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European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 105–113

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

The pH-independent release of fenoldopam from pellets with insoluble film coats[1]

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Received 18 April 1997; accepted 12 November 1997

Abstract

Various ratios of succinic acid to fenoldopam mesylate, ranging from 0:1 to 18:1 were incorporated in pellets and coated with 1.5–12% w/w Surelease. Even though the coating level did influence the rate and amount of fenoldopam release, the influence of the succinic acid to drug ratio was much more important and evident at all coating levels. Being a weakly basic drug, fenoldopam release ceased when testing in SIF for succinic acid to drug ratios of 0:1–4:1, with the end of release being more abrupt for the 0:1 than for the 4:1 ratio. Only for a succinic acid to drug ratio of ≥5 was fenoldopam release constant for 6–8 h and independent of the pH-value of dissolution media. For a thin coat of about 2.5% w/w Surelease, those pellets showed an ideal controlled release behaviour with release rates of about 5–10%/h and a total release of almost 80% in 8 h. The dissolution profiles of Surelease coated pellets with high succinic acid to drug ratios (≥5) and different coating levels, were evaluated for best fits to commonly used kinetic models. Sustained release mechanisms are discussed according to best fit models. The quantification of the pH-adjuster succinic acid, released from pellets with an acid to drug ratio of ≤1 showed, that despite their failure as a controlled release system for fenoldopam, the investigated coats could control the release of succinic acid effectively at optimized coating levels. For increasing succinic acid to drug ratios (≤4) succinic acid was released at an ever more constant rate and release rates, though still faster than the release rates of fenoldopam, decreased steadily for increasing ratios. At a 5:1 ratio finally release rates of succinic acid and fenoldopam were almost identical. Therefore those pellet cores were almost completely emptied during dissolution testing, with both fenoldopam and succinic acid leaving at a constant rate and a total release of about 80% each for a 2.5% Surelease coat, while lower succinic acid to drug ratios had failed to show any sustained release for such thin Surelease coats. A similar formulation with fumaric acid instead of succinic acid failed to show the desired release pattern, indicating that it is the presence of a sufficiently high amount of succinic acid rather than the presence of an acidic compound in general, that ensures fenoldopam solubility at higher pH-values.

Keywords: Weakly basic drug; Succinic acid and fumaric acid as pH-adjuster; Sustained release; Surelease; Kinetic models

1. Introduction

The biggest problem facing development of diffusion controlled release dosage forms of weakly basic drugs, is the immense variability in the solubility of such drugs depending on the pH of the dissolution medium. At the low pH found in the stomach, weakly basic drugs are freely soluble resulting in fast dissolution rates. However, this rate decreases dramatically once the sustained release dosage form has been transferred to the higher pH regions of the small intestine. Therefore, pH-adjusters, i.e. organic acids of sufficient acidic strength (low pK_a-values), have been described by many authors [1–4] for the design of sustained release dosage forms, in order to create an acidic micro-pH inside the cores. Provided the acidic compound does not diffuse through the barrier membrane or out of the matrix faster than the drug itself is desired to be released, an almost linear drug release profile should be achievable for 8–10 h.

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[1] Dedicated to Dr Bertold Moser, Landau/Pfalz, on the occasion of his 65th birthday.

0939-6411/98/$19.00
PII S0939-6411(97)00164-1

Thoma and Zimmer [1] stated, that the amount of acid present in the core has a major influence on the total release rates achieved. Consequently, a high level of acid is required to maintain the acidic micro-pH. Highly soluble organic acids like citric acid and tartaric acid, were therefore shown by Thoma and Zimmer [2] to be generally less effective, than the less soluble succinic acid. Other authors also mention the dependence of both the slowing down of release rates for acidic drugs in the small intestine and the maintenance of drug release in the small intestine for weakly basic drugs, on the ratio of the acidic compound to drug [5,6].

As fenoldopam mesylate (6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol, methanesulfonate) is a selective DA_1 agonist, causing an increased splanchnic and renal blood flow with a strong diuretic and natriuretic effect, it possesses several decisive advantages as an antihypertensive and for the treatment of congestive heart failure over commonly used other drugs [7].

However, for an effective therapeutic use a twice daily application as a sustained release formulation would be necessary. The solubility of fenoldopam mesylate is 9.1 mg/ml in a HCl/KCl buffer pH 1.5, but decreases to 0.13 mg/ml in buffer pH 6.8 and to 0.06 mg/ml in SIF pH 7.5 [8]. This decreased solubility then causes the failure of all diffusion controlled sustained release systems in the small intestine, even though the drug is well absorbed throughout the gastrointestinal tract [9]. Even when using equal parts of succinic acid as a pH-adjuster and fenoldopam mesylate in a pellet formulation coated with diffusion membranes, total release rates for fenoldopam were scarcely higher than about 60% [10].

Therefore, the precise changes in the release rates of fenoldopam with gradually increasing succinic acid to drug ratios should be investigated and the coating levels necessary for a total release of the drug within 8–10 h should be determined for succinic acid as well as other acids as pH-adjusters. In order to evaluate the importance of the amount of succinic acid present in the pellets on the release of fenoldopam from such pellets, not only the dissolution rates of fenoldopam, but also of succinic acid had to be measured in the different dissolution media.

The two coating dispersions used for those trials were Surelease and Celluloseacetate without any pore formers, due to their previously observed favourable performance during coating and storage [10].

2. Materials and methods

2.1. Pelletization

Details of basic pellet formulation are shown in Table 1. The quantities for all pellet components are calculated as percent w/w of the dry formulation, while water contents are given as percent loss on drying, and are thus calculated on the wet mass as 100%. The pellet components are: fenoldopam mesylate, fenoldopam succinate (Smith-Kline Beecham, Epsom), Avicel PH 101 (Lehmann and Voss, Hamburg), succinic acid, fumaric acid (Merck, Darmstadt) and sodium laurylsulphate (Fluka, Neu-Ulm).

Powders were mixed in a Kenwood Chef mixer with a K-shaped mixer (Kenwood, Hampshire) for 15 min at a setting of 2–3 digits and then granulated with water containing the dissolved sodium laurylsulphate and the Eudragit NE for 10 min at maximum speed. When used, L-HPC LH 31 was directly added to the dry powder mix. The moist granulates were extruded on a Alexanderwerk GA 65 gravity feed extruder with a 1.0 mm die at 132 rev./min (Alexanderwerk, Remscheid), spheronized on a 23 cm spheronizer (Caleva, Dorset) at a load of 200–250 g and a speed of 1000/1240 rev./min for 15 min and then dried in an oven at 40°C for 24 h.

Each pellet batch was sieved (vibrating sieve shaker Retac 3D, Retsch, Haan) and only the size fraction between 710 and 1250 μm was used for coating.

2.2. Coating

Batches (200 g) were coated in a bottom spray fluid bed apparatus, exhibiting a sprouted fluidization pattern (Strea 1 with stainless steel chamber; Niro-Aeromatic, Bubendorf). Aqueous coating dispersions were pumped to the nozzle using a peristalitc pump and stirred constantly during coating.

Coating levels are determined as % weight gain as the difference in batch weights before and after coating, taking the polymer contents of coating dispersions into account. As the water content of dried fenoldopam pellets was about 1–2% only and the same water contents were found again after coating [10], possible changes of the moisture content of pellets during the coating process were considered to be low and therefore not taken into account. Pellets were always dried for at least 5 min in the fluid bed after spraying had

Table 1
Pellet formulation

Basic pellet formulation	%	Function
Fenoldopam mesylate/ fenoldopam succinate	4–71	Drug compound
Organic acid (succinic acid/ fumaric acid)	0–79	pH-adjuster
Avicel PH 101	12–15	Spheronization aid
Eudragit NE/L-HPC LH 31	3–5	Binder[a]
Sodium laurylsulphate	0.05	Wetting agent to facilitate extrusion/spheronization[a]
Purified water	28–36	Depending on the amount of Avicel, type of binder and type of organic acid

[a]Those low concentrations were found to have no influence on drug dissolution from the uncoated or coated pellets.

been completed, before taking any samples or emptying the coating container. Coating efficiency is calculated as the correlation between actual weight gains and the theoretical weight gains, that would have been expected from the polymer content and the amount of coating dispersion applied. Additional excipients in the coating dispersions, such as plasticizers or pore formers are given in % of polymer weight.

Surelease 7–7050 white (Colorcon, Königswinter) is an aqueous ethylcellulose pseudolatex dispersion with 25% solids, consisting of ethylcellulose, dibutylsebacate (DBS; ca. 17%), fumed silica and ammonia. This ready to use dispersion was diluted with water to a content of 15% solids and stirred with a few drops of silicon emulsion for 30 min prior to use. Coating levels for Surelease coats given in this work include the DBS and additional excipients. Batches were coated at an inlet air temperature of 60°C and a spray rate of 5 g/min and cured for 2 h at 60°C and 24 h at 35°C after coating to ensure complete coalescence of films, but prevent excessive thermal stress over longer time periods.

HPMC (Opadry clear OY 29020, Colorcon, Königswinter) and HPMCAS (Aquot HF, Syntapharm, Mühlheim-Ruhr) were used as pore formers and redispersed according to the manufacturers' suggestions before being added to the coating dispersions.

2.3. Dissolution testing

Batches were tested only after having been stored for at least 3 days after coating. These dissolution data are then considered as post manufacturing, while counting storage time from then onwards.

Drug dissolution was determined with a novel flow-through dissolution method in its automated version, as described in Ref. [10], that has been designed to meet the special requirements of fenoldopam, as to ensure drug stability and sink conditions even in high pH media. Release curves are mean values of $n = 3–6$ for a standard test of 2 h in SGF pH 1.2, USP 23 (1995) and 6 h in SIF pH 7.5, USP 23 (1995). Alternatively tests were also carried out in SIF pH 7.5 or buffer pH 3.0 only. Released fenoldopam and organic acids were quantified in dissolution media by HPLC. After the test, the samples are removed from the dissolution cells, homogenized in 0.1 N HCl, filtered and assayed by HPLC for remaining quantities of fenoldopam and organic acid. Released amounts are then calculated as percent of total contents, as obtained from the sum of mg released during the test and the mg that had remained inside the pellets.

2.4. HPLC-assay of fenoldopam and succinic acid/fumaric acid

Fenoldopam and succinic acid contents in dissolution media and final amounts in the pellets after dissolution testing were assessed by a stability indicating HPLC method with a Nucleosil 5 C18-ODS 5.4×25 cm column (Macherey and Nagel, Düren) as described in detail in Ref. [10]. Mobile phase = 20 parts methanol (gradient grade, Merck, Darmstadt) + 80 parts 0.025 M phosphate buffer pH 2.5 (Fluka, Neu-Ulm).

2.5. Kinetic modelling

Dissolution data were fitted to the models using linear regression analysis (Quattro Pro 5.0, Borland, 1994) and calculating correlation coefficients and slopes for the regression lines.

2.6. IR investigations

IR investigations were carried out by SmithKline Beecham, Analytical Sciences, The Frythe, Wellington Garden City, UK.

3. Results and discussion

3.1. Importance of the ratio of succinic acid to fenoldopam mesylate for the release of fenoldopam

Even at a rather high coating level of 8% w/w Surelease, the importance of the incorporated succinic acid for the release of fenoldopam already becomes clear, despite the generally low release of all investigated formulations. Without any succinic acid drug release ceases almost immediately, when the pH is changed from 1.2 to 7.5, while batches with succinic acid show at least some continuation of drug release even at the higher pH-value.

The interesting observations, however, arise from the dissolution data of much thinner coats of only 2.5% w/w Surelease, depicted in Fig. 1. Here the influence of the succinic acid to fenoldopam mesylate ratio clearly overrides the influence of the coating level and exerts its influence even in SGF. As the coats are extremely thin, fenoldopam release is quite fast for low ratios of succinic acid (0:1–2:1), when testing in SGF, where fenoldopam solubility is high. Notably here, in contrast to the observations made for the higher coating levels of 8% w/w Surelease and the observations Thoma and Zimmer [3] made for 10% w/w Eudragit coats on papaverine and codeine formulations, fenoldopam release decreases during the first 2 h of testing (i.e. while testing in SGF), as the succinic acid to drug ratio increases. In addition to this reduction of the initial release in SGF, the remaining fenoldopam is released at a more constant rate during the following 7 h in SIF for high ratios of succinic acid to drug.

But all batches with a succinic acid to drug ratio of 5:1 or higher depicted in Fig. 1b, show a similar release profile and release rates at a coating level of 2.5% w/w

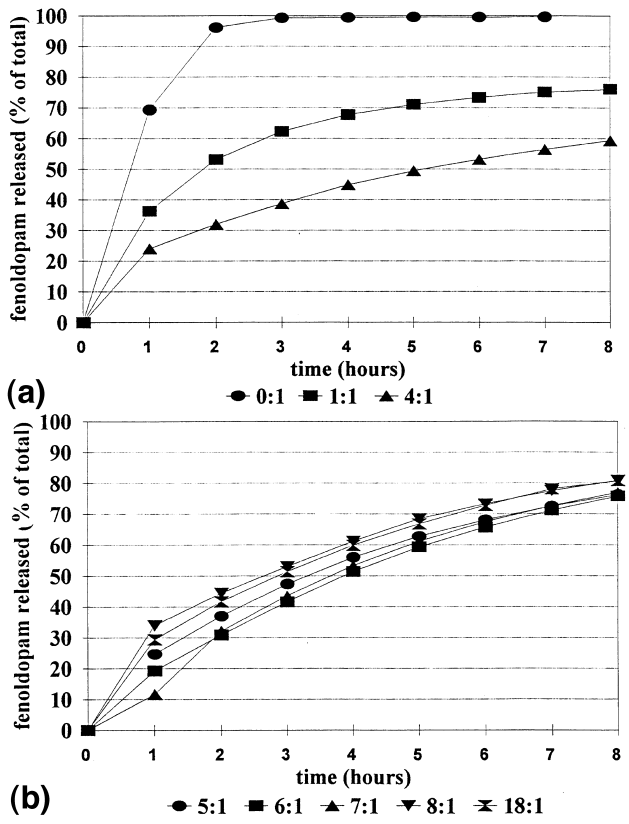

Fig. 1. Dependence of fenoldopam release on the succinic acid to fenoldopam mesylate ratio for 2.5% w/w Surelease coats; (pellets = 15% Avicel PH 101, 5% Eudragit NE, 0.03% sodium laurylsulphate (fenoldopam mesylate content of 0:1 formulation = 12% w/w, binder = L-HPC LH 31, Avicel PH 101 = 85% w/w); standard dissolution test, as mean of $n = 2–6$). (a) Low ratios of succinic acid to fenoldopam mesylate. (b) High ratios of succinic acid to fenoldopam mesylate.

Surelease. This marks a significant change in the dissolution behaviour, when rising the succinic acid to drug ratio to 5:1, as the 4:1 ratio was unable to achieve such a sustained release profile for the 2.5% Surelease coat. For all ratios ≥5:1 differences in the release rates are only observed during the first hour, while thereafter fenoldopam release is about 5–10%/h for each of them. As the drug loading for fenoldopam is highest when using the 5:1 ratio, this ratio is considered to be the optimum level for an effective retardation of fenoldopam. While a batch without any succinic acid but an identically low drug content of 12% could not maintain fenoldopam release in SIF, the dissolution rates of the 5:1 ratio batch (12% fenoldopam mesylate) resembles an almost ideal sustained release profile with 35–45% of fenoldopam being released within the first hour and a subsequent 5–10% of fenoldopam being released each hour independently of the pH-value of the dissolution medium. Total release rates sum up to about 70–80% of the incorporated drug and are thus well within the usually observed total release for other sustained release systems.

3.2. Investigation of low coating levels for high succinic acid to drug ratios and Surelease coats

Fig. 2 shows, that a coating level of 3.4% w/w Surelease or greater shows an almost linear release of fenoldopam, but generally quite low rates and a maximum release of about half of the incorporated drug within 8 h. Excessively thin coats of 1.1–1.8% w/w on the other hand show almost no sustained release of fenoldopam, but a fast, total release within 1–3 h instead. Only within the rather narrow range of about 2.3–2.6% w/w of Surelease, do pellets show the desired release profiles. This means that rather tight specification limits on coating levels would have to be postulated for any commercial use of this formulation, which is generally considered as a drawback for any coating formulation. However, if a good reproducibility of the intended coating levels can be assured and the specification thus be met for all batches, the short coating times necessary for the described formulation might be very beneficial even on a commercial scale.

Therefore the reproducibility of coating levels and of film properties had to be investigated for the thin Surelease coats as they are a major prerequisite to ensure a reproducible fenoldopam release from batch to batch and the possible use of those films.

One of the most important influences on film properties and coating levels during coating is the product temperature, which determines both the efficiency of the coating process and the coalescence of the pseudolatex dispersions. While coating efficiency can be calculated from the percent weight gain after coating, the quality of film coalescence can only be estimated by the dissolution behaviour.

As far as coating efficiency is concerned, all batches showed an excellent reproducibility of the desired coating levels as demonstrated by an actual weight gain of more than 99% of the theoretical weight gain, despite the rather small batch sizes of only 200 g pellets. However, fenoldo-

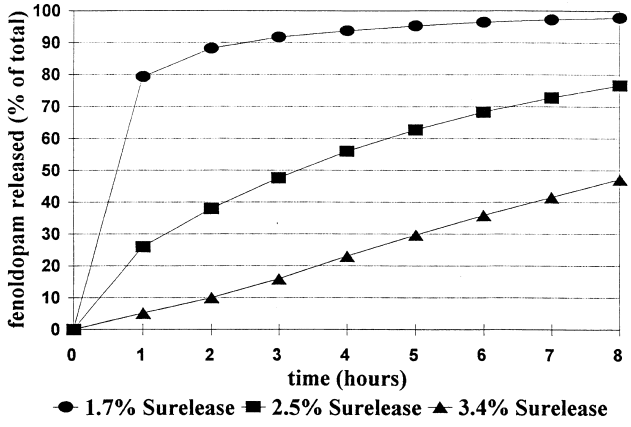

Fig. 2. Dependence of fenoldopam release from the coating level for pellets with a 5:1 ratio of succinic acid to fenoldopam mesylate and Surelease coats; (pellets = 15% Avicel PH 101, 5% Eudragit NE, 0.03% sodium laurylsulphate; standard dissolution test, as mean of $n = 2–6$).

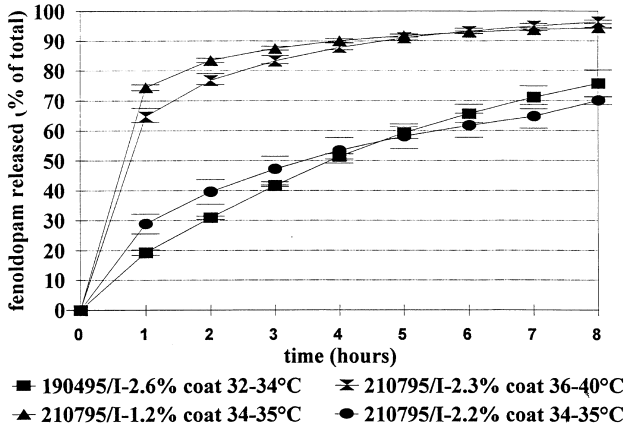

Fig. 3. Influence of coating temperature on the reproducibility of dissolution profiles for 2.5% w/w Surelease coats on pellets with a succinic acid to fenoldopam mesylate ratio of 6:1. Standard dissolution test.

pam dissolution and thus film coalescence showed a strong dependence on the coating temperature. (For small batch sizes, that do not fill the volume of the coating container when fluidized, the product temperature is much better defined by the outlet air temperature rather than the inlet air temperature). As demonstrated in Fig. 3, fenoldopam release shows good reproducibility for 2.5% w/w Surelease batches, with a c.v. of 5% between batches, that had been determined during the validation of the flow-through dissolution system [10] to be the usual variation coefficient in the release of samples from the same batch. However, when the coating temperature had exceeded the usual range for the outlet air temperature (30–35°C), fenoldopam release was much faster and identical with the release observed for a 1.2% w/w Surelease coat, despite a coating efficiency of 99.8%.

Due to the high coating efficiency, spray drying of the dispersion during coating was quite unlikely to be the reason for those faster dissolution rates. They could thus only be explained by an inferior film coalescence occurring when water dries off at a faster rate at elevated temperatures. The less homogeneously coalescenced films are more porous causing faster drug release post manufacturing, as also observed by other authors for even higher coating levels of 10% w/w ethylcellulose [11]. Therefore the only critical parameter in the reproducibility of dissolution profiles is the product temperature during coating, which has to be ensured by an appropriate control of inlet air temperature, humidity and spray rate.

3.3. Determination of the kinetics of fenoldopam release

In order to get more detailed information on the actual release mechanisms for Surelease coated pellets with different ratios of succinic acid to fenoldopam mesylate, the dissolution profiles were plotted in different plots and regression analysis (significance $F < 0.05$) was performed for each of them. Best fits were calculated on basis of the correlation factors as r^2 and dissolution rate constants were determined for each model.

Out of all of the tested models, the first order kinetics, the zero order kinetics and the Weibull distribution showed the best fits for the investigated batches.

$$W(\%R(t_i)) = \ln(\ln(1/(1-\%R(t_i)/100))) \quad (1)$$

where R is the percentage of drug released at the time t_i.

The Higuchi square root of time model, which is often used for the evaluation of release kinetics from pellets [12], showed less good fits and the Hixon Crowell's cube root of time model [13] could not be used at all, as none of the pellet batches showed a disintegration of pellets during dissolution testing, not even for the uncoated pellets. Jander's plot [14] showed partially good fits, but could not help to explain the observed release behaviour as appropriate as the Weibull equation, which represents a cumulative probability distribution. It is known to be very sensitive to differences in dissolution rates based on differences in film thickness, but also to differences due to different testing conditions [15]. When plotting the Weibull rates as a function of $\ln(t_i)$, where $\ln(t_i)$ = natural logarithm of the time t_i, the slope of the regression line β represents a shape factor and is used together with the intercept α, to calculate a scale parameter τ, that represents the time when 63.2% of the drug has been dissolved.

$$\tau = \exp(-\alpha/\beta) \quad (2)$$

Table 2 shows all fits for different levels of Surelease coats. Dissolution of fenoldopam out of Surelease coated pellets is best described by a zero order kinetic for the 3.4% w/w coating level for the complete dissolution time. Zero order kinetics indicate, a solely membrane controlled diffusion through a film with a saturated drug solution inside the pellet and a constant surface area, representing a steady state system with a constant drug release rate according to Fick's first law. For the 2.6% w/w coat the best fit was observed for a first order kinetic model, indicating a diffusion controlled release despite the low coating level. Diffusion rates, however, depend on the concentration of drug inside the pellets and are thus influenced by both the membrane and the pellet matrix. The film coat is not yet thick enough to control drug diffusion entirely on its own without

Table 2

Model fits and release rate constants for 6:1 succinic acid to fenoldopam mesylate batches coated with Surelease at different coating levels

Pellet batch % coat w/w	Zero order kinetic		First order kinetic		Weibull distribution	
	r^2	$k = h^{-1}$	r^2	$k = h^{-1}$	r^2	$\tau_{63.2\%} = h$
1.7% Surelease	0.5493	8.399	0.9416	0.953	0.9984	0.74
2.6% Surelease	0.9571	9.106	0.9996	0.404	0.9976	5.61
3.4% Surelease	0.9983	7.265	0.9926	0.247	0.9961	9.54

r^2, quadratic correlation coefficients of regression lines; k, release rate constants.

the contribution of the pellet matrix. For the extremely thin 1.7% w/w coat the Weibull distribution is the only model describing fenoldopam release with an acceptable regression fit. At this extremely low coating level fenoldopam release is mainly controlled by the pellet core as the coats are too thin to sustain drug dissolution effectively. Pellets without any coat at all had shown similar release profiles to these ones.

The $\tau_{63.2\%}$ obtained from Eq. (2), rises from 0.7 to 5.6 h and finally 9.5 h as coating levels increase from 1.7 to 2.6% w/w and finally 3.4% w/w.

When investigating model fits for batches with various succinic acid to drug ratios and 2.5% Surelease coats, the same good first order kinetic fits could only be achieved at a minimum ratio of 4:1. For the 2:1 ratio and even more pronounced for the 1:1 ratio, fits were insufficient, indicating that at those ratios no diffusion controlled drug release mechanism was responsible for the dissolution of fenoldopam.

3.4. Storage stability of Surelease batches at room temperature

Several authors have reported changes in drug release from film coated dosage forms, in particular from aqueous film coats [16,17] with time. It was therefore important to examine the stability of the thin films used in this work and especially when considering the extremely acidic milieu in the pellet cores, caused by the high amounts of succinic acid that might easily cause a change in the film properties over storage time.

Fenoldopam release from pellets coated with 2.5% w/w Surelease was therefore monitored for at least 3 months, while being stored at room temperature. Fenoldopam dissolution remained, however, almost unchanged after storage, despite the high amount of succinic acid inside the cores and despite the thin coating level of only 2.5% w/w.

3.5. The release of succinic acid from pellets with various succinic acid to drug ratios

The development of a simple HPLC method to determine succinic acid and fenoldopam together in dissolution media [10], enabled the simultaneous quantification of each of the compounds even at low concentrations.

In Fig. 4 release rates of succinic acid and fenoldopam mesylate are compared for different pellets with a <1:1 or 2:1 ratio of succinic acid to drug. As already discussed, fenoldopam release was either almost complete within 2–3 h, i.e. showing no sustained release for thin coats of 2–3% w/w Surelease, or it totalled in only 30–35% of potential fenoldopam content within 8 h for higher coating levels. This limit of about 30% was also observed by Gabr [6] for another weakly basic drug, despite the incorporation of organic acids, when testing at pH 6.8. In the present work an incorporation of 10% HPMC or 50% HPMCAS HF into the film coat as a pore former could also not improve drug dissolution from high coating levels.

Succinic acid, however, was released at a much more constant and generally higher rate than fenoldopam showing good sustained release properties for the films with pore formers or for 3% w/w Surelease films. While being always faster than the release rates of fenoldopam, the differences between the release rates of succinic acid and fenoldopam mesylate decrease as the succinic acid to drug ratio increases from <1:1 to 2:1.

As the ratio increases, the release rates of both compounds grow more and more similar, despite the different solubility of both compounds, being 1000 times higher for succinic acid in SIF and still 10 times higher in SGF, than for fenoldopam.

As Fig. 5 shows, at a ratio of 5:1 and 6:1 the percentage of succinic acid released from 2.5% w/w Surelease coats is the same as for fenoldopam mesylate, so that both compounds now show identical release rates. For higher ratios of 7:1, 8:1 or 18:1, succinic acid release is slowed down even further, while fenoldopam release shows no further improvement for those higher ratios.

Succinic acid dissolution slows down even for lower coating levels, while fenoldopam dissolution improves especially at higher pH-values, in the presence of increasing amounts of succinic acid. Fenoldopam release is improved and gets more linear, as it matches the dissolution rates of

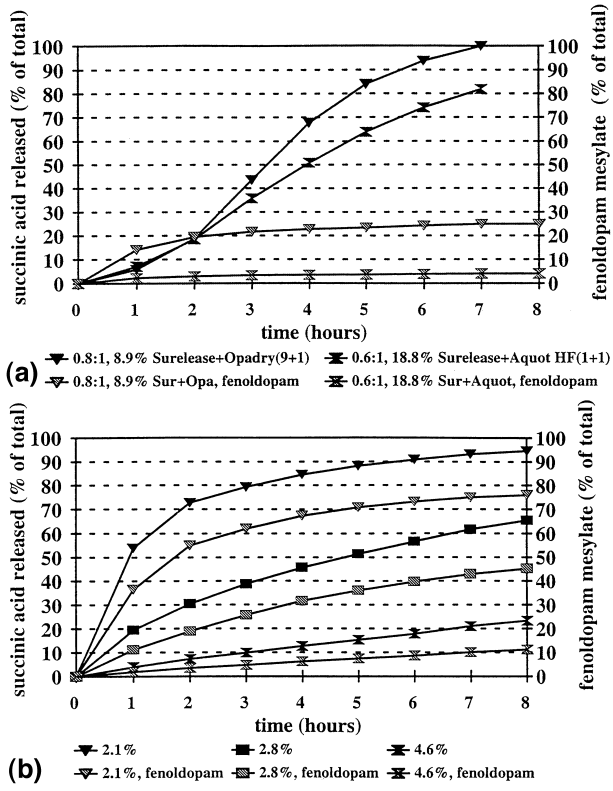

Fig. 4. Comparison of the dissolution rates of succinic acid and fenoldopam mesylate in the standard dissolution test from pellets with a succinic acid to drug ratio of (a) < 1:1; (b) 2:1.

the succinic acid. Both compounds influence each other in their dissolution rates, as they are released together. The succinic acid does not just have to stay inside the pellet cores and maintain an acidic pH-value there, but it has to be released at a sufficiently high amount over time, in order to enable fenoldopam to be released as well. The more succinic acid there is, the higher the percentage of fenoldopam, that is released over the complete testing time. Dissolution ratios were higher for low succinic acid to drug ratios and almost all succinic acid was gone by the end of the test period. For high succinic acid to drug ratios, the dissolution ratio was lower, with almost all of the fenoldopam gone at the end.

In conclusion, high ratios of succinic acid improve fenoldopam solubility inside the core, allowing for a diffusion controlled drug release, while lower ratios of succinic acid cannot achieve this, but show a termination of fenoldopam release at higher pH-values.

3.6. Truly pH-independent fenoldopam release

The next point to investigate, was whether this behaviour of fenoldopam and succinic acid was completely independent of the pH-value of the dissolution media, or whether the discussed dissolution profiles could be only achieved for a 2 h SGF + 6 h SIF test.

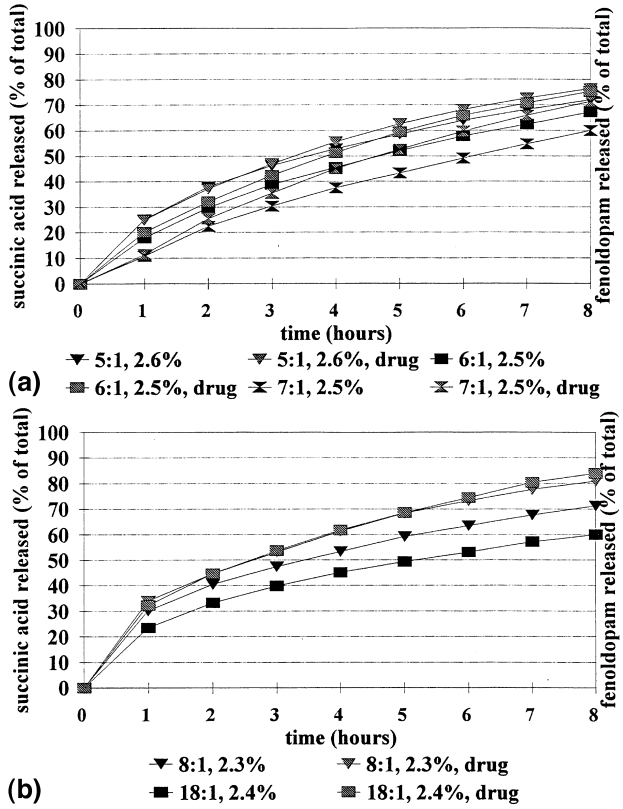

Fig. 5. Comparison of the dissolution rates of succinic acid and fenoldopam mesylate from pellets with a succinic acid to drug ratio of (a) 5:1–7:1 and 2.5% w/w Surelease coats; (b) 8:1–18:1 and 2.5% w/w Surelease coats.

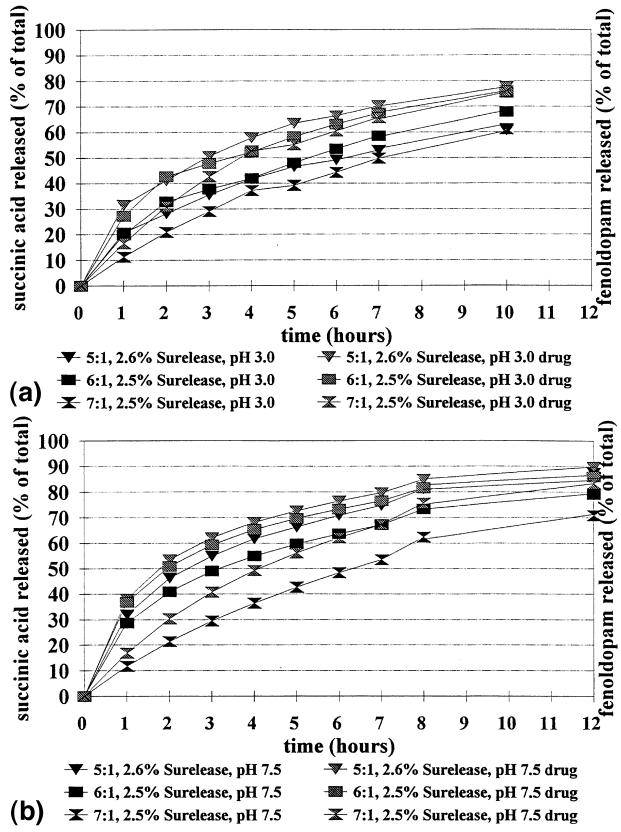

Fig. 6. Comparison of the dissolution rates of succinic acid and fenoldopam mesylate during dissolution tests for pellet batches with 5:1–7:1 succinic acid to drug ratios and 2.5% w/w Surelease coats (as mean of $n = 2$–3); (a) 10 h in buffer pH 3.0; (b) 12 h in buffer pH 7.5.

Gabr [6] reported, that constant dissolution profiles could be achieved only when using a pH-gradient for dissolution testing, while drug release ceased despite the presence of pH-adjusters, when testing in SIF only. For fenoldopam pellets with a succinic acid to drug ratio of at least 5:1, however, similar release rates and profiles were observed irrespective of whether testing only in buffer pH 3.0 (Fig. 6a), where fenoldopam solubility is high, in SIF (Fig. 6b) or for 2 h in SGF and 6 h in SIF. Comparing the actual dissolution rates for both succinic acid and fenoldopam mesylate, a higher overall dissolution was achieved in buffer pH 7.5, where almost 80% of the total fenoldopam had been released within 8 h as compared to 80% released within 10 h in buffer pH 3.0. In both media succinic acid release rates were lower than the drug release rates, even though they were slightly higher in buffer pH 7.5 than in buffer pH 3.0, as would have been expected for an organic acid.

3.7. The uniqueness of succinic acid to improve fenoldopam solubility at a ratio of 5:1

If the favourable release profiles of fenoldopam mesylate are achieved solely by the creation of an acidic micro-pH inside the pellets, other organic acids with low water solubility and sufficient acidic strength, such as fumaric acid or

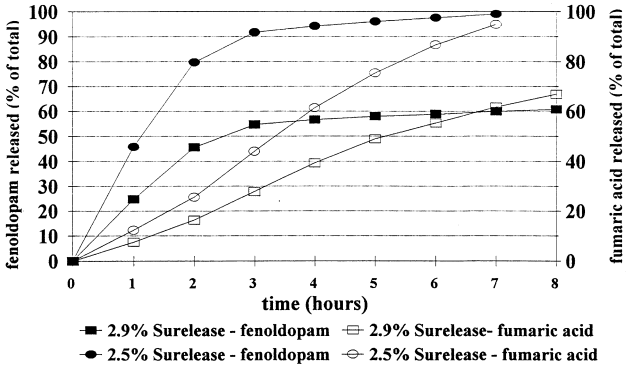

Fig. 7. Dissolution rates of fumaric acid and fenoldopam mesylate from 2.5% w/w Surelease coated pellets with a fumaric acid to fenoldopam mesylate ratio of 5:1.

adipic acid, should be able to achieve a similar fenoldopam release as succinic acid. However, as demonstrated in Fig. 7, fumaric acid, when incorporated at a 5:1 ratio to fenoldopam mesylate was unable to improve drug dissolution at higher pH-values. A 2.5% Surelease coat, showed no sustained release for fenoldopam at all and was thus comparable to the release profiles achieved for thin coats at a 2:1 ratio for succinic acid, even though fumaric acid was released at a rather constant release rate over the 8 h test period. At a higher coating level of 3% Surelease, fenoldopam release persisted in SIF, but showed much lower release rates in SIF than in SGF, and a total release of only 60% in 8 h, as it had been observed for high coating levels and low ratios of succinic acid to drug. Pellets containing adipic acid at a 1:1 ratio and a 10% w/w coat of 80% Surelease + 20% pore former had shown fenoldopam release only in SGF, while no further release had occurred in SIF.

Despite its lower solubility, fumaric acid showed to be less effective in improving fenoldopam dissolution than succinic acid and adipic acid was also unsuccessful in doing so. This indicates, that it is not so much the solubility of the succinic acid, but the succinic acid itself and its amount present and released, that controls fenoldopam release at higher pH-values. While even at high ratios, the release of fumaric acid is independent from the release of fenoldopam, succinic acid and fenoldopam at those high ratios are released together, with the succinic acid release determining the release rate of fenoldopam.

The importance of the 5:1 ratio is further supported by a trial using fenoldopam succinate instead of fenoldopam mesylate as the drug compound. Fenoldopam succinate is a dibasic salt built from 1 mol of succinic acid and 2 mol of fenoldopam.

Two batches of pellets were produced and coated according to standard processing parameters, as described for fenoldopam mesylate.

- Succinic acid/fenoldopam succinate 5:1 (2.2–3.0% Surelease)
- Succinic acid/fenoldopam succinate 1:1 (1.1–4.0% Surelease)

Containing fenoldopam succinate instead of the mesylate, the batch showed an altogether similar release profile at a 5:1 ratio (Fig. 8a). Linearity was, however, inferior to the mesylate batch and total release was only slightly higher than 55%. The dissolution plots for succinic acid and fenoldopam differed to a larger extent than for the mesylate batch, that had shown almost identical release rates for both compounds.

The batch with a 1:1 succinic acid to fenoldopam succinate ratio (Fig. 8b), showed no constant fenoldopam release in SIF, while showing rather high release rates in SGF for thin coating levels of 1.1–1.9%. At higher coating levels fenoldopam release in SGF decreased, but did not continue in SIF, releasing a total of only 35% for a coat of 2.7% Surelease. This goes together with the observations made for succinic acid to fenoldopam mesylate batches at a 1:1 ratio and resembles a typical pH-dependent dissolution profile. Succinic acid on the other hand shows linear, sustained release properties at a coating level of 2.7%.

To sum up those results, the succinate salt did not improve fenoldopam dissolution from pellets and could not increase drug loading at which a linear, pH-independent fenoldopam release is achieved. It therefore seems to require a certain amount of succinic acid (as incorporated in the 5:1 succinic acid to fenoldopam mesylate pellets) to

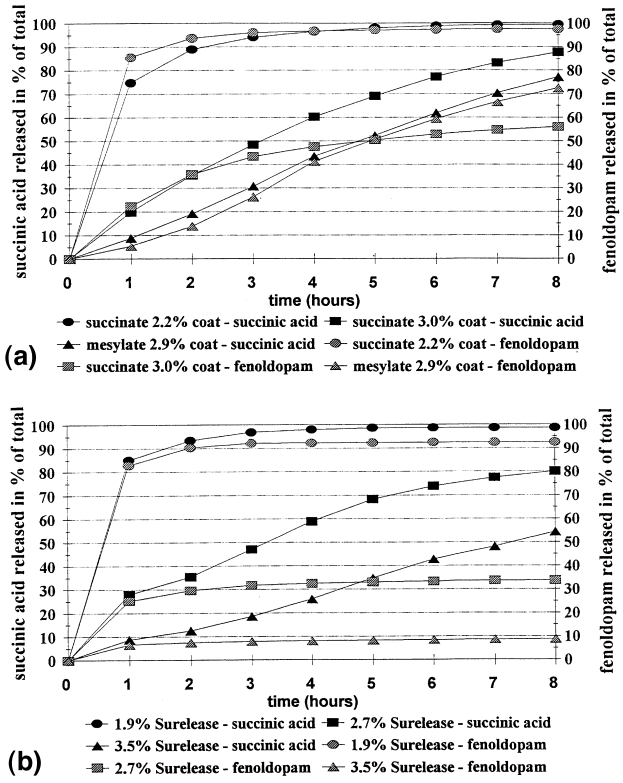

Fig. 8. Drug dissolution from Surelease coated pellets with a succinic acid to fenoldopam succinate ratio of 5:1 (a) and 2:1 (b) in the standard dissolution test.

ensure a pH-independent drug release for this weakly basic compound and high total amounts of drug to be released over an 8 h test. Due to the 2:1 molar ratio of fenoldopam to succinic acid in the fenoldopam succinate, the actual ratio of fenoldopam base to succinic acid is lower for the 5:1 succinic acid to fenoldopam succinate pellets than for the 5:1 succinic acid to fenoldopam mesylate pellets. The dissolution behaviour of the 5:1 succinate batch was therefore also inferior to the behaviour of the mesylate batch.

4. Conclusions

Therefore some other explanation has to be found, to explain the ability of succinic acid at ratios of 5:1–8:1 to improve fenoldopam dissolution at higher pH-values.

The formation of a solid dispersion of fenoldopam in succinic acid or a complex of succinic acid and fenoldopam, where drug solubility is increased even for the free base are possible explanations.

The IR-investigations of pellets with different succinic acid to drug ratios, showed a similar tendency as the dissolution tests, when examining the IR-spectra after the subtraction of succinic acid. While no interaction at all could be found for the 0.6:1 ratio, the 2:1 ratio showed a slight interaction, that was further increased for the 5:1 ratio. Only, for the 8:1 ratio however, this interaction was a major one, dominating the spectrum. The type of these interactions could so far not be established from the IR-investigations, but seems to increase for increasing succinic acid to drug ratios, with a maximum degree for the 8:1 ratio. It thus overlaps with the improvement of fenoldopam dissolution, as the succinic acid to drug ratio increases.

Therefore, the formation of a solid dispersion or a complex of fenoldopam and succinic acid, might be responsible for the improved dissolution rates. A further investigation of this theory would have to include x-ray diffraction measurements, as no signals originating from the crystalline drug should be present in a solid dispersion then.

Acknowledgements

We are grateful to the ‘Fonds der Chemischen Industrie’ for grants to support this work.

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