ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
18 (1998) 281–285

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Validation study of the conductometrical analysis. Application to the drug release studies from controlled release systems[1]

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Received 7 November 1997; received in revised form 16 March 1998; accepted 28 March 1998

Keywords: Conductometrical technique; Potassium chloride; Morphine hydrochloride; Naltrexone hydrochloride; Validation study; Inert matrices

1. Introduction

The conductometrical technique avoids extraction and further treatment of the samples and allows a very close study of the in vitro release kinetics. In order to perform the release studies from drug release systems as inert matrices containing water-soluble drugs (naltrexone hydrochloride, morphine hydrochloride and potassium chloride) and water-insoluble excipients (Eudragit® RS-PM), the increase in conductivity due to the dissolution of the drug can be related to the amount of drug dissolved at this time. Therefore, using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and a personal computer, it is possible to quantify the amount of drug released at each time. One of the advantages of this technique is the great number of data provided in time (one concentration datum per second). Therefore, a very close approach to the drug release kinetic is obtained. This analytical technique has already been employed to quantify the amount of KCl (a water-soluble ionic compound) released from inert matrices [1].

In this work, a conductometrical technique to quantify naltrexone hydrochloride and morphine hydrochloride has been validated. Both substances produce much lower increase in conductivity of the solution than KCl. Data obtained from the validation study have been compared to those obtained from a very similar validation study carried out for KCl (an usual standard in conductometry). Furthermore this technique has been used to study the release profiles obtained from naltrexone and morphine hydrochloride controlled delivery systems.

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[1] Presented at the 7th Meeting on Recent Developments in Pharmaceutical Analysis, Island of Elba, Italy, September 16–20, 1997.

PII S0731-7085(98)00180-0

Table 1
Precision values for the quantification of the studied substances

		Mean conductivity	Standard error	Standard deviation	CV (%)
Intra-assay	Naltrexone × HCl	29.44	0.05	0.22	0.74
	Morphine × HCl	34.35	0.02	0.09	0.25
	KCl	231.89	0.51	0.11	0.22
Inter-assay	Naltrexone × HCl	28.93	0.16	0.72	2.50
	Morphine × HCl	33.77	0.12	0.53	1.58
	KCl	230.86	0.75	0.17	0.33

Naltrexone hydrochloride is used as complement to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent, individuals. This drug is a potent narcotic antagonist, 30 to 40 times more active than nalorphine, two to three times more active than naloxone [2,3]. It is a poorly ionic drug with an aqueous solubility value of 85.43 mg ml^{-1} [4].

Controlled release oral morphine hydrochloride compressed tablets offer the clinical advantage of less frequent dosing, with an increase in quality of life for patients with chronic pain requiring repeated-dose opioid analgesia [5].

2. Materials and methods

2.1. Materials

Naltrexone hydrochloride was a gift from Zambón S.A. (E-Barcelona) and Eudragit® RS-PM was a gift from Hüls Española, S.A. (E-Barcelona). Morphine hydrochloride (Alcaliber, E-Madrid) and KCl (Acofarma, E-Barcelona) were also used.

2.2. Experimental procedures

In order to validate the conductometrical

Table 2
Recovery data (mean ± SE, $n = 4$) for the quantification of naltrexone hydrochloride, morphine hydrochloride and KCl

	Concentration (μg ml^{-1})	Mean conductivity	CV (%)	Recovery (%)
Naltrexone hydrochloride	1000	186.19 ± 0.48	0.51	99.04 ± 0.25
	600	114.06 ± 0.16	0.29	100.64 ± 0.15
	300	58.71 ± 0.19	0.64	102.38 ± 0.34
	150	29.34 ± 0.13	0.92	99.79 ± 0.48
	75	15.16 ± 0.04	0.48	98.23 ± 0.26
	50	10.23 ± 0.08	1.56	94.55 ± 0.85
Morphine hydrochloride	1000	215.69 ± 0.85	0.79	99.07 ± 0.39
	600	131.42 ± 0.24	0.37	100.23 ± 0.19
	300	66.64 ± 0.12	0.37	100.73 ± 0.19
	150	34.35 ± 0.02	0.25	102.02 ± 0.06
	75	16.94 ± 0.11	1.27	96.82 ± 0.67
	35	8.3 ± 0.07	1.67	93.37 ± 0.92
KCl	1000	1582.89 ± 0.64	0.22	99.56 ± 0.04
	600	970.69 ± 0.75	0.08	101.61 ± 0.08
	300	448.44 ± 1.08	0.15	101.86 ± 0.23
	150	231.89 ± 0.11	0.44	95.80 ± 0.10
	50	84.76 ± 0.29	0.69	102.35 ± 0.38
	7	12.02 ± 0.17	2.77	74.29 ± 1.50

Table 3
Validation study of the quantification of naltrexone hydrochloride and morphine hydrochloride using spectrophotometrical, chromatographical and conductometrical methods

		Spectrophotometry UV	HPLC	Conductometry
Naltrexone hydrochloride				
Precision (CV%)	Intra assay	0.57	0.34	0.74
	Inter assay	0.41	0.58	2.50
Recovery (%)	Mean	103.57	97.56	99.11
	SE	2.19	0.93	1.11
Morphine hydrochloride				
Precision (CV%)	Intra assay	—	1.40	0.25
	Inter assay	—	2.22	1.58
Recovery (%)	Mean	—	101.05	100.24
	SE	—	0.70	1.21

method proposed for the quantification of KCl, morphine hydrochloride and naltrexone hydrochloride, the following parameters were evaluated [6–8].

The linearity of the conductivity response has been studied for the three substances. The standard solutions were prepared by diluting the stock solution (1000 μg ml^{-1}) with water to the following concentrations: 600, 300, 150, 75 and 35 μg ml^{-1} for morphine hydrochloride; 600, 300, 150, 75 and 50 μg ml^{-1} for naltrexone hydrochloride and 600, 300, 150, 50 and 7 μg ml^{-1} for KCl.

For all the three substances, the precision of the method was studied by analysing solutions containing 150 μg ml^{-1} in 20 replicates (intra-assay precision). Furthermore, these same solutions were analyzed in five replicates on four different days (inter-assay precision). The coefficients of variation (CV%) have been used to estimate the precision of the conductometrical assay.

The accuracy of the method was evaluated by quadruplicate at several concentrations. The recovery data obtained demonstrate the adequate accuracy of the conductometrical method.

The linearity, precision and accuracy were evaluated using standard solutions due to the variability of the drug load of the controlled release systems that could mask the experimental error of the analytical method. The validation studies for morphine hydrochloride and naltrexone hydrochloride were compared to the parameters obtained from a validation study for KCl.

This technique has been used to study the release profiles obtained from naltrexone hydrochloride, morphine hydrochloride or KCl controlled release inert matrix tablets. The inert matrix tablets were prepared by direct compression of binary mixtures drug: excipient at different drug loads. Biopharmaceutical characterization of these inert matrix tablets was carried out using a USP 23 apparatus (Turu Grau, mod. D-6). The dissolution assay was performed at 37 ± 0.5°C in distilled water during 9 h at a constant rotation speed of 50 rpm.

3. Results and discussion

3.1. Linearity

In order to investigate the linearity of the conductivity response, calibration curves are performed for the studied substances. The calibration curve obtained for naltrexone hydrochloride [$y = (0.187 \pm 0.0008)x + (1.42 \pm 0.71)$] using the conductometrical method previously described was linear from 50 to 1000 μg ml^{-1}, giving $r = 0.99996$ as correlation coefficient ($n = 6$) and $F = 48328.2$ as Snedecor ratio ($P < 0.0001$). The regression analysis of the morphine hydrochloride calibration curve [$y = (0.216 \pm 0.0008)x + (1.22 \pm 0.67)$] gave $r = 0.9994$ as regression coefficient ($n = 6$) and $F = 73666.6$ as Snedecor ratio ($P < 0.0001$). These parameters show that the detector

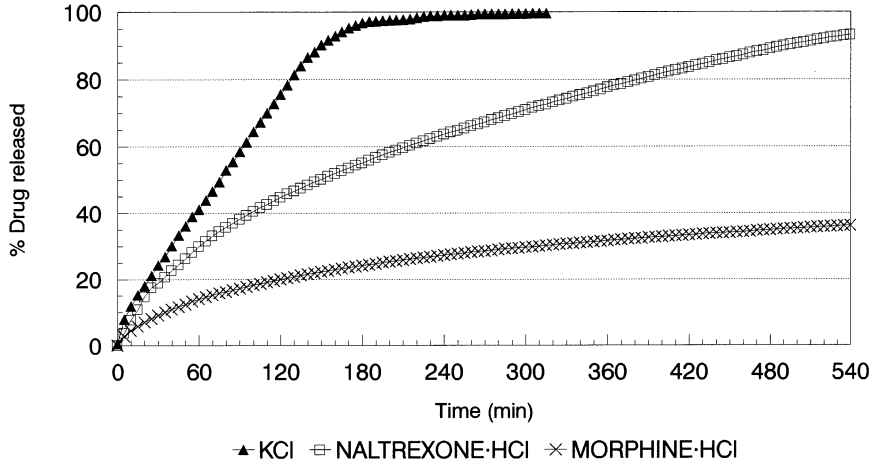

Fig. 1. Release profiles obtained by conductometrical analysis from KCl, naltrexone hydrochloride and morphine hydrochloride controlled release inert matrix tablets (containing 60, 45 and 12% w/w of drug, respectively).

response is linear from 35 to 1000 μg ml^{-1}. The linearity of the conductivity response for the quantification of KCl has been studied from 7 to 1000 μg ml^{-1}. A good linearity has been found from the regression analysis of this calibration curve: $[y = (1.585 \pm 0.0115)x + (3.89 \pm 9.87)]$ with $r = 0.99989$ as correlation coefficient ($n = 6$) and $F = 18967.0$ as Snedecor ratio ($P < 0.0001$).

The linearity shown by the calibration curves for KCl (ionic substance), naltrexone hydrochloride and morphine hydrochloride (poorly ionic substances) was excellent in the assayed concentration ranges.

3.2. Precision

As can be observed in Table 1, the results of intra- and inter-assay precision for the quantification of naltrexone hydrochloride were $< 3\%$. Furthermore, the intra- and inter-assay precision values for morphine hydrochloride were $< 2\%$ (see Table 1). The results show the adequate precision of the proposed conductometrical method for the analysis of morphine hydrochloride and naltrexone hydrocloride. The obtained CVs for intra- and inter-assay precision (see Table 1) were of the same order that those obtained for KCl ($< 1\%$).

3.3. Accuracy

Table 2 shows the recovery data for naltrexone hydrochloride, morphine hydrochloride and KCl; the mean recovery data were 99.11 ± 1.11, 98.71 ± 1.21 and 100.24 ± 1.21, respectively. In all the cases the accuracy of this method is adequate at the concentrations ranges studied. The obtained values were -5.45 and -6.63% for the quantification of naltrexone and morphine hydrochloride, respectively. As it can be observed in Table 2, the conductometrical method for the quantification of KCl showed a linear calibration curve from 7 to 1000 μg ml^{-1}. The accuracy, calculated from the recovery data, was acceptable (-4.2%) for concentrations between the range 50–1000 μg ml^{-1}.

As a summary, accuracy values were acceptable for all the studied substances. Therefore, the conductometrical method evaluated is accurate and precise for an ionic substance such as KCl and for two poorly ionic drugs, in the concentration ranges between 50 and 1000 μg ml^{-1}. This range allows the use of the conductometrical method for the study of the in vitro release kinetic of these drugs. The results of the validation study for the quantification of naltrexone hydrochloride and morphine hydrochloride, using the conductometrical method, are comparable to those obtained

using other usual analytical methods such as HPLC and UV spectrophotometry (see Table 3) [4].

Our proposed technique was applied to quantify all the studied substances during in vitro dissolution assays. The obtained release profiles are illustrated in Fig. 1. The conductometrical technique can be successfully used to study the release kinetics of morphine hydrochloride and naltrexone hydrochloride from controlled release inert matrix tablets containing no soluble excipients such as Eudragit® RS-PM. These matrix compositions, like all other inert matrices, do not interfere with drug quantification. The inert matrix tablets were prepared using only one soluble component, the drug, and a single insoluble excipient. The obtained release profiles show a very low noise that indicates the adequate precision of the analytical method. On the other hand, with a view to the matrices that release all the drug load (KCl and naltrexone × HCl), very low deviation from the theoretical drug content can be observed (99.6 and 93.3%, respectively). This circumstance suggests the good accuracy of the analytical method, as well as the homogeneity of the studied inert matrix tablets.

Acknowledgements

The present paper is part of a research project developed in collaboration with Laboratorios Zambón, S.A. with a grant from the Ministry of Education and Science of Spain.

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