International Journal of Pharmaceutics 392 (2010) 189–191

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Correlation between the FT-IR characteristics and metoprolol tartrate release of methylcellulose-based patches

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ARTICLE INFO

Article history:
Received 26 January 2010
Received in revised form 22 March 2010
Accepted 27 March 2010
Available online 3 April 2010

Keywords:
Methylcellulose
Hypromellose
Metoprolol tartrate release
Transdermal patch
FT-IR spectroscopy

ABSTRACT

The aim of the present study was to investigate how the drug release and FT-IR characteristics of metolose patches were influenced by the changes of Metolose SM 4000 (methylcellulose) and Metolose 90SH 100.000SR (hypromellose) proportions.

FT-IR spectroscopy measurements were performed in parallel with the metoprolol tartrate release study to track the effect of the composition on the drug release. The metoprolol tartrate release profile of the patches was evaluated by Weibull distribution. Linear relationship was found with good correlation between the logarithm of time interval necessary to release 63.2% of metoprolol tartrate (τ_d values) and the peak area measured within the characteristic FT-IR wavenumbers of patches. The application of FT-IR measurements can be recommended as a rapid, non-destructive screening method during the in-process control of patches.

1. Introduction

Transdermal patches have many advantages in the case of drugs which have to reach a standard concentration in the circulating system for a longer period of time to achieve their therapeutic effect. These TTS systems have gained more importance also in the application of drugs which have to avoid first pass metabolism (Aqil et al., 2004, 2007).

In this work we investigated metoprolol tartrate, a selective hydrophilic β-blocking agent for the treatment of hypertension. The pharmacological properties of this drug – intensive first pass metabolism and short biological half-life (4 h) – show that the transdermal application is more preferred than the oral administration (Ganga et al., 1996; Bhatt et al., 2008).

Cellulose ethers can be applied in the pharmaceutical technology with different chain length, different substituents and different degree of substitution of hydroxyl groups which result in different properties, which can be applied in the forming of films with controlled drug release (Vueba et al., 2004, 2005; Baumgartner et al., 2005; Conti et al., 2007; Ferrero et al., 2008). In the formulation of TTS patches different polymers alone and/or in combination are applied respecting the interaction with the applied drug. Drug release profile, water-solubility of the film must fulfill the requirements of the planned application. Infrared absorption (FT-IR) spectroscopy has been employed extensively in order to get information about the chemical bonding or molecular structure of materials, whether organic or inorganic (Kumar and Mishra, 2006; Sakata and Otsuka, 2009).

The aim of the present study was to establish a correlation between the release characteristics of metoprolol tartrate and the peak area measured within the characteristic FT-IR wavenumbers of Metolose patches of different compositions.

2. Experimental

2.1. Materials and methods

Methacrylate ester copolymer (Eudragit NE 30D) was supplied by Röhm Pharma GmbH (Germany). Metoprolol tartrate USP XXII was purchased from Welding GmbH and Co. (Hamburg, Germany), two types of Metolose were provided by Mitsubishi Chemical Co. (Japan). The methoxyl content of Metolose SM 4000 (methylcellulose) is in the range of 27.5–31.5%, while in the case of Metolose 90SH 100.000SR (hypromellose), 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

Patches were prepared as follows: 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

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doi:10.1016/j.ijpharm.2010.03.053

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

Sample number	Metoprolol tartrate w/d	Eudragit NE w/d	Metolose SM4000 w/d	Metolose 90SH 100.000SR w/d	τ_d (min)	β
1	5.00/27.61	11.11/61.35	1.80/9.94	0.20/1.10	905.23	0.58
2	5.00/27.61	11.11/61.35	1.60/8.83	0.40/2.21	189.53	0.42
3	5.00/27.61	11.11/61.35	1.40/7.73	0.60/3.31	178.61	0.46
4	5.00/27.61	11.11/61.35	1.20/6.62	0.80/4.42	150.17	0.59
5	5.00/27.61	11.11/61.35	1.00/5.52	1.00/5.52	121.54	0.55

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 (22 ± 1 °C) for 72 h in desiccators. Each matrix contained 11.11% (w/w) Eudragit NE and 2% (w/w) of Metolose SM4000 and Metolose 90SH 100.000SR. The ratios of the two types of Metolose are summarized in Table 1.

2.2.1. FT-IR experiments

FT-IR spectra of the cast blank patches and that of containing metoprolol tartrate without pretreatment were obtained using a JASCO FT/IR-4200 spectrometer in 4000–400 cm^{-1} wavenumber range. 16 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}.

2.2.2. 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 was kept at 32 ± 1 °C and mixed at the rate of 25 rpm with rotating pad. Samples were taken at predetermined time points with Auto Plus 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.

2.2.3. Analysis of the release profiles

To characterize the dissolution profile of patches the Weibull distribution was applied in the following form in Eq. (1) (Langenbucher, 1976):

$$M_t = M_\infty \left[1 - \exp - \left(\frac{t - t_0}{\tau_d}\right)^\beta\right] \quad (1)$$

where M_t is the dissolution (%) at time 't' (min); M_∞ is the dissolution (%) at infinite time; t_0 is the lag-time (min) of the dissolution; β is the shape parameter of the curve; τ_d is the time (min) when 63.2% of M_∞ has been dissolved.

No lag-time ($t_0 = 0$) values were detected in the case of the samples examined.

The nonlinear parameter estimation of the release models applied for matrices was made with the Solver function of the computer package Microsoft Excel 5.0.

3. Results and discussion

The applied polymers alone were not able to form adhesive and flexible patches of controlled drug release, thus a mixture of Eudragit NE 30D and two types of Metoloses were used to obtain the required characteristics. The water insoluble, pH independent, water swellable, and water permeable Eudragit NE enables the barrier function of the homogeneous polymer composite. Since the concentration of the Eudragit NE 30D was kept constant in each patch (11%, w/w), the drug release profile was controlled by the various proportions of water-soluble Metolose SM4000 and Metolose 90SH 100.000SR. Fig. 1 represents the release profiles and Table 1 summarizes the drug release characteristics of the different matrix type patches containing metoprolol tartrate. No lag-time ($t_0 = 0$) values were detected. The extending ratio of hypromellose enables higher extent of metoprolol tartrate release, which indicates the presence of the hydroxypropoxyl groups in the polymer matrix. Hydroxyl groups are able to form H-bonds with water while methoxyl groups are not. The higher the proportion of methylcellulose 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 hypromellose. As a result of the water penetration in the course of dissolution, the polymer swelled and consequently the size of free volume holes became larger (Papp et al., 2009, 2010) causing faster release. Since the β values were within 0.42 and 0.59 in the case of each patch, the metoprolol tartrate release followed Fickian diffusion.

Fig. 2 illustrates the FT-IR spectra of blank patches and of that containing metoprolol tartrate. Characteristic peaks at 1867 cm^{-1}, 1922 cm^{-1} and 1987 cm^{-1} wavenumbers were found independently from the presence of metoprolol tartrate, which refer to the carbonyl group of methacrylate ester copolymer. Characteristic peaks could be observed at 2208 cm^{-1}, 2270 cm^{-1}, 2444 cm^{-1} and 2626 cm^{-1} wavenumbers in each blank patch that could be

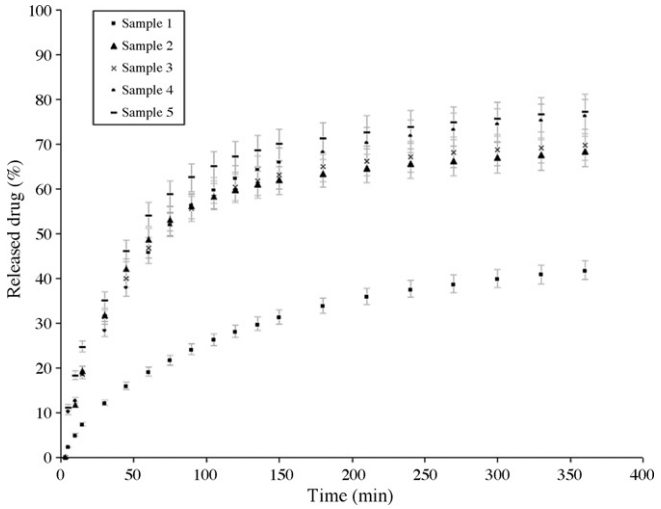

Fig. 1. Drug release profiles of different patches.

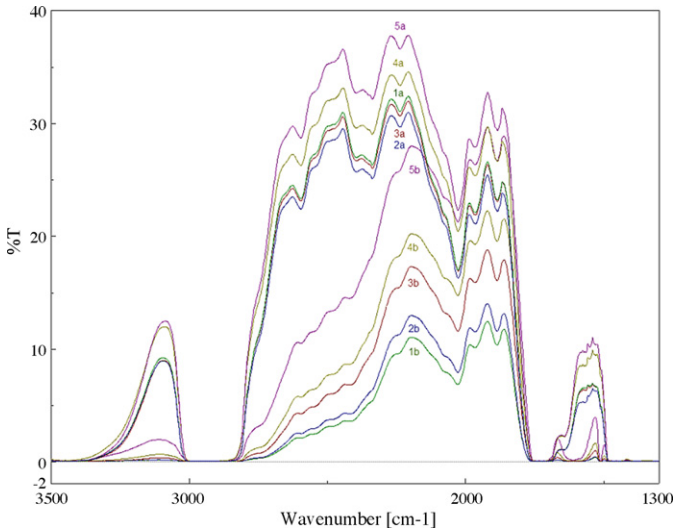

Fig. 2. FT-IR spectra of different patches. Sample 1: Metolose SM 4000 relative concentration: 90%; 1a, blank; 1b, with metoprolol tartrate. Sample 2: Metolose SM 4000 relative concentration: 80%; 2a, blank; 2b, with metoprolol tartrate. Sample 3: Metolose SM 4000 relative concentration: 70%; 3a, blank; 3b, with metoprolol tartrate. Sample 4: Metolose SM 4000 relative concentration: 60%; 4a, blank; 4b, with metoprolol tartrate. Sample 5: Metolose SM 4000 relative concentration: 50%; 5a, blank; 5b, with metoprolol tartrate.

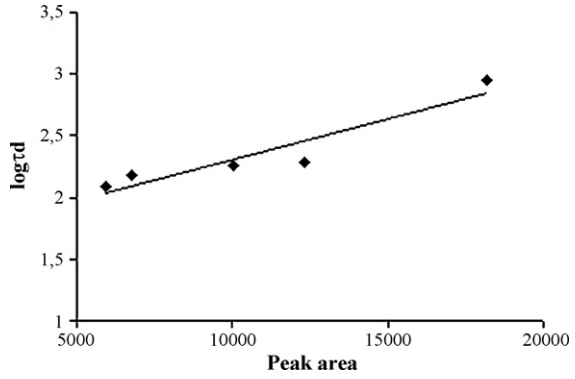

Fig. 3. Correlation between the peak area measured within the wave number range of 1757.7–2811.8 cm^{-1} and the log τ_d values of Metolose patches containing metoprolol tartrate.

attributed to the ester groups derived from the methylcellulose and hypromellose. These peaks were disappeared in the presence of metoprolol tartrate. Only one new peak appeared at 2196 cm^{-1} referring to the aromatic ring of metoprolol tartrate.

A broad hydroxyl absorption band was found at 3087 cm^{-1} indicating the presence of hypromellose. The signs of the OH bands will be much more intensive with the growing ratio of hypromellose. The latter was dominant in the empty patches. In the presence of metoprolol tartrate the specific absorption band disappeared. The possible explanation for this phenomenon could be the interaction between the polymer and metoprolol tartrate forming homogeneous polymeric composite patches in which metoprolol tartrate is entrapped. The increase of the transmission values of the characteristic peaks along with the hypromellose content indicates the microstructural changes of the patches via H-bridges with the OH groups of hypromellose. The latter enables the non-invasive quantitative analysis of patches based on the determination of the AUC values measured within the characteristic wavenumber range. Linear relationship was found with good correlation ($r = 0.9380$) between the peak area values of the FT-IR curves of Metolose patches measured within the characteristic wavenumber range and the log τ_d values of metoprolol release (Fig. 3). The obtained relationship enables a rapid in-process control of patches without destructive sample analysis.

4. Conclusions

The drug release profile of patches can be controlled by modifying the ratio of Metolose SM4000 and Metolose 90SH 100.000SR components. A linear relationship was found to describe the effect of the peak area values of the FT-IR curves of Metolose patches measured within the characteristic wavenumber range and the logarithm of time interval necessary to release 63.2% of metoprolol tartrate. 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.

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