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Research paper

Simultaneous quantification of released succinic acid and a weakly basic drug compound in dissolution media

Karl Thoma*, Iris Ziegler

Institute for Pharmacy and Food Chemistry, Munich, Germany

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Abstract

A HPLC-method was developed to determine both fenoldopam, a weakly basic drug and succinic acid, a pH-adjuster for this drug in dissolution media. The usual assays for succinic acid were not applicable due to its low UV-absorption, the low pH-value of samples or the presence of buffer salts and fenoldopam. The described method is a simple non-ion-pair reversed phase HPLC-method using a fast scanning UV-detector and a PC software program for the quantification of both components. Succinic acid is detected at 205 nm and fenoldopam at 225 nm. The UV-spectrum is used to determine peak purity and to identify peaks (carried out at a 99.9% match). This is especially important as in some of the investigated samples an unknown peak elutes immediately after succinic acid, resulting in spurious high contents, if mistaken for succinic acid. The simple method accomplished the simultaneous quantification of both, succinic acid and fenoldopam, by an accurate, precise, specific and reproducible assay, with a linear range covering all concentrations relevant for dissolution testing. The method is stability indicating and can also be used for the quantification of fumaric acid, another pH-adjuster in dissolution media together with fenoldopam. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Fenoldopam; Weakly basic drug; Succinic acid; pH-adjuster; HPLC-method; Simultaneous quantification; Stability indicating method

1. Introduction

In order to investigate the role of succinic acid on the sustained release of fenoldopam, a weakly basic compound that has been reported [1] to require the presence of sufficient succinic acid in the pellet cores to maintain drug dissolution irrespective of pH, it was considered important to determine the release of succinic acid itself. Therefore, an assay to quantify both compounds together in the dissolution media was developed.

When using purified water as a dissolution medium, the released succinic acid could be determined by a simple acid-base titration with 0.5 N NaOH, but only, in the absence of fenoldopam mesylate. Fenoldopam mesylate uses up base equivalents and thus interferes with the determination of succinic acid. In SIF USP 23 or SGF USP 23 as dissolution media, titration was also inadequate, due to the buffer capacity of these dissolution media. An enzymatic determination of succinic acid, though highly specific, could not be used either, due to the low pH-values of dissolution media when using SGF and the acidification of samples in the automated dissolution testing system [1], which is necessary to ensure fenoldopam stability. Nor could capillary electrophoresis be used, that provides an excellent assay for succinic acid in water, but not in 0.1 N HCl, due to the extremely high mobility of the chloride ion towards the anode.

A stability indicating HPLC-method [2], that has been used for fenoldopam, was unsuitable since it employs an ion-pair chromatographic method for the determination of the weakly basic compound fenoldopam. In the presence of hexane sulfonic acid, sodium salt, no succinic acid peak

* Corresponding author. Sophienstrasse 10, D-80333 München, Germany. Tel:. +49 89 5902334; fax: +49 89 5902447;
e-mail: prof.thoma@lrz.uni-muenchen.de

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could be detected at any time. Furthermore, UV-detection is difficult, as succinic acid has no double bonds and thus shows an absorption maximum only at a low wavelength of 204 nm. At wavelengths of 200–205 nm, the low frequency noise of HPLC-pumps leads to an increased noise level and a poor quality baseline. This results in a decreased signal to noise ratio and a decreased sensitivity of the detector.

Therefore an alternative, yet simple method was required, that should also be capable to separate possible degradation products and require no purification or dilution of samples prior to injection. As Bodmeier and Chen [3] had used a reversed phase HPLC-method for the determination of carboxylic acids, such as acetic, propionic and butyric acid, a similar method should work for the dicarboxylic acid, succinic acid, while being suitable for fenoldopam as well. The simple method required neither the use of any ion-pair reagent, nor of a column oven, ion-exchange column, or a gradient pump.

2. Materials and methods

2.1. HPLC-methods

2.1.1. Ion-pair HPLC-method for fenoldopam

Isocratic HPLC-pump Waters 6000 A, Autosampler for 49 samples, WISP 712, Integrator Data module, Waters Associates, Milford, MA, USA; Variable wavelength UV-detector, BT 3030, Biotronik, Frankfurt; Beckmann Ultrasphere-ODS 4.6 mm × 25 cm column, 5 μm filling, Beckmann Instruments, San Ramon, CA, USA.

The column had been pre-treated with a 0.1% aqueous solution of 1,4,8,11-tetraaza-cyclotetradecane sodium phosphate monobasic, monohydrate ('Cyclam' Fluka, Neu-Ulm). Methanol gradient grade, hexane sulfonic acid sodium salt, Merck, Darmstadt. Mobile phase: methanol (34 parts) and buffer pH 2.5 (66 parts). Buffer pH 2.5:0.01 M sodium phosphate monobasic, monohydrate, 0.01 M hexane sulfonic acid, sodium salt. Run conditions: flow 1 ml/min; run time: 16 min; detection 225 nm.

2.1.2. Simple, non-ion-pair HPLC-method for fenoldopam and succinic acid

Isocratic HPLC-pump Waters 6000 A, Waters Associates, Milford, MA, USA; Autosampler for 120 samples, TSP, Darmstadt; Fast scanning UV-detector Focus and software package PC 1000, TSP, Darmstadt; PC 486-DX 6–66, 8 MB RAM, OS/2 Warp; Nucleosil 5 C_{18}-ODS column 5.4 × 25 cm, 5 μm filling, Macherey and Nagel, Düren; Methanol gradient grade, Merck, Darmstadt; Sodium phosphate monobasic, monohydrate, Fluka, Neu-Ulm.

Mobile phase: methanol (20 parts) and 0.025 M sodium phosphate monobasic, monohydrate buffer pH 2.5 (80 parts).

Run conditions: flow 1 ml/min; run time: 10 min; detection: scan 200–300 nm (5 nm interval, 1.0 s rise time, 11.08 Hz data rate); injection: 20 μl; bunching factor: 1; peak threshold 0–4 min: 70, 4–11 min: 200; inhibit integration 0–3 min; integration: signal 1 = 205 nm for succinic acid, signal 2 = 225 nm for fenoldopam; report: library match: on, peak purity: on.

Table 1

Chromatographic characterisation of components for the non-ion-pair HPLC-method

Peak	Retention time (min)	Peak symmetry[a]	Relative separation factor between two neighbouring peaks[b]	Peak resolution[c]
Succinic acid	3.2	1.89		
Unknown	3.5	1.87	1.4	1.2
Degradation product	6.6	1.83		
Fenoldopam	8.5	1.61	1.4	3.3

[a] $T = b_{0.1}/a_{0.1}$.
[b] $\alpha = k_2/k_1$ where $k = t - t_0/t_0$.
[c] $R = 2(t_2 - t_1)/(w_2 + w_1)$.
Detection wavelength is 205 nm for succinic acid and unknown, 225 nm for fenoldopam and its degradation product.

Samples from dissolution testing are injected as obtained and pellet samples were dispersed in either buffer pH 2.5 for the stability indicating HPLC-method or in 0.1 N HCl for the non-ion-pair method, after having been ground. They were filtered before being injected.

The chromatographic characterisation of fenoldopam and succinic acid in the non-ion-pair method can be seen in Table 1.

2.2. Dissolution testing

Fenoldopam and succinic acid release from pellets was determined by a novel flow-through dissolution method in its automated version, as described by Ziegler [1]. Release curves are mean values of $n = 3–6$ for a standard test of 2 h in SGF pH 1.2, USP 23 and 6 h in SIF pH 7.5, USP 23. The system operates as an open flow-through method and collects volume fractions for predetermined time periods. The dissolution medium is acidified to a pH of 1–2 by the automatic addition of 0.1 N HCl immediately after having left the dissolution cells, to ensure drug stability. This is necessary due to the poor stability of the drug fenoldopam mesylate at pH-values above pH 5.

2.3. UV-spectroscopy

UV-spectrophotometer Uvikon 810 with PC Anacomp 220 and plotter 800 for automatic scanning of UV-spectra, Kontron, Eching; 0.1 N HCl, Merck, Darmstadt.

Samples from dissolution testing were used as obtained from the automated flow-through system, showing a pH of 1–2, while pellets had to be ground, dispersed in 0.1 N HCl and filtered prior to the assay. Spectra of samples are deter-

mined between 245 and 330 nm. The absorption was calculated as $A = A_{282\ nm} - A_{300\ nm}$, with 282 nm being the maximum and 300 nm the minimum absorption.

$$mg/100\ ml = \frac{A_{282-300}}{A^{1\%}_{1\ cm}} \times 1000 \quad A^{1\%}_{1\ cm} = 84.9 \qquad (1)$$

3. Results and discussion

3.1. Chromatographic system

The described HPLC-method is a simple non-ion-pair method, that employed a standard 25 cm Nucleosil 5 C_{18}-column, UV-detection and a mobile phase consisting of methanol (20%) and phosphate buffer pH 2.5 (80%). The rather hydrophilic mobile phase ensures that succinic acid is retained sufficiently strongly on the reversed phase column. In its protonated form it shows a retention time of 3.2 min and is thus clearly separated from the unretained peak of the mobile phase at 2.4 min. The weakly basic fenoldopam with its relevant p*K*a-values of 9.5 and 8.0 [1] also passes the column in its protonated form, but is still lipophilic enough to show a much longer retention time as succinic acid of 8.5 min. Not being masked by an ion-pair reagent, this retention time is shorter than the fenoldopam retention in the stability indicating HPLC-method, which employs hexane sulfonic acid sodium salt as an ion-pair reagent [2]. The resolution between fenoldopam and its degradation product, however, remains unchanged, despite the shorter total run times of 10 min as compared to 16 min for the stability indicating HPLC-method. Both criteria, the resolution between fenoldopam and its degradation product = 3.3 and the peak symmetry of peaks < 2.5 meet the commonly demanded requirements for good HPLC-systems [4]. A further advantage of this non-ion-pair method is that no conditioning of the column with 1,4,8,11-tetraazacyclo-tetradecane (cyclam) is required prior to its first use [2]. This increases the ruggedness of the whole method, as changes in the retention times of fenoldopam were observed over a time period of 18 months, when using columns that had been conditioned with cyclam [1].

3.2. UV-detection

As a detection wavelength 205 nm was chosen for succinic acid, but 225 nm had to be used for fenoldopam, in order to avoid extremely large and broad peaks, that would deteriorate peak integration. Quantifying each compound at a different wavelength made up for the differences in UV-absorption, but required the use of a multiple-wavelength detector. A fast scanning detector was therefore used, as it enabled not only the quantification of peak areas at two wavelengths, but also provided a complete spectrum for each component, similar to a diode array detector. The detector transmits all signals (linear range = 1.7 V) to a PC, where the software package achieves the integration of all signals, irrespective of the momentary detector range. Therefore, the small signals of succinic acid can be integrated just as precisely as the much larger ones of fenoldopam. Despite the generally decreased detector sensitivity at low detection wavelengths, succinic acid quantification can thus be carried out accurately. As a complete spectrum is obtained from 200–300 nm for each component and run, the computer compares each peak with a library for peak identification. This library contains standard spectra of fenoldopam and succinic acid and only when the correlation between a peak and the library spectrum is better than 99.9% is the peak identified as either fenoldopam or succinic acid. Only peaks with a positive library match are then used for quantification, which further adds to the accuracy of succinic acid detection. The same aim is also pursued by an automatic peak purity analysis for each peak, which requires a peak purity of at least 99.9% for integration and quantification of peaks. The obtained UV-spectra between 200 and 300 nm are used and the first derivations of the spectra at five different peak positions are correlated with each other, after having been normalised.

Fig. 1 shows chromatograms of standards and a sample solution obtained from dissolution testing, that contain both fenoldopam and succinic acid.

3.3. Analysis of samples containing succinic acid

When analysing pellets or dissolution samples of pellets, containing succinic acid and/or fenoldopam, a third peak was often eluted immediately after the succinic acid peak at 3.5 min (Fig. 1c,d), which always showed higher peak areas than the succinic acid peak itself. This unknown peak was never observed in succinic acid or fenoldopam bulk substance, that had been used for the preparation of standard solutions, or in samples of succinic acid, that had been coated in a fluid bed coater with either Surelease or Eudragit NE [1]. In mixtures of succinic acid with Avicel PH 101 or fenoldopam, with succinic acid contents of more than 40%, the unidentified peak was observed, after these samples had been exposed to an energy inducing process, like powder mixing or granulation. It was observed in both uncoated and coated pellets, containing at least 40% of succinic acid and fenoldopam or 40% of succinic acid only. Therefore, its existence cannot be explained by an interaction of succinic acid with fenoldopam, even though it seems to be always present in these pellet batches, that showed good controlled release properties of fenoldopam, while being absent in those batches, that did not.

Apart from the different absorption maxima at 204 and 208 nm, the UV-spectra of succinic acid and the unknown peak show a constant correlation between each other, as demonstrated by the UV-spectra in Fig. 2. The quotient between the two spectra shows a linear relationship for succinic acid and the unknown peak.

Taking all these incidences together, the unknown peak

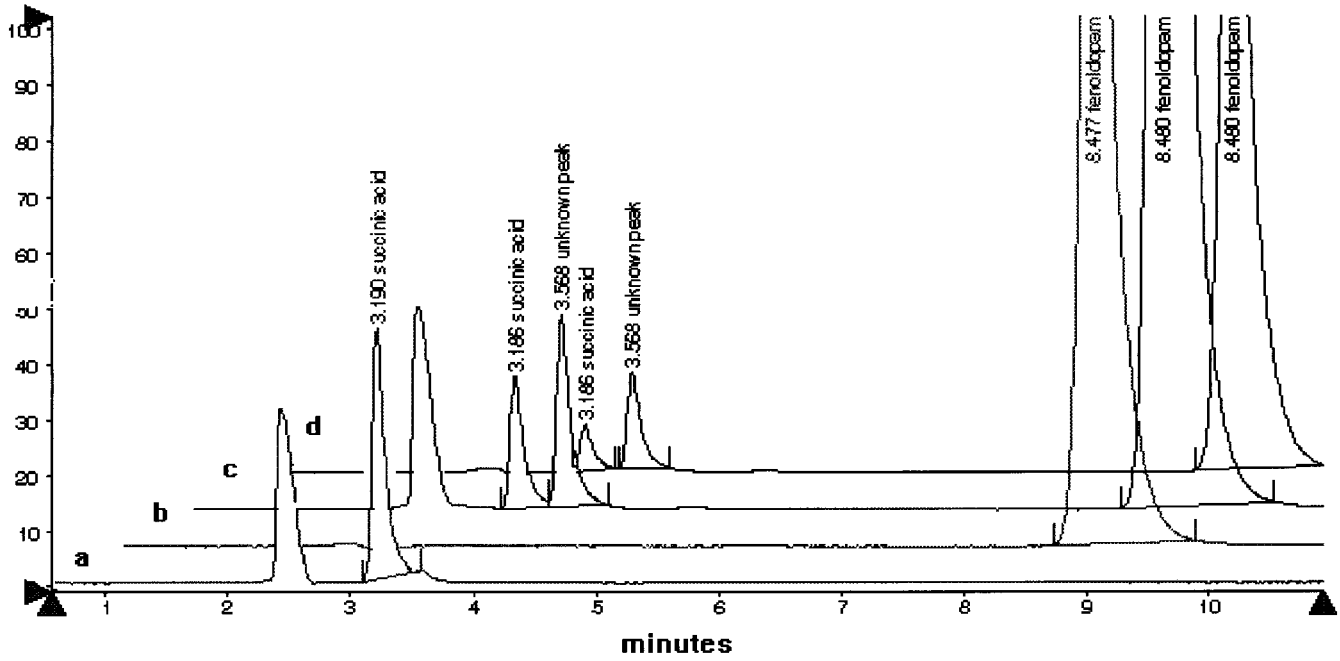

Fig. 1. Chromatograms of (a) succinic acid standard at 205 nm, (b) fenoldopam standard at 225 nm, (c) dissolution test sample for the second hour of dissolution in SGF pH 1.2 at 205 nm, (d) dissolution test sample for the second hour of dissolution in SGF pH 1.2 at 225 nm.

has to derive from succinic acid, when exposed to energy in highly concentrated solutions. The decarboxylation of succinic acid, however, requires temperatures of 290–310°C [5] which does not explain the unidentified peak. The described [6] formation of succinic acid anhydride from succinic acid during the preparation of solid dispersions by the fusion method, appears to be also unrealistic, as such a process includes much higher temperatures as possibly observed during pelletisation, and succinic acid anhydride would probably be hydrolysed back into succinic acid in aqueous solutions. The chemical structure of the unknown peak would therefore have to be identified using e.g. HPLC-MS, NMR or IR investigations. However, succinic acid recovery always exceeded 97%, indicating, that no substantial amount of succinic acid could have been transformed into either product. The large peak areas of the unknown component indicate that it possesses a higher extinction coefficient at the detection wavelengths than succinic acid itself.

As listed in Table 1 peak resolution for these two peaks was only 1.2 and as a limit of 1.25 is usually demanded [4] as an acceptable resolution for quantitative analysis, special care had to be taken in analysing succinic acid in the presence of this additional peak. The library match analysis, however, was able to differentiate between the spectrum of the unidentified peak and the spectrum of succinic acid, despite the apparent similarities. Succinic acid shows a peak purity of 99.99 and the unknown peak shows a peak purity of 99.95, but the library match of this unknown peak with succinic acid is only 97.30 at the peak maximum of 3.563 min and thus worse than the minimum match of 99.9% needed for identification. The unknown peak is therefore not mistaken for succinic acid by the computer.

Sometimes, a shoulder of the succinic acid peak is observed for higher concentrations of succinic acid in standard solutions. This shoulder shows a similar retention time as the unknown peak, but a library match with succinic acid of still better than 99.1 and the same absorption maximum as succinic acid. Furthermore, only 6.9% of that impurity can be detected in a standard solution of 0.43 mg/ml, while peak areas for the unknown peak in a sample solution of only 0.2 mg/ml succinic acid amount to 162% of the area of succinic acid. Therefore the unknown peak is not identical with the impurity of succinic acid present in the bulk material.

To improve the reliability of quantification, neither the unknown peak, nor the shoulder observed at higher succinic acid concentrations are included in the peak areas used for succinic acid quantification.

No interference with any other components present in the samples was observed for the quantification of either fenoldopam or succinic acid. Irrespective of the dissolution medium or the pellet formulation, peak purity was always better than the required 99.9%. Therefore all samples only had to be filtered, but needed neither purification nor concentration prior to injection, which were both necessary for Bodmeier and Chen's method [3]. This allowed the analysis of dissolution samples immediately after the dissolution test without any time consuming procedures.

3.4. Method validation for the quantitative analysis of succinic acid and fenoldopam

In order to rely on the results, the new HPLC-method had

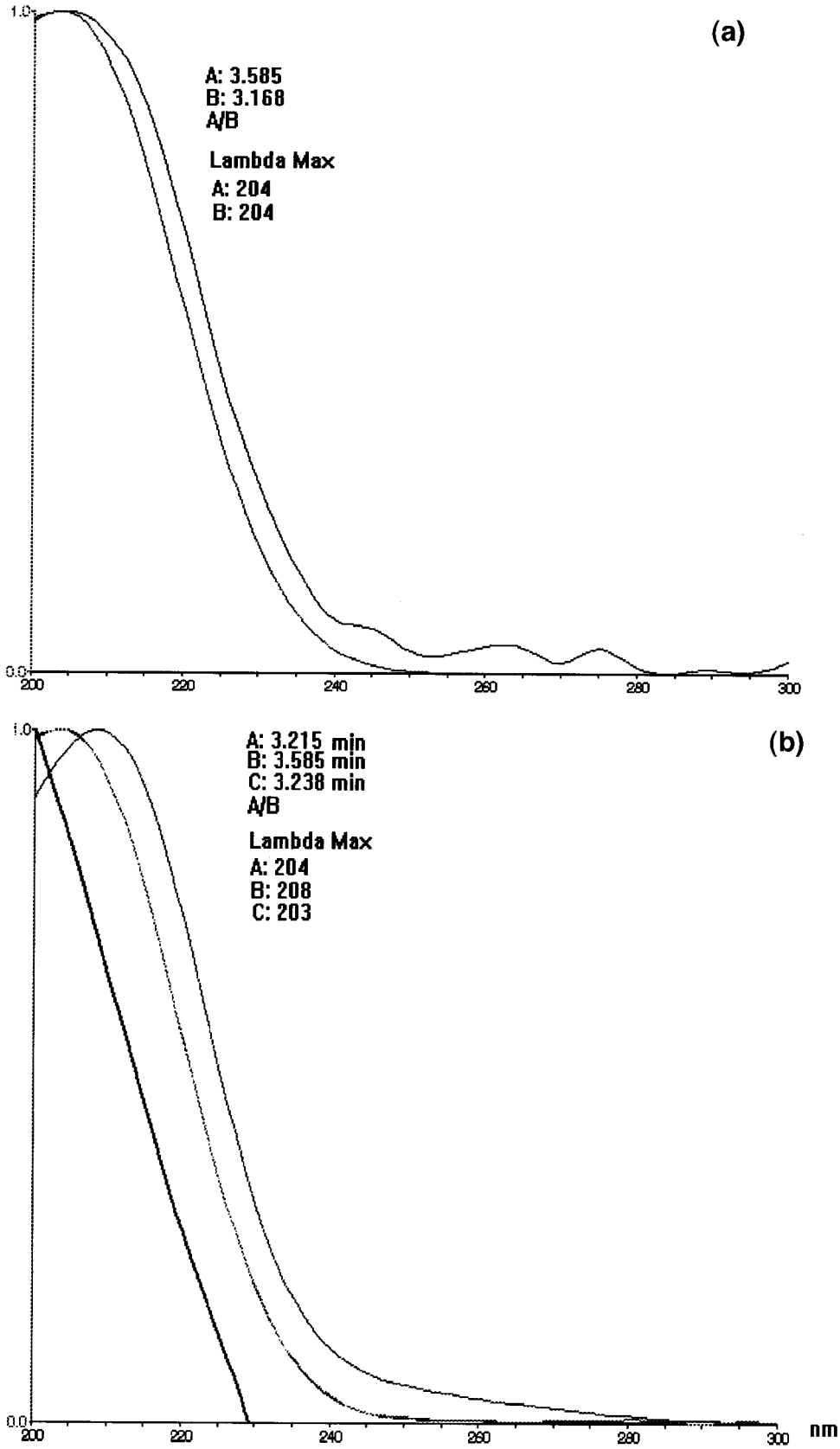

Fig. 2. UV-spectra of HPLC-chromatograms at retention times of 3.2 and 3.6 min; the spectra of the two peaks are compared with the quotient obtained, when dividing the spectrum at 3.2 through the spectrum at 3.6 min. (a) Succinic acid standard solution (0.427 mg/ml); (b) sample solution obtained for the second hour of dissolution testing in SGF for pellets with a succinic acid to fenoldopam ratio of 6:1 and a 2.5% w/w Surelease coat (succinic acid, 0.207 mg/ml).

to be validated for its use in the determination of dissolution samples, that contained fenoldopam and succinic acid.

The validation procedure is principally based on the recommendations of the USP 23 [7] for the validation of quantitative, analytical methods.

3.4.1. Linearity and range of linearity

Linearity and the ranges for linearity were determined for standard solutions of succinic acid or fenoldopam in 0.1 N HCl, as dissolution samples are automatically acidified to a pH of 1–2 in the flow-through dissolution testing system after leaving the dissolution cells [1]. Linear regression analysis was then performed for each compound and the range of concentrations for which a correlation coefficient r^2 of 0.999 or better could be achieved, was determined as the range for linearity. Succinic acid solutions showed a correlation coefficient of 0.9993 for concentrations of 0.05–1.35 mg/ml, while fenoldopam (used as fenoldopam mesylate) could be determined with a correlation coefficient of 0.9999 for 0.008–0.2 mg/ml. Due to its higher UV-absorption, fenoldopam can be determined even at extremely low concentrations, while leaving the linear range for higher ones. As no dilution of samples was intended and sample volumes obtained for 1 h dissolution fractions amounted to 500 ml (including the quantity of 0.1 N HCl required for acidification), these ranges covered drug release rates between 25 and 675 mg/h for succinic acid and between 4 and 100 mg/h for fenoldopam mesylate. Desired dissolution rates for fenoldopam were about 25–35 mg/h as free base (equals 33–46 mg/h fenoldopam mesylate) [8]. In order to ensure constant, pH-independent fenoldopam dissolution, succinic acid has to be incorporated in the pellet cores at a ratio of at least 5:1 (succinic acid/fenoldopam mesylate) [1]. Therefore, the achieved range for succinic acid is capable of covering all possible occurring concentrations during dissolution testing and may also be used for pellet batches, exhibiting lower ratios of succinic acid to drug.

3.4.2. Precision

The precision was determined as the CV of peak areas for 3–4 injections, done at the beginning and at the end of a day, using standard solutions of various concentrations of succinic acid and fenoldopam in 0.1 N HCl. Fenoldopam showed a coefficient of variation of 0.2–0.9%, while it was generally somewhat higher (0.4–1.8%) for succinic acid. Lower succinic acid concentrations showed a higher variation than higher concentrations, whereas the variance of fenoldopam hardly depended on its concentration, as long as it lay within the range of linearity.

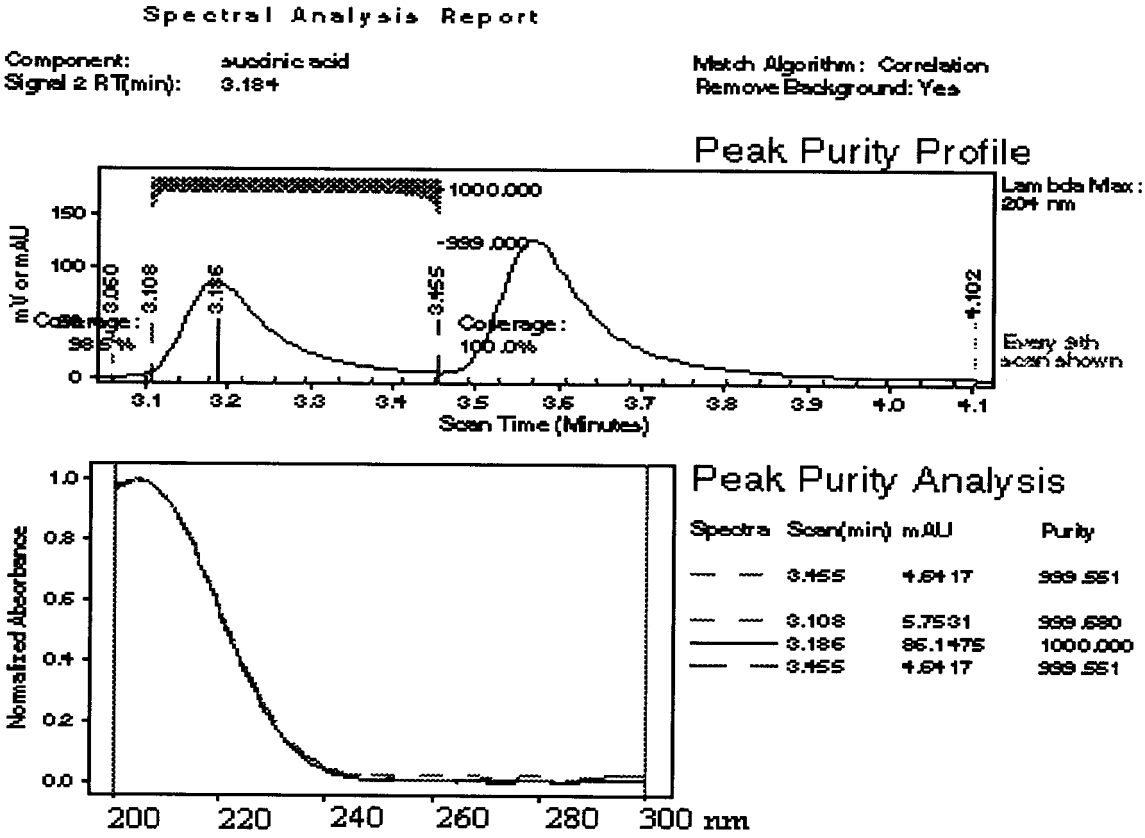

Fig. 3. Peak purity analysis of the succinic acid peak (carried out automatically by the PC 1000 for each peak and run) for a dissolution sample (second hour of testing in SGF pH 1.2) from pellets that contained succinic acid and fenoldopam mesylate pellets at a ratio of 6:1 and were coated with 2.5% w/w Surelease (succinic acid content in the sample, 0.207 mg/ml).

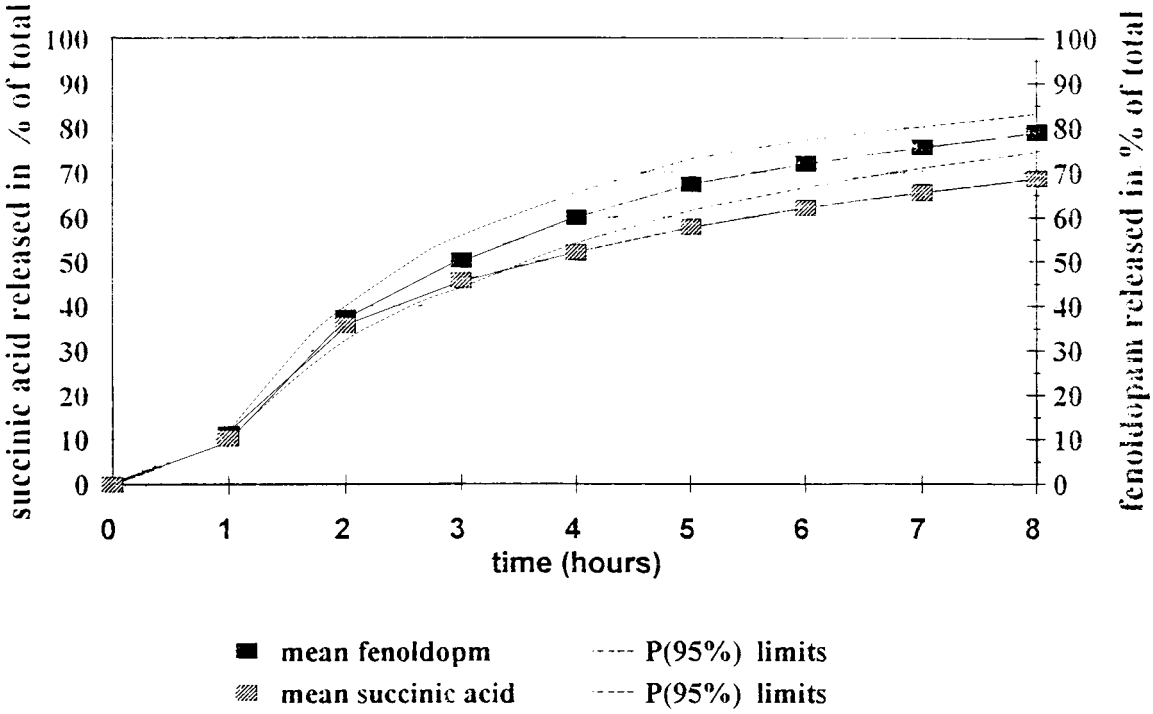

Fig. 4. Dissolution rates of succinic acid and fenoldopam mesylate from pellets with 10% fenoldopam mesylate and 71% succinic acid, coated with 2.5% w/w Surelease; mean of $n = 5$; error bars indicate the SD.

3.4.3. Selectivity

The selectivity of an analytical method is defined as its ability to generate the correct results, without any interference of other components with those results. Other components, that may be present in the sample have to be clearly separated from the component which is to be analysed by the method [6].

As fenoldopam and succinic acid had to be analysed together, assays of standard solutions containing both components were run and the peak areas of both were compared with the areas, calculated from the individual calibration curves for those concentrations. Secondly, the peak purity was determined for both components in the presence of each other and other excipients (e.g. soluble components of sustained release film coatings, sodium lauryl sulphate) and then compared with the peak purity determined from the standard solutions.

The area units of solutions containing succinic acid and fenoldopam together, showed good fits with the calibration curves of the individual components. The results ranged between 97 and 101% for fenoldopam and 98–100% for succinic acid, even though both fenoldopam concentrations were outside the range of linearity. The peak purity analysis, performed automatically for each assay, showed a purity of better than 99.9% for all samples. This is demonstrated in Fig. 3, where peak purity was determined for succinic acid in a dissolution run sample containing succinic acid and the unknown peak. Covering the complete elution time of the peak between 3.108 and 3.455 min peak purity ranged between 99.9551 and 100%. When compared with the purity of the corresponding standard solution the same purity was found for fenoldopam and succinic acid. No deterioration of peak purity was observed, even in the presence of the degradation product of fenoldopam, which was, however, never detected when testing with the novel flow-through dissolution method, ensuring optimal fenoldopam stability [1].

3.4.4. Accuracy

Due to the different requirements for the quantification of both components, assessment of the accuracy of the results had to be done differently for succinic acid and fenoldopam.

For succinic acid, the contents of samples were calculated on the basis of the theoretical composition of pellets and film coats. Theoretical contents were compared with the actual contents obtained when adding up all dissolved drug, together with the amount that remains inside the pellets after dissolution testing. For 64 samples of different pellet batches, the succinic acid contents showed a mean correlation of 97.3% with the theoretical content and a confidence level of ±1.49. Actual contents were thus somewhat lower than the theoretically expected ones, when using only the succinic acid peak at 3.2 min for quantification, which might be due to the existence of the unknown peak at 3.5 min in pellet samples.

For the accuracy of fenoldopam contents, the dissolution rates obtained by the non-ion-pair HPLC-method were compared with the UV-spectroscopic quantification. UV-spectroscopy has shown to provide accurate results for the flow-through dissolution testing of fenoldopam, as demonstrated

for the validation of the dissolution method. The comparison of 224 dissolution samples with high or low concentrations of fenoldopam and succinic acid at various ratios, when tested in different dissolution media over a time period of 6 months, showed a mean correlation of 99.6% for the HPLC-method and the UV-spectroscopic method. The 95% confidence interval was ±0.68 and the correlation coefficient r^2 of the regression analysis between the two methods was always better than 0.999.

3.5. Quantification of fenoldopam and succinic acid in dissolution media

The described method could be used in routine dissolution testing of pellets containing succinic acid and fenoldopam mesylate at various ratios, coated with different coats to sustain drug dissolution. No influence by the components of pellet cores or film coats was ever observed. Fig. 4 shows the good reproducibility of release rates for both, succinic acid and fenoldopam mesylate, when tested in the flow-through dissolution system [1] and quantified by the simple non-ion-pair HPLC-method. Coefficients of variation between different samples $n = 6$ tested at the same time were about 5% for both compounds and thus within the usual variation of release rates determined for different samples of the same batch tested simultaneously in the flow-through dissolution system [1].

4. Conclusion

The described HPLC-method provides a simple, but highly reliable tool to determine fenoldopam and succinic acid simultaneously, even in complicated media such as buffered dissolution media. The validation of the method ensures that only the correct peak areas are automatically calculated for both compounds and no peaks other than the true fenoldopam and succinic acid peaks are used for quantification, even if peak resolution is below 1.25.

The same method might be even applied to determine fumaric acid or other dicarboxylic acids used for pellet formulations with fenoldopam [1].

The unknown peak found in samples containing processed succinic acid seems to be unique for succinic acid, with its existence depending on the presence of succinic acid, but being no impurity of it. Therefore its presence might be connected with the favourable dissolution results, that were observed for fenoldopam at certain high ratios of succinic acid [1]. A further identification of this peak by HPLC-MS and IR might reveal information on the precise nature of this relationship.

Acknowledgements

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