Journal of Pharmaceutical and Biomedical Analysis 51 (2010) 244–247

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Correlation between the free volume and the metoprolol tartrate release of Metolose patches

József Papp[a], Virág Szente[b], Károly Süvegh[c], Romána Zelkó[b,*]

[a] Semmelweis University, School of PhD Studies, Budapest, Hungary
[b] University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hogyes Endre Str. 7-9, H-1092 Budapest, Hungary
[c] Laboratory of Nuclear Chemistry, Eötvös Loránd University/HAS Chemical Research Center, P.O. Box 32, H-1518 Budapest 112, Hungary

ARTICLE INFO

Article history:
Received 1 April 2009
Received in revised form 22 May 2009
Accepted 8 July 2009
Available online 15 July 2009

Keywords:
Drug release
Positron annihilation lifetime spectroscopy
Free volume
Metoprolol tartrate
Metolose polymers

ABSTRACT

The correlation between the release characteristics of metoprolol tartrate and the free volumes of Metolose patches containing Metolose 90SH 100.000SR (hypromellose) and Metolose SM 4000 (methylcellulose) of various proportions was studied. Positron annihilation lifetime spectroscopy (PALS) measurements were performed in parallel with the metoprolol tartrate release study to track the free volume changes of patches. Second-order polynomial relationship was found, with good correlation, between the metoprolol tartrate released at the 6th hour, the o-positronium lifetime, indicating the free volume of the polymer, and the Metolose SM 4000 relative proportions. The main reason for this correlation is the change in the free volume size of the polymer patches embedding metoprolol tartrate as a function of the relative proportion of Metolose 90SH 100.000SR containing hydroxypropoxy substitution. Since there were no significant changes between the free volumes of Metolose polymers at any ratio of the constituents in the case of lack of metoprolol tartrate, the free volume changes refer to a possible intermolecular interaction between the polymer and the active agent.

1. Introduction

The application of transdermal patches could be useful in the case of drugs which have to be taken frequently to achieve standard blood level for a long period of time for the expected therapeutic effect. Their application also results in increased bioavailability and in better patient compliance. Transdermal delivery systems usually make for the administrated drug possible to avoid the first-pass metabolism. Despite these benefits they have also some disadvantages, e.g., using TTS (Transdermal Therapeutic System) for the first time a certain period is needed to reach the therapeutic blood level [1–4].

The oral administration of metoprolol tartrate, a widely used hydrophilic therapeutic agent for mild and moderate hypertension, leads to intensive first-pass metabolism and it has a short biological half-life (about 4 h). To avoid the necessity of frequent dosing, the administration can be carried out via transdermal route [5–7].

The physico-chemical properties of cellulose ethers can be changed in a broad-range spectrum depending on their structure. Due to their different degree of substitution of hydroxyl groups, their various chain lengths and their different substitutions, they are suitable for certain applications, such as controlled drug release and film forming. These properties enable their application in TTS systems [8–10].

Authors investigated in their previous work the kinetics of metoprolol tartrate release of Metolose patches as a function of the relative concentrations of hydroxypropoxyl content of Metolose type polymers and the tracking of the possible changes in their free volume distributions by positron annihilation lifetime spectroscopy [11].

The purpose of the present study was to find a correlation between the metoprolol tartrate released at the 6th hour, the o-positronium lifetime values, indicating the free volume of the polymers, and the various proportions of different cellulose-type polymers. Another aim was to compare the free volume changes of patches containing metoprolol tartrate with those of the empty patches as a function of the relative proportion of methylcellulose.

2. Experimental

2.1. Materials and methods

Methacrylate ester copolymer (Eudragit NE 30D) was supplied by Evonik Röhm GmbH (Germany). Metoprolol tartrate USP XXII was purchased from Welding GmbH and Co. (Hamburg, Germany), two types of Metolose (SM 4000 and 90SH 100.000SR) were pro-

* Corresponding author.
E-mail address: zelrom@hogyes.sote.hu (R. Zelkó).

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doi:10.1016/j.jpba.2009.07.011

Table 1
Composition of the prepared patches (%, w/w) on wet and dry basis (w/d).

Sample number	Water (w/d)	Metoprolol tartrate (w/d)	Eudragit NE (w/d)	Metolose SM 4000 (w/d)	Metolose 90SH 100.000SR (w/d)
1	81.89/0.00	5.00/27.61	11.11/61.35	2.00/11.04	0.00/0.00
2	81.89/0.00	5.00/27.61	11.11/61.35	1.80/9.94	0.20/1.10
3	81.89/0.00	5.00/27.61	11.11/61.35	1.60/8.83	0.40/2.21
4	81.89/0.00	5.00/27.61	11.11/61.35	1.40/7.73	0.60/3.31
5	81.89/0.00	5.00/27.61	11.11/61.35	1.20/6.62	0.80/4.42
6	81.89/0.00	5.00/27.61	11.11/61.35	1.00/5.52	1.00/5.52

vided by Mitsubishi Chemical Co. (Japan). Metolose SM 4000 and 90SH 100.000SR differ from each other in their level and kind of substitutions. The methoxyl content of Metolose SM 4000 is in the range of 27.5–31.5%, while in the case of Metolose 90SH 100.000SR, the methoxyl content is lower, 22.0–24.0%, but the latter also contains 8.0–12.0% hydroxypropoxyl groups.

2.2. Preparation of patches

In the first step, 2/3 part of water was heated to 70 °C. Metoprolol tartrate and the two types of Metolose of various proportions were dissolved homogeneously in the hot water. The remaining 1/3 part of the water, stored at 5 °C, was added after homogenizing. This mixture was stirred and cooled and, at room temperature (25 °C), Eudragit NE 30D was added to the system applying a low stirring rate to avoid forming of air bubbles. The ready-prepared mixture was filled into a gum ring of a constant diameter (54 mm). Each sample contained 7.5 g of this mixture. The metoprolol tartrate concentration of the mixture was 5% (w/w) in each sample. The drying of the samples was performed at room temperature for a 3 days period. Each matrix contained 11.11% (w/w) Eudragit NE and 2% (w/w) of Metolose SM 4000 and Metolose 90SH 100.000SR. Table 1 summarizes the composition of the prepared patches.

2.3. Examination of the release of metoprolol tartrate

This test was performed by Hanson SR8-Plus (Hanson Research, Chatsorth, USA) according to Ph. Eur. regulation—Paddle over disk (Ph. Eur. 5.0 Vol. 1. 2.9.4) TTS samples after 3 days of storage were placed into a disk apparatus. Then they were immersed into the temperature-controlled 400 ml acceptor medium (pH = 6.00 buffer solution). The acceptor medium kept at 32 ± 1 °C and mixed at the rate of 25 rpm with rotating pad. Samples were taken at predetermined time points with AutoPlus Maximizer system and an Auto Plus MultiFill collector (Hanson Research, Chatsorth, USA). The sample volume was 10 ml, which was replaced each time. The active content of the samples was determined with an Auto Plus On-LineUV/VIS Autosamples spectrophotometer at 274 nm on the basis of a calibration curve recorded earlier.

2.4. Positron annihilation lifetime spectroscopy (PALS)

PALS is a unique method since it is exceptionally sensitive to the free volume of substances. It is frequently used to determine the size distribution of free volume holes in polymers. All of these measurements are based on the interaction of the free volume holes and the so-called ortho-positronium (o-Ps) atom. In polymers, the formed o-Ps atoms tend to be trapped in free volume holes and their lifetime is associated with the size of the free volume around them:

$$\tau_{\text{o-Ps}} = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \quad (1)$$

where $\tau_{\text{o-Ps}}$ is the o-positronium lifetime, R is the radius of the free volume hole, and ΔR is a constant. Note that the number 1/2 has a dimension, namely ns, in this equation. Consequently, applying Eq. (1), we gain a detailed picture on the size of free volume holes on the basis of o-Ps lifetime [12].

The positron source applied for the measurements was made of carrier free ^{22}NaCl with an activity of 6×10^5 Bq. The active sodium chloride was sealed between two very thin kapton foils. The source was then placed between two pieces of the sample treated identically before. Positron lifetime spectra were recorded by a conventional fast–fast coincidence system. The system was constructed from standard ORTEC electronic units, while the detectors from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 220 ps. The spectra were evaluated into three lifetime components. The two shorter lifetime components (165 ps, 460 ps) are mixtures of different positron and positronium states. As they are too complicated to interpret physically, they were ignored in the evaluations. The longest living positron state is due to ortho-positronium. The lifetime of this positronium state is, in the case of polymers, connected with the size of free volume holes [13]. In general, the longer this lifetime, the larger the holes are.

3. Results and discussion

Fig. 1 illustrates the release profiles of different patches. It can be clearly stated that the higher the ratio of the Metolose 90SH 100 000SR in the patches, the higher the extent and rate of metoprolol tartrate release are. Fig. 2 represents the effect of Metolose SM 4000 relative concentrations on the amount of metoprolol tartrate released at the 6th hour. Along with the increase of the hydroxypropoxy substitution of patches (Metolose 90SH 100 000SR), the extent of drug release also increases. The Metolose structure containing hydroxypropoxyl groups enables the formation of H-bonds which initiates the water penetration through the patches. The expanded swelling increases the size of free volume holes in the film and that, consequently, increase the rate and extent of drug release [11]. As it is obvious from Figs. 2 and 3, the drug release properties and the free volume of the films change similarly. Both the released amount of metoprolol tartrate at the 6th hour and the ortho-positronium lifetime could be described by a second-order

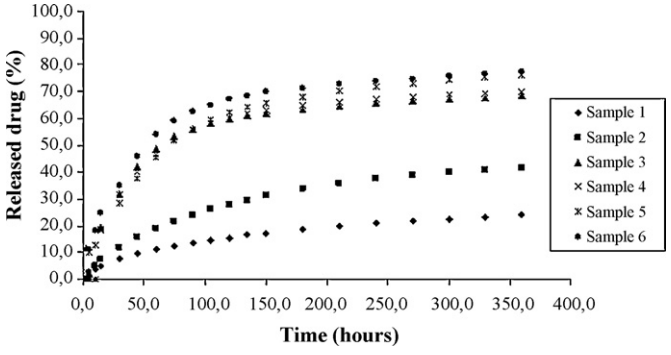

Fig. 1. Metoprolol tartrate release profiles of different Metolose patches. Sample numbers refer to the Metolose SM 4000 relative concentrations in the patches. Sample 1: 100%; Sample 2: 90%; Sample 3: 80%; Sample 4: 70%; Sample 5: 60%; Sample 6: 50%.

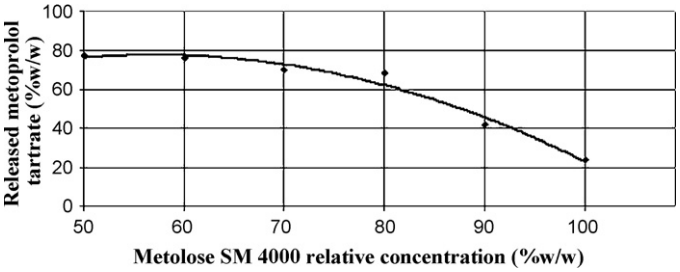

Fig. 2. Metoprolol tartrate released (%, w/w) at the 6th hour as a function of the Metolose SM 4000 relative concentration.

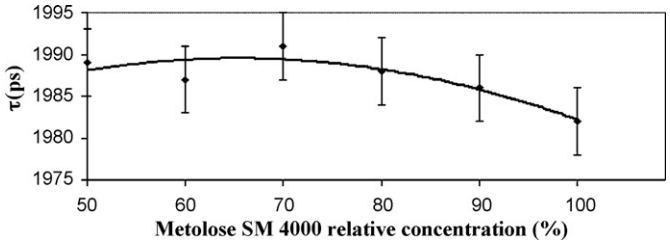

Fig. 3. Ortho-positronium lifetime values of metoprolol tartrate patches as a function of the Metolose SM 4000 relative concentration.

polynomial equation as the function of the relative concentration of Metolose SM 4000 (%, w/w) in the patches:

$$y = ax^2 + bx + c \quad (1)$$

where a, b, and c are constants.

The constants of the polynomial curve were the following in the case of the released metoprolol tartrate vs. Metolose SM 4000:

$a = -0.00296$, $b = 3.3729$,

$c = 18.295$; correlation coefficient $= 0.9857$.

In the case of the ortho-positronium lifetime values vs. Metolose SM 4000, the constants were the following:

$a = -0.00061$, $b = 0.7936$,

$c = 1963.6$; correlation coefficient $= 0.8981$

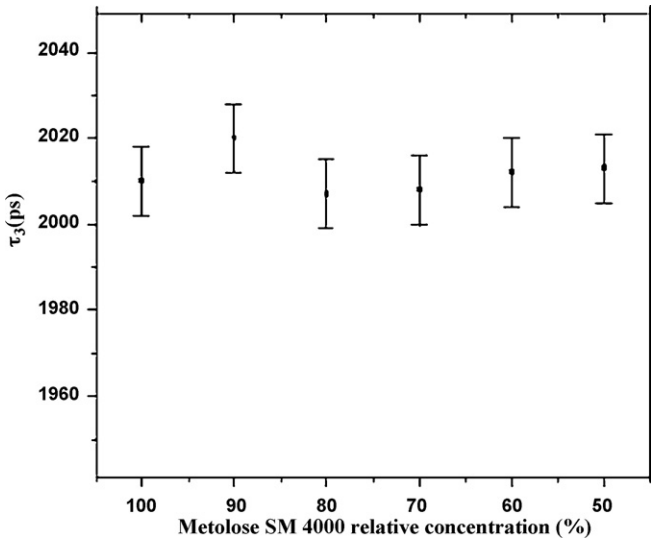

Fig. 4. Ortho-positronium lifetime values of patches as a function of the Metolose SM 4000 relative concentration.

We should note here that the lifetime of o-Ps atoms does not really change in samples containing metoprolol tartrate. The above calculation just shows that positronium lifetime data do not contradict drug release results.

Although positronium lifetime data do not indicate a dramatic free volume change (some tenth of an angstrom at most), their correlation with the drug release properties of the films is obvious. This indicates a very slightly different structure for films containing metoprolol tartrate depending on their Metolose SM 4000 content. To clear this problem, we have studied the same films without metoprolol tartrate. In this case, all of the films were identical from the viewpoint of positron lifetime spectroscopy. All produced the same lifetime of 2010 ps within the statistical error, i.e., all of the films had the same free volume size (Fig. 4). This indicates that the two Metoloses (Metolose SM 4000 and Metolose 90SH 100.000SR) are interchangeable and have a very similar structure. However, the drug encapsulated in them might react differently for the two variants of Metolose. In the case of metoprolol tartrate as a drug, 90SH 100.000SR provides a faster and a more complete release than SM 4000.

4. Conclusions

Metolose SM 4000 and Metolose 90SH 100.000SR produce mixed films that have very similar structures at any ratio of the constituents. However, the incorporated drug may react differently to the two brands of Metolose. In the case of metoprolol tartrate, a clear connection was found between the constitution of the films and their drug release properties. The effect of the Metolose SM 4000 in the patches on the free volume of the polymeric matrix and on the released metoprolol tartrate at the 6th hour can be characterized by a second-order polynomial relationship with good correlation. Positronium lifetime results revealed that the incorporated drug itself might have an effect on the drug release properties of the mixtures. According to our data, the drug, metoprolol tartrate reacts differently to the two kinds of Metolose.

Acknowledgement

A part of the work was supported by the Hungarian Science Found (OTKA) under the grant number of 49815.

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