# CONTROLLED RELEASE OF RANITIDINE FROM CONDUCTIVE POLYPYRROLE FILMS

**ORIGINAL SCIENTIFIC PAPER**

*Fehim Korać[1]*, Dinka Muratović[2]*

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[1] Faculty of Science, University of Sarajevo, Zmaja od Bosne 33-35, 71000 Sarajevo, Bosnia and Herzegovina
[1] Faculty of Pharmacy, University of Sarajevo, Zmaja od Bosne 8, 71000 Sarajevo, Bosnia and Herzegovina
*✉ fkorac@pmf.unsa.ba

**ABSTRACT: Incorporation and controlled release of active substances from the conductive polypyrrole films by electric stimulation were investigated. Change of the redox state of the conductive polymer was induced by this stimulation, which allowed the incorporation and release of the drug at different rates. Polymerization of pyrrol on a stainless steel substrate was performed by cycling the potential 40 times in predetermined potential window, after which uniform polymeric film was formed and used as a medium for incorporation and release of the active substance. Stability of obtained films, as well as the electrochemical behaviour of ranitidine hydrochloride was investigated by cycling the potential of the film electrode in 0.9 % NaCl in the same potential window used for the polymerization. Uptake and release of the active substance was performed at constant potential and monitored by chronoamperometry. Although incorporation of the ranitidine hydrochloride was not obvious from the measured infrared spectra, incorporation and release was confirmed and quantified by monitoring the concentration of the active substance in the electrolyte. It was determined that maximum reversible uptake was 351 μg $cm^{-2}$. However, successive potential stimuli did not result in the equal released quantity, as expected for the ideal controlled-release system based on conducting polymers.**

**KEYWORDS: conductive polymers, ranitidine hydrochloride, controlled release**

## INTRODUCTION

It has always been considered that any substance can be seen either as a medicine or as a poison. It is important in all this to have a specific measure or dosage, by which we can manipulate the amount of active substance we need. Dosage, subjectively speaking, has different effects for each person, but each one has different visions and experiences. There are various variations on this subject, namely that the dosage alone depends on the physicochemical characteristics of the drug, the organism and its metabolism, to what extent the drug is dosed and in general how many times a day the drug is administered.

A special concept of administration and release of the drug into the organism has been developed through indirect "vectors", which will allow the release of the required amount of medication at a given time interval. In addition, apart from having a long-term effect and controlling the release rate, multiple administration of the drug is avoided.

In order to achieve such an effect, it is necessary to pack the drug in a particular substance, which will be compatible with it, and which will exhibit such traits that will enable it to be released at the given location. More and more considerations come from polymers, where the drug is incorporated into their structure and as such release into the organism. In recent years, polypyrrole (PPy) is in the focus of many studies compared to other conductive polymers due to its high chemical stability and air stability and simple preparation. Oxidation of pyrrole into polypyrrole can be achieved by using an electrochemical or chemical method, with the addition of strong oxidizing agents ([1] Anuar et al., 2004). It can be easily modified to be more suitable for biomedical applications through the incorporation of bioactive molecules. Polipyrrole also responds to stimuli, enabling a dynamic control of its properties by applying electric potential ([2] Ateh et al., 2006). The need to prepare these materials in various forms in order to enable integration or linkage with other structures, including living beings, is of vital importance ([3] Wallace et al., 2009). Polypyrrole is an electronically conductive polymer with conductivity up to 1000 $Scm^{-1}$, demonstrating its versatile application in batteries, electronic devices, functional electrodes, electromagnetic devices, sensors, etc. It can be manufactured with a large surface, with different porosity or can be easily modified to be more suitable for biomedical applications through the incorporation of bioactive molecules. Polypyrrole also responds to stimuli, enabling dynamic control of its properties by applying electric potential ([2] Aten et al., 2006). These properties are well exploited in potential controlled-release systems based on PPy ([4] Geetha et al., 2006; [5] Alshammary et al., 2016; [6] Thompson et al., 2006; [7] Kontturi et al., 1998) and derivatives ([8] Krukiewicz et al., 2016), while some authors

claimed the preparation of PPy-based chip for controlled release ([9] Ge et al., 2009). Also, some authors addressed biocompatibility of PPy and PPy-based materials, essential for their potential application in biological systems ([2] Aten et al., 2006).
The dosage represents the amount of active substance (drug) administered to a human or an animal. The dose-response and drug effect can be graded and quantal. Drug concentration in body after oral administration can be simplified and presented as concentration-time profile (Figure 1). The rate at which the drug appears in the blood is defined by $t_{max}$, the time at which the drug achieves maximum concentration, and $c_{max}$ or maximum concentration ([10] Mehmedagić, 2002).

In this paper, incorporation of ranitidine hydrochloride into the electropolymerized polypyrrole matrix, and its controlled release was performed by electrochemical transformation of polymeric film. Ranitidine is a non-imidazolyl-blocker of histamine receptors that competitively antagonizes the action of histamine on all $H_2$ receptors, but is mainly used to inhibit gastric acid secretion. Ranitidine is used in the treatment of the following diseases: intestinal sores and stomach ulcers; gastro-oesophageal reflux; erosive esophagitis (http: 1). Ranitidine is administered orally and is well absorbed.

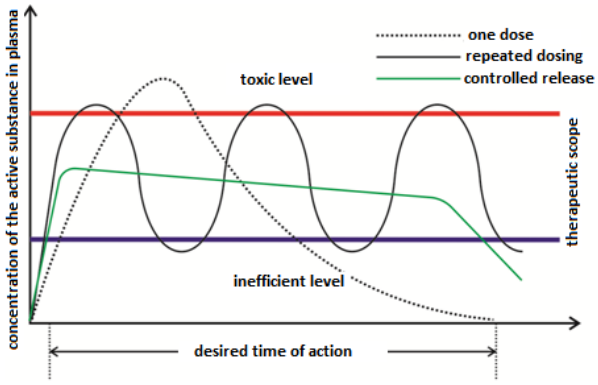


**Figure 1.** Level of active substance concentration in plasma after: one dose, repeated dose, controlled release ([11] Babić, 2015)

## EXPERIMENTAL

Pyrrole, lithium perchlorate and camphorsulfonic acid (CSA) were of analytical grade and obtained from Sigma-Aldrich, USA. Pyrrole was distilled under the reduced pressure prior to use. Ranitidine hydrochloride was of analytical grade and was obtained from Hemofarm, Serbia. Phosphate buffer was prepared as following solution, with analytical grade chemicals: NaCl 8 $gL^{-1}$, KCl 0.2 $gL^{-1}$, $Na_2HPO_4$ 1.42 $gL^{-1}$, $KH_2PO_4$ 0.24 $gL^{-1}$ + redistilled water.

The substrate was made of stainless steel with high content of nickel and chrome. It was used in the form of plates which were coated with Teflon tape in order to achieve the geometric surface area of 2 $cm^2$ exposed to the electrolyte (Figure 2).

**Figure 2.** Stainless steel plate (in the middle)

The polymerization of pyrrole was performed using cyclic voltammmetry in a three electrode system with $Ag/AgCl/KCl_{sat}$ as the reference (0.197 V vs. SHE) and platinum foil (2 $cm^2$) as auxiliary electrode, by cycling the potential 40 times between -0.6 and 0.6 V in 0.05 mol $dm^{-3}$ pyrrole solution with 0.1 mol $dm^{-3}$ camphorsulfonic acid or lithium perchlorate as the inert electrolyte. Stainless steel plate was the working electrode.

Chronoamperometry was employed in order to incorporate the active substance, as well as to release it from the polypyrrole film. All electrochemical experiments were performed with potentiostat/galvanostat PAR 263A controlled by PowerSTEP interface. The argon stream was passed through the cell several minutes prior to the start as well as during the measurement to remove oxygen from the electrolyte. The camphorsulfonate anions were used as large anions, which can be incorporated into the polymer to balance the positive charge caused by oxidation of the polymer during synthesis. After polymerization, the obtained film was washed with redistilled water and left in water until the next treatment. Characterization of polymer films was performed by infrared spectroscopy with Fourier transform using Perkin Elmer Spectrum BX. UV spectrophotometry was used to determine the concentration of ranitidine hydrochloride in the buffered electrolyte after release. In this case a phosphate buffer was used as a blind test. The absorption spectrum in the ultraviolet and visible area was recorded for the active

component dissolved in phosphate buffer. Molar absorption coefficient of the active substance is determined from the slope of absorbance-concentration dependence at the maximum absorbance. Measurements were performed on the UV-Vis ultrasonic spectrophotometer 2000. The cyclic voltammmetry of the active component in the sodium chloride solution was performed to determine the electrochemical behaviour of this substance. Measurements were performed in the previously described three electrode system, where the glassy carbon electrode was used as the working electrode. Measurements were made within the limits of the potential electrolyte window.

**Figure 3.** The prochrome plate after using cyclic voltammmetry

Loading of the conductive polymer film with the active component was performed using a potentiostatic method of highly concentrated aqueous solution (100 g/L) of the active component in the standard three electrode system. Charging of the polymer was performed at a potential of +0.60 V and monitored using chronoamperometry.

Controlled release was performed in the same cell in a small volume of phosphate buffer solution (10 $cm^3$), where the excitation signal was at the potential of +0.55 V. After each signal from the cell, small volume was sampled and analyzed by means of UV spectrophotometry, after which analyzed solution was transferred back to the electrochemical cell for subsequent stimuli of PPy matrix. In addition, another sample of the charged polymer was left for 24 hours in the buffer solution, after which the buffer was analyzed for the content of the active component, in order to determine spontaneous release.

## RESULTS AND DISCUSSION

Figure 4 shows the voltammograms recorded during polymerization of pyrrole in two electrolytes: lithium perchlorate and camphorsulfonic acid. In both cases, voltammograms show the gradual growth of polymer film.

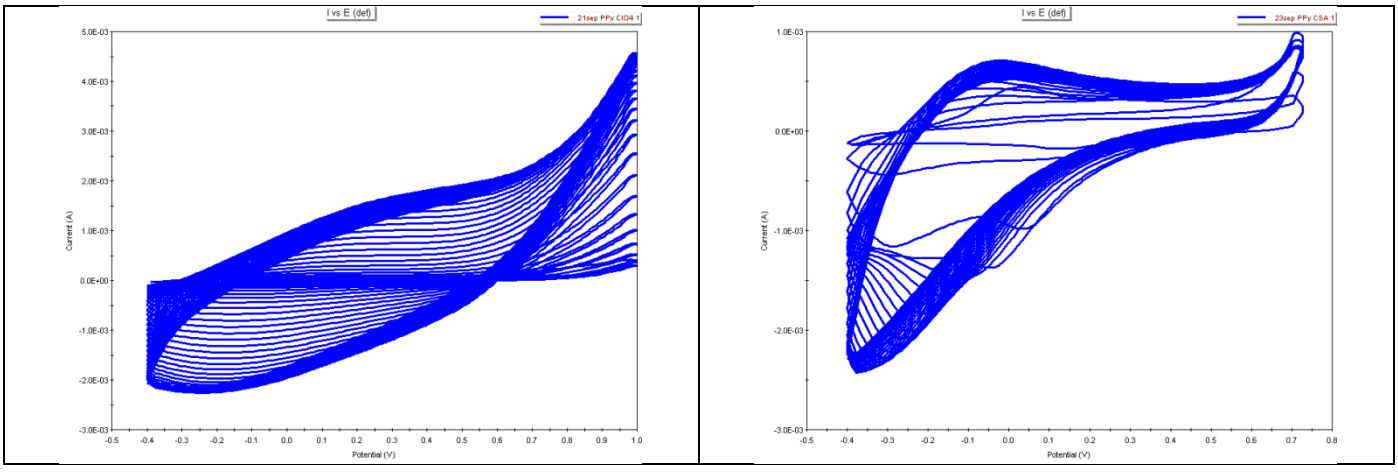


**Figure 4.** Cyclovoltammograms of pyrrol polymerization on stainless steel; left: with $LiClO_4$; right: with CSA as auxiliary electrolyte

However, in the case where the supporting electrolyte is camphorsulfonic acid, it is noticeable that the current peaks induced by the redox transformation of the polypyrrole are considerably sharper and better defined, which is a result of significantly better kinetics of these processes than those in polypyrrole obtained with lithium perchlorate. Since the electronic transfer is a fast process and therefore cannot limit the speed, the reason for the different kinetics of redox transformation in the polypyrrole film lies at different diffusion rates of counter ions (perhlorate or camphor sulfonate) in the mass of the

polymer, which is in accordance with different sizes of these ions. Namely, using a relatively larger camphorsulphonate anion, the formed polymer structure is looser, but also the anion is captured in the polymer structure. For this reason, during the redox transformation of this system, the cation diffusion (in the case of camphorsulfonic acid, $H^+$ ions) becomes the dominant process. This fact represents an important precondition for the incorporation of cationic active components, such as ranitidine.

Figure 5 shows an infrared spectrum of electrochemically prepared polypyrrole with marked characteristic vibration strings.

At 1422 $cm^{-1}$ there are vibrations of C=C elongation of the pyrrol ring. At 1035 $cm^{-1}$ there are N-H vibrations. At 1460 $cm^{-1}$, the asymmetric stretching of the C-C bond was noticeably observed. At 1545 $cm^{-1}$ there is a characteristic peak of the pyrrol ring.

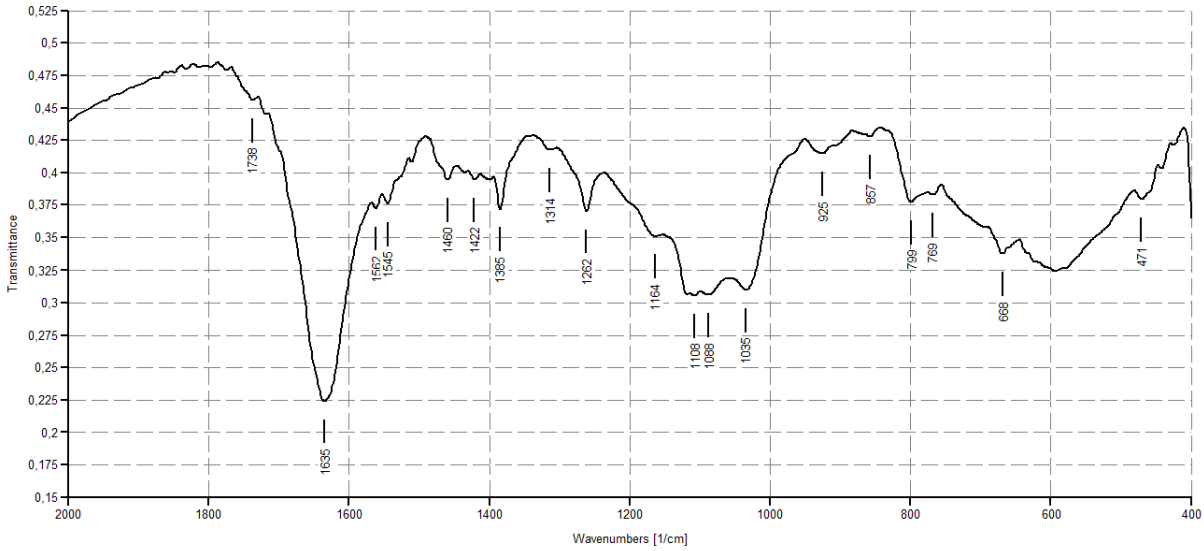


**Figure 5.** Infrared spectrum of polypyrrole

## SPECTROSCOPIC CHARACTERIZATION AND ELECTROCHEMICAL PROPERTIES OF THE ACTIVE SUBSTANCE

Figure 6 shows the absorption spectrum of the active component. Ranitidine hydrochloride has two absorption maxima, at 230 nm and 310 nm.

Figure 7 shows the standard calibration curve, respecting Beer's law in a given range of 0.04 to 0.2 g $dm^{-3}$. When subjected to a regression analysis, the value of the coefficient of regression in ranitidine hydrochloride is the value of coefficient 0.942.

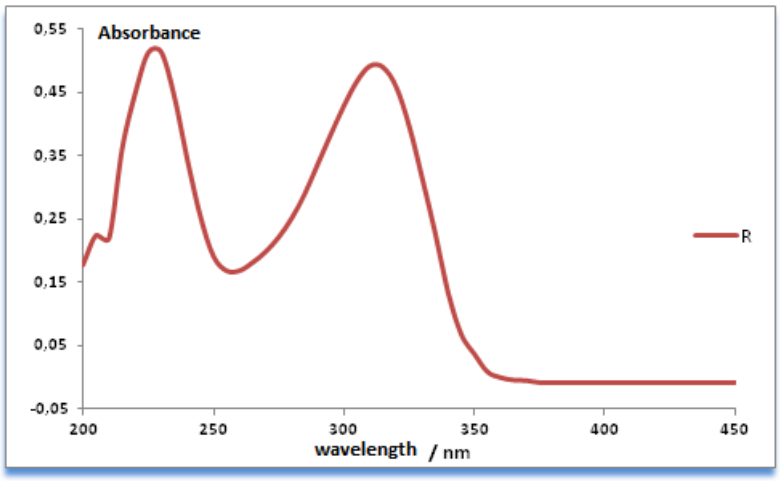


**Figure 6.** The absorption spectrum of ranitidine in the ultraviolet and visible area

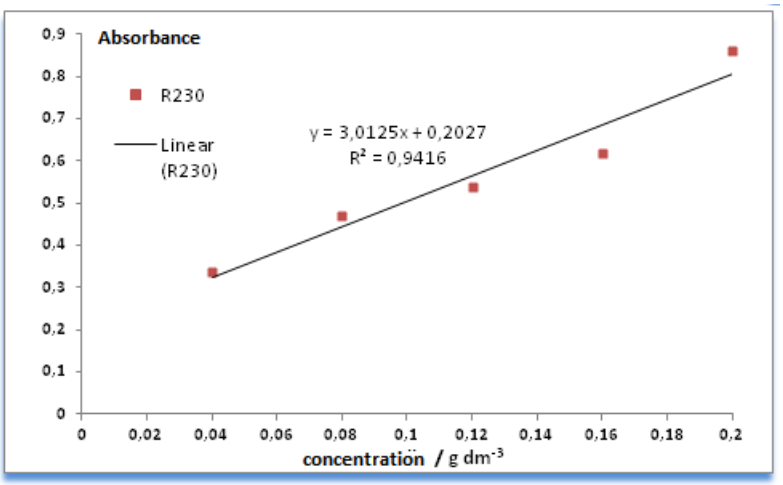


**Figure 7.** The standard calibration curve of ranitidine hydrochloride

Figure 8 shows the infrared spectrum of ranitidine hydrochloride. For ranitidine hydrochloride the following peaks are characteristic: from 3260 $cm^{-1}$ to 3100 $cm^{-1}$ for OH group stretching and symmetrical stretching of N-H peaks, bands around 3066 and 3017 $cm^{-1}$ are attributed to C-H bond of furan which is a part of the chemical structure of the active substance. 2970, 2950 and 2908 $cm^{-1}$ bands are present in the C-H aliphatic group.

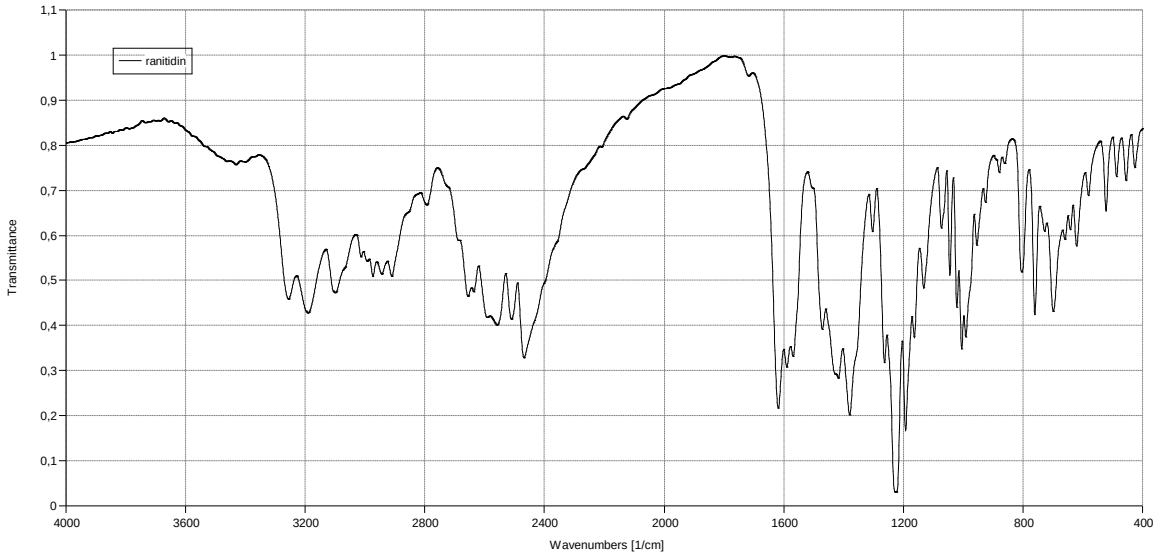


**Figure 8.** Infrared spectrum of ranitidine

Figure 9 shows the infrared spectrum of ranitidine incorporated in a PPy film. Based on this IR spectrum, it is not possible to establish with certainty the presence of ranitidine hydrochloride, and the reason for this may be the low concentrations of the active substances in the conductive PPy film. However, our conclusion that the substance is actually absorbed into the film is based on the fact that the polymer film was oxidized in the solution containing only the active substance (no other counter ion to compensate the charge introduced by potentiostat), as well observation that it is released after the opposite stimuli.

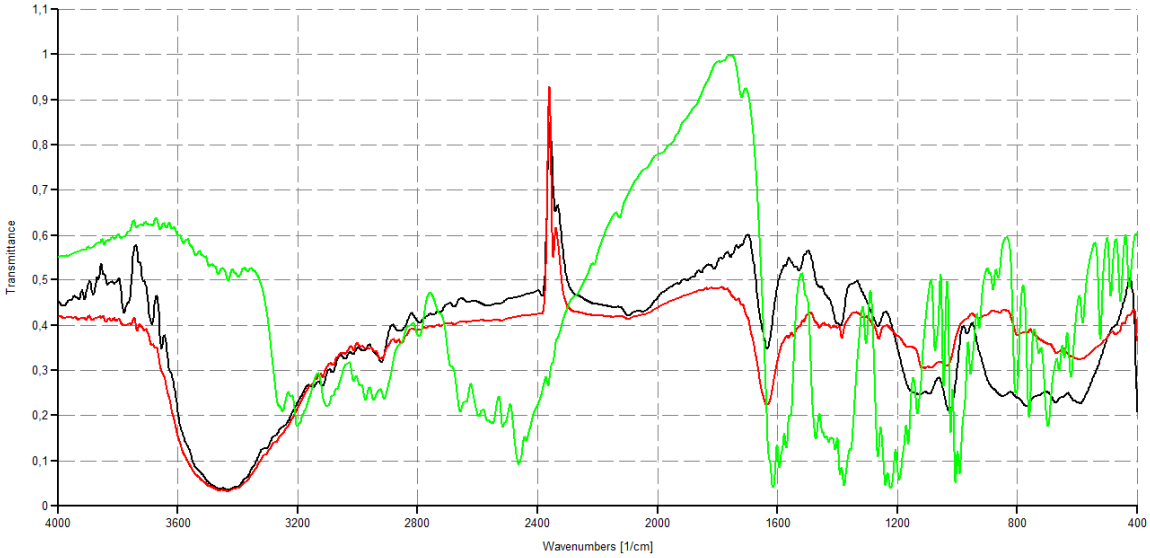


**Figure 9.** Infrared spectrum of ranitidine hydrochloride incorporated in polypyrrole film; the black spectrum - ranitidine hydrochloride and polypyrrole, the red spectrum - polypyrrole spectrum, the green spectrum - ranitidine hydrochloride

## CONTROLLED RELEASE

Figure 10 shows the cyclovoltammogram of the active component in 0.9% NaCl. Given that the measurements worked in a potential window, it is concluded from this data that the active component in this potential range cannot be electrochemically dissolved.

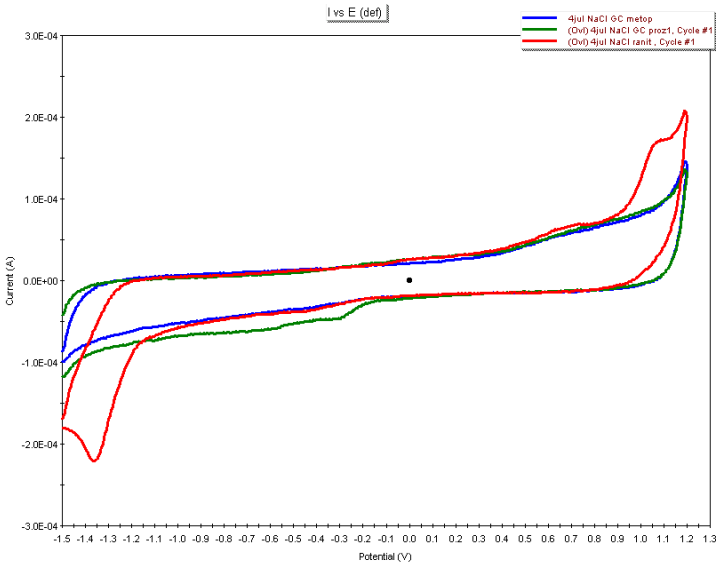


**Figure 10.** Cyclovoltammogram of ranitidine hydrochloride in 0.9% NaCl

Since the loading of polymer film implies its redox transformation, whereby the counter-ions of the electrolyte (in this case, the ions of the active substance) are incorporated into the polymer to maintain its electroneutrality, the amount of incorporated active substance can be estimated from the total charge passed through the electrochemical cell during the charging of the film. This charge is obtained from the chronoamperamograms scanned during film loading (Figure 11), and it amounts to 96.53 mC for ranitidine hydrochloride. Based on Faraday's law:

$$Q = znF, \text{ i.e. } n = \frac{Q}{zF},$$

where z=1, F=96500 C mol$^{-1}$ and Q the above mentioned charge, the estimated incorporated amount of the active substance is $1.00 \times 10^{-6}$ mol or 351 μg ranitidine hydrochloride.

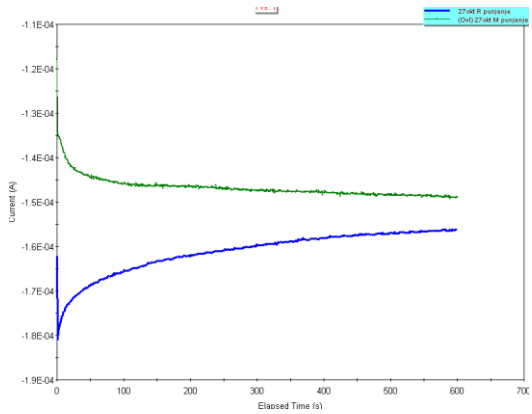


**Figure 11.** Chronoamperogram showing the incorporation of ranitidine hydrochloride into a polypyrrole film at a given time

The release was carried out in a small volume of phosphate buffer (10 $cm^3$) to obtain a concentrated solution for spectrophotometric analysis. Table 1 shows the abundance absorbance values after each excitation signal (1 second), as well as the calculated values of the concentration of the released active substance in the buffer. By measuring absorbance of buffer solution with control samples that were left for 24 h without the excitation signal, it was found that no measurable release of the active substance had occurred. Based on this, using the estimated value of the weight of the drug incorporated, the relative amount of drug release was calculated in percentages, which is also shown in the table. Figure 12 gives graphical representation of data from the table above.

**Table 1.** Controlled release of ranitidine

| Number of excitation signal | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| A | 0.011 | 0.029 | 0.046 | 0.052 | 0.063 |
| $c$ / mmol $dm^{-3}$ | 3.65 | 9.63 | 15.27 | 17.26 | 20.91 |
| $n_{uk}$ / μmol | 36.5 | 96.3 | 152.7 | 172.6 | 209.1 |
| $n_{dif}$ / μmol | 36.5 | 59.8 | 56.4 | 19.9 | 36.5 |
| % released in total | 10.40 | 30.00 | 47.57 | 53.77 | 65.14 |

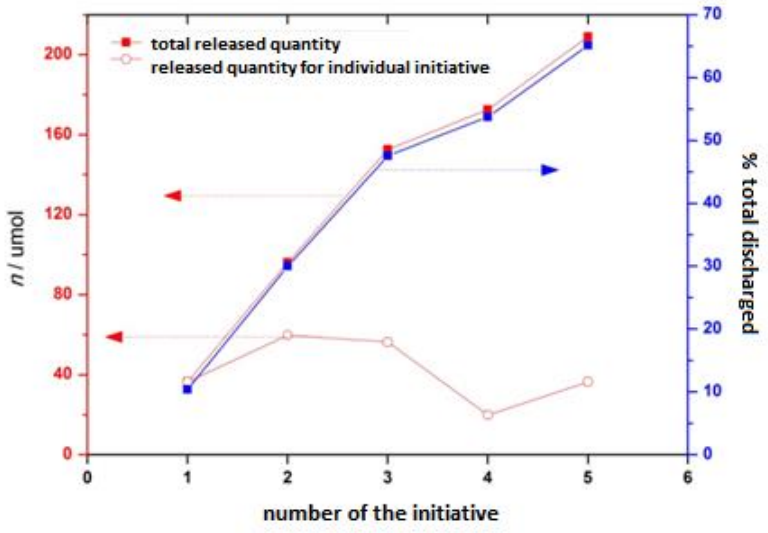


**Figure 12.** Total and individual amounts of released ranitidine and percentage of total released amount in the function of the stimulus

From the data shown above, it is apparent that at each excitation potential signal, a controlled release of the active substance is achieved. It is noteworthy, however, that the released amount varies during successive stimuli, which would ideally be the same (open circles in Figure 12), whereas the total released amount has a steady trend of growth.

## CONCLUSION

From the results of the research it can be concluded:

- that after cyclic voltammmetry, the polymerization of polypyrrole on a thin plate was successfully performed. After 40 cycles over a period of 45 minutes, a unique film was formed, which was used as a medium for incorporating and releasing active substances.
- The use of camphorsulfonic acid as an electrolyte has proven to be a better choice because the bulk anion creates a looser polypyrrole structure, which will allow the recipience of a greater number of anions, which will later be important in the

ion exchange with the active substance (in this case cations).

- Through infrared spectroscopy it was possible to obtain infrared spectra for polypyrrole and the active substance, but after the incorporation of the active substance into the polypyrrole film, spectral spikes could not be read clearly. The reason may be insufficient concentration of the active substance, which on the other hand means a small amount of incorporated active substance in the conductive polypyrrole film.
- Cyclovoltammmetric analysis of ranitidine was also performed in 0.9% NaCl solution within the potential window (potential range in which there is no electrolyte degradation). Based on this it can be concluded that the active substance in the range of these potentials will not be electrochemically dissolved.
- Chronoamperometry can be used to determine the amount of active substance incorporated into a conductive polypyrrole film, following Faraday's law, where for ranitidine hydrochloride amounts to $1.00 \times 10^{-6}$ mole or 351 μg.
- In addition to loading, chronoamperometry was also used for the release of the active substance from the conductive polypyrrole film. Low values of absorbances may indicate low concentrations of the active substance, instrument failure, or much more advanced techniques and materials are needed to enable higher concentrations of active component, as well as their loading and release from the polypyrrole film.
- It is noteworthy, however, that the released amount varies with successive stimuli, which should ideally be the same as the total released quantity has a steady growth trend.

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