Preparation and evaluation of metoprolol tartrate patches containing different polymer components

Ph.D. thesis

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Budapest
2012

INTRODUCTION

Transdermal therapeutic systems (TTSs) allow delivery of contained drug into the systemic circulation via permeation through skin layers at a controlled rate. These systems are easy to apply and remove as and when desired. This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long-term dosing to maintain therapeutic drug concentration. Transdermal delivery of cardiovascular drugs offers several advantages, and transdermal forms of nitroglycerin and clonidine have been marketed. Transdermal delivery of one of the common class of cardiovascular drugs, – blockers –, has also been investigated and can offer benefits. Metoprolol tartrate is a selective hydrophilic ß-blocking agent for the treatment of mild and moderate hypertension and also for long term management of angina pectoris. Metoprolol tartrate with hydrophilic character is 95% absorbed and has a bioavailability of 40- to 50% in oral dosage forms. Peak plasma concentrations are achieved after 2–3 hours and half life of the molecule is 3 to 7 hours. This makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for long-term treatment. The n-octanol/water partition coefficient is 0.98 at pH 7.4. Therefore, metoprolol is an ideal drug candidate for transdermal drug delivery, which makes a once-a-day dose treatment possible, thus improving the patient compliance.

Matrix-type TTS could be an appropriate vehicle for sustain-release of metoprolol tartrate. The application of different polymer matrices enables to control the rate and the amount of the released drug. Acrylic polymers (Eudragit) and cellulose ether polymers (Metolose) are often used in pharmaceutical preparations with different purposes, such as binding-, coating- and sealing tablets, and also for retarding the drug release from tablets. Acrylic polymers have good skin compatibility are able to form films. Metolose polymers can also be characterized with good skin compatibility and film forming ability. Applying the casting method they can be ideally combined with each other for film forming. Choose of different types of these excipients enables to influence the drug release rate- and amount from the vehicles containing metoprolol tartrate.

In order to reveal information about the structure of polymer films containing drugs are mainly NMR, X-ray diffraction and thermoanalytical methods applied. The use of atomic force microscopy enables to get much more detailed information about their 3D surface properties. A new promising method for the analysis of polymer films is the

application of positron annihilation lifetime spectroscopy (PALS), which gives valuable data about the supramolecular characteristics of patches with the determination of the sizes and distributions of free volume holes of polymers.

OBJECTIVES

In the literature overview of the thesis I summarized the references which are connected with the transdermal delivery and their applications in the pharmaceutical practice. I gave an overview about transdermal delivery devices, especially focused on the matrix-type ones. I represented the different polymers which were used to form matrices and enable the drug release from the obtained transdermal systems. The kinetic aspect of the controlled drug release in transdermal therapeutic systems is also presented regarding to their drug depot characteristics.
The objectives of the experimental part of my thesis were:

- to formulate patches containing standard amount of metoprolol tartrate and different amounts of polymers, which are official in the European Pharmacopoeia,

- to characterize *in vitro* the metoprolol tartrate release from the prepared patches,

- to analyze the relationship between the drug release and the composition of the patches regarding to the different polymer ratios,

- to evaluate the applicability and reliability of different mathematical kinetic model to describe the drug release from the patches,

- to give a relationship between the drug release and the ability of the polymer matrix to form secondary structures,

- to evaluate in process the patches with appropriate polymer ratio for the desirable drug release by non-invasive FT-IR spectroscopy.

METHODS

Method for preparation of patches

In the first step, 2/3 part of water was heated to 70 ºC. Metoprolol tartrate, the different types of Metolose of various proportions and the different additives were dissolved homogeneously in the hot water. The remaining 1/3 part of the water, stored at 5 ºC, was added after homogenizing. This mixture was stirred until dissolving of the components and afterwards it was cooled. At room temperature (25 ºC) the different acrylic polymer solutions were added to the system applying a low stirring rate to avoid forming of air bubbles.

This preparation method enabled that metoprolol tartrate is completely dissolved before embedded in the matrix and is fully dispersed in the polymer system in the course of the drying process. In the cooling step of the preparation of the patches there is an increase in the viscosity of the solution containing Metolose which makes more difficult to mix it with the polyacrylate solution thoroughly.

The homogenous 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 1.11 % w/w in each sample. The drying of the samples was performed at room temperature for a 3 days period. The further investigations were done after this 3 days period.

For the determination of the incompatibility between the model drug and the polymer matrix forming components I prepared patches and after 3 days of storage in exsiccator with organoleptic observation I chose the macroscopically homogeneous candidates for further examinations. First the thickness of patches was checked and in each formulation was found similar.

Viscosity measurements

The prepared gel formulations at room temperature were filled into the cylinder of the viscosimeter (HAAKE VT550 Rheometer, Haake GmbH, Karlsruhe, Germany). The measurements were done at 25 °C. For the evaluation the balance viscosity values of

each formulation (n=3) were taken. The viscosity – time curves were recorded with the following parameters: disc SV2, G= 50 1/min, measurement time was 15 min.

Optimization of composition according to the drug liberation examinations

This test was performed by Hanson SR8-Plus (Hanson Research, Chatsorth, USA) according to Ph. Eur. regulation – Paddle over disk. 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 with the equivalent of dissolution medium. The active content of the samples was determined with an Auto Plus On-Line UV/VIS Autosamples spectrophotometer at 274 nm on the basis of a calibration curve recorded earlier.

Analysis of the release profiles according to different kinetic models

Different mathematical models were evaluated considering the drug release profiles of the patches. The non-linear parameter estimation of the release models applied for matrices was made with the Solver function of the computer package Microsoft Excel 5.0.

FT-IR examinations

FT-IR spectra of the cast film patches were obtained using a JASCO FT/IR-4200 spectrometer in 4000-400 cm^{-1} wavenumber range. 32 scans were performed at a resolution of 4 cm^{-1}. The system was operated in the transmission mode. Spectra Analysis software was applied for the determination of the peak area within the wavenumber range of 1757.7-2811.8 cm^{-1}.

Non-invasive stability screening of patches with ATR-FTIR examinations

The prepared matrices with and without metoprolol tartrate were stored 1 month at 40±2 °C and 75±5% relative humidity in open container.

The ATR-FTIR spectra of the stored patches with and without metoprolol tartrate samples were scanned over wavenumber range of 4000–600 cm^{-1} using Able Jasco FT-IR 4200 type A spectrometer with ATR Pro470H single reflection ATR accessory. 32 scans were performed at a resolution of 4 cm^{-1}.

Positron annihilation lifetime spectroscopy (PALS)

Positron annihilation lifetime spectroscopy (PALS) is a unique method since it is exceptionally sensitive to the free volume. 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 atoms.

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 200 picoseconds. The spectra were evaluated into three lifetime components, from which the longest one is suitable for the determination of the average size of the free volume holes.

RESULTS

According to the results of the preformulation examinations and of the drug liberation, we found that the application of Eudragit NE 30 D, Metolose SM 4000 and Metolose 90 SH 100.000 SR can be used for preparing matrix type patches containing metoprolol tartrate.

Viscosity data showed, that the application of metoprolol tartrate in smaller concentrations has effect on the viscosity in the case of both cellulose polymers. It leads at low concentration level of Metolose 90 SH 100.000 SR to small increase of viscosity and at low concentration level of Metolose SM 4000 it tends to lower the viscosity of the solution. The application level of Metolose 90 SH 100.000 SR increases much more intensively the viscosity of the solution, which results in a lower application level of this polymer for preparing the patches. On the grounds of the viscosity measurements and the empirical experiences, Metolose 90 SH 100.000 SR can be applied up to 1.0% w/w, Metolose SM 4000 can be used up to 2.0% w/w for the preparation of the patches.

According to the drug release profile of the patches the water insoluble, pH independent, water swellable, and water permeable Eudragit NE 30 D enables the barrier function of the homogeneous polymer composite. Since the concentration of the Eudragit NE 30 D was kept constant in each patch (6.67% w/w on wet basis), the drug release profile was controlled by the various proportions of water soluble Metolose SM 4000 and Metolose 90 SH 100.000 SR. No lag-time ($t_0 = 0$) values were detected.

The extending ratio of Metolose 90 SH 100.000 SR enables higher extent of metoprolol tartrate release, which indicates that the presence of the hydroxypropoxyl groups in the polymer matrix facilitates and controls the drug release. The increased ratio of the hydroxypropoxyl groups had no significant effect on the value of the shape parameter (β). Since the β values were within 0.42 and 0.59 in the case of each patch, the metoprolol tartrate release followed Fickian diffusion. Hydroxyl groups are able to form H-bonds with the water while methoxyl groups are not. This explains the change of drug release profile of the studied polymers. The higher the proportion of Metolose SM 4000 in the patches, the less the interaction between the water and the polymer is. The formation of H-bonds, consequently the water penetration through the polymeric patch is more supported with the application of Metolose 90 SH 100.000 SR thus increasing

the extent and rate of metoprolol tartrate release from the patches. The initial slower release refers to the formation of H-bonds due to the swelling process.

The presence of metoprolol tartrate can be identified primarily with the characteristic peak at 1507 cm^{-1} which could refer to the CO_2 asymmetric stretching in the molecule. This peak can be identified in all samples containing the drug. The most characteristic peak of the patch can be found at 1726 cm^{-1}. This peak can be also identified in each formulation. After 1 month of storage, neither in the spectra of patches containing metoprolol tartrate nor in those without the active agent any other peak could be identified. The results enable quick non-destructive stability screening of patches.

FT-IR spectra in the transmission mode show an increase of the transmission values of the characteristic peaks along with the Metolose 90 SH 100.000 SR content. This phenomenon can be described with the microstructural changes of the patches via H-bridges with the OH groups of Metolose 90 SH 100.000 SR. Since no extraneous peaks were found, the spectra are masking-like and feasible to make quantitative analysis due to their positions in the analytical wavenumber range. This non-invasive quantitative analysis of patches is based on the determination of the AUC values measured within the characteristic wavenumber range.

Linear relationship was found with good correlation between the area under the peak values of the FT-IR curves of Metolose containing patches measured within the wavenumber range of 1757.7-2811.8 cm^{-1} and the log $\tau_{63.2}$ values (y) of metoprolol tartrate release.

On the basis of our results, the application of FT-IR measurements can be recommended as a useful non-destructive means during the in-process control of patches.

PALS spectroscopy data showed that the o-Ps distributions are shifted towards higher lifetimes in patches, which contain greater amount of Metolose 90 SH 100.000 SR. However, there is no significant difference between the free volume sizes of the different compositions. The microscopic and macroscopic porosity in the different patches increased with the increased amount of Metolose 90 SH 100.000 SR, which leads to increased permeability, thus resulting in faster initial rate and higher extent of drug release.

The released amount of metoprolol tartrate at the 6. hour (% w/w) and ortho-positronium lifetime (τ, ps) values could be described with the following polynomial equation as a function of the relative concentration of Metolose SM 4000 (% w/w) in the patches containing 2% w/w Metolose polymers:

$$y = ax^2 + bx + c$$

where a, b, 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
R^2 = 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
R^2= 0.8981

The effect of the relative concentration of the Metolose SM 4000 in the patches on the free volume of the polymeric matrix and on the released metoprolol tartrate at the 6. hour can be characterized by a polynomial relationship with good correlation. This relationship helps to design therapeutic systems of predicted drug release.

Although positronium lifetime data do not indicate a dramatic free volume change, 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 and Metolose 90 SH 100.000 SR ratio. To clear this problem, the same films without metoprolol tartrate were also studied. 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. This indicates that Metolose SM 4000 and Metolose 90 SH 100.000 SR 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, Metolose 90 SH 100.000 SR provides a faster and a more complete release than Metolose SM 4000.

NEW SCIENTIFIC RESULTS

- Eudragit and Metolose based patches containing metoprolol tartrate were created with different ratios of the applied polymers to evaluate the drug liberation from the different compositions.

- As a result of the pre-formulation work I determined which polymers from the different types of Eudragit and Metolose enable the formation of TTS patches containing metoprolol tartrate. The combination of Eudragit NE 30 D and different Metolose polymers resulted in novel composition which enabled the formation of TTS patches.

- The supramolecular structural elements, connected via H-bonds, strongly influenced the drug release from the patches. The changes of the supramolecular structure were sensitively tracked with positron annihilation lifetime spectroscopy. The latter enabled the visualization of the free volume changes as a function of the polymer composition.

- The different ratio of Metolose SM 4000 and Metolose 90 SH 100.000 SR could sensitively control the release extent and kinetics of metoprolol tartrate from the patches.

- Eudragit NE 30 D enables the barrier function of the polymer composite, while the drug release profile was controlled by the various proportions of water-soluble Metolose SM 4000 and Metolose 90 SH 100.000 SR.

- The effect of the relative concentration of the Metolose SM 4000 in the patches on the free volume of the polymeric matrix and on the released metoprolol tartrate after the 6. hour can be characterized by a polynomial relationship with good correlation.

- FT-IR spectroscopy was successfully applied as a quick non-destructive method to monitor the stability of intact patches in the course of storage.

- Linear relationship was found with good correlation between the area under the peak measured within the characteristic wavenumber range of the FT-IR curves of Metolose containing patches and the log $\tau_{63.2}$ values of metoprolol tartrate release. The application of FT-IR method enables the fast non-invasive in process control of patches of required drug release profile.

LIST OF PUBLICATION

Publications

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Lectures

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ACKNOWLEDGEMENTS

This thesis was created with the help of my tutor, Professor Sylvia Marton (Department of Pharmaceutics, Semmelweis University). I am greatly thankful about her guiding and supporting with her knowledge. I am also very grateful for providing me the opportunity to work in the institute.

I am greatly indebted to Professor Romána Zelkó for her energy and unselfish support in my thesis. The discussions and collaboration during the work will always stay in my memory.

Furthermore, I express my special thanks to Dr. Gabriella Csóka, whom with I was introduced into the pharmaceutical practice. The participation of Pálné Reimann in my practical work was very inspiring.

I am very thankful to Dr. Károly Süvegh for the PALS analysis. *I am grateful to my parents and family.*