60% drug release within 6 h. In order to achieve pH-independent drug release, two classes of pH-modifying agents (water-soluble vs. water-insoluble) were studied. The addition of water-soluble salts of weak acids (sodium carbonate and sodium citrate) failed in order to achieve pH-independent drug release. In contrast, addition of water-insoluble salts of strong bases (magnesium hydroxide and magnesium oxide) was successful to reach pH-independent release of 8-PN. Various formulation parameters such as the amount of matrix former, nature of added excipient, and manufacturing method have been assessed with regard to their impact on the drug release patterns.

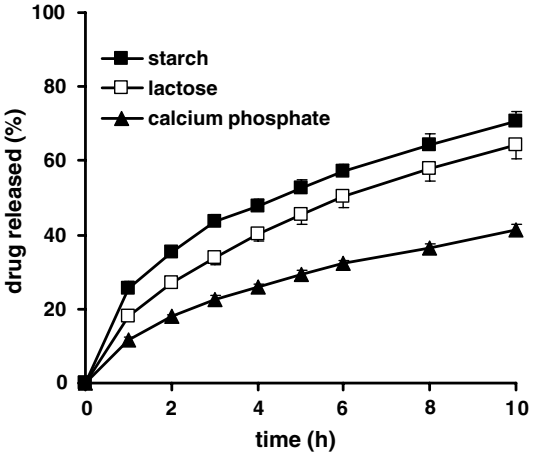

Fig. 7. Effect of the nature of excipient on the release of 8-PN at pH 1 from mini matrix tablets containing 16.7% (w/w) magnesium hydroxide.

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