

Process optimization of preparation of pentoxifylline – extended release tablets

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Received 3 April 2019 ♦ Accepted 27 May 2019 ♦ Published 9 July 2019

Citation: Tzankov S, Tzankov B (2019) Process optimization of preparation of pentoxifylline – extended release tablets. Pharmacia 66(2): 45–48. <https://doi.org/10.3897/pharmacia.66.e35132>

Abstract

The possibilities for correction of the rate of drug release by minimal changes in the technology process and by maintaining the quantitative and qualitative composition of the product pentoxifylline – extended release tablets were explored. Correction was made by addition of different quantity of HPMC (4000 cPs) to a granulating solution of PEG 6000. The main characteristics of the granules (compressibility index and density) were established. The swelling of the hydrogel tablets in water was determined in order more information on the release process to be obtained. Dissolution profiles of produced tablets were determined.

Keywords

pentoxifylline tablets, swelling index, dissolution profiles

Introduction

Pentoxifylline is a xanthine derivative with vasodilatory activity, which improves the microcirculation by increasing of erythrocyte flexibility (Aviado and Porter 1984) and reducing blood viscosity and decreases the ability for platelet adhesion and aggregation and thrombus formation (McCarty et al. 2016). Pentoxifylline is soluble in water drug (~77 mg/mL) (Teksin et al. 2009), which is readily absorbed in the gastro-intestinal tract. Pentoxifylline has short half-life of 0.4–0.8 h (Sweetman 2011) and low oral availability (19±13%) (Hardman et al. 1992). The maximum drug concentration in blood after oral administration reach in 1–3 hours and 98% of drug is eliminated within 24 hours (USP 2000). Because of an extensive intra- and extrahepatically (Mauro et al. 1992) first-pass metabolism, about 60–70% of the administered dose will be lost with enzymatic degradation in the blood and just

20% will be actually available to the body (Raz et al. 1998). These characteristics make it suitable for incorporating in extended release formulations.

The usual oral dose of pentoxifylline is 400 mg three times daily (<http://www.drugs.com>). The half-life of the original (referent) product Trental 400 is 4 to 6 hours (Trental, product information). Delayed release in the original product is provided by a hydrophilic matrix on the basis of hydroxyethyl cellulose. Different polymers are studied as matrix for extended release formulations containing pentoxifylline. E. Mircia et al. (2015) explored drug release from hydrophilic (HPMC, HEC, HPC), lipophilic (glyceryl palmitostearate) and neutral (Eudragit RL, RS, L and S) matrices. The best results (in comparison to the original product Trental) were determined using HPC matrices, granulated with PEG 6000. The change in the rate of drug release was achieved by variation in the amount of HPC and the ratio HPC/PEG (Mircia et al. 2010). Rahman et al.

(2009) studied the release of pentoxifylline from HPMC matrix. Drug release process was controlled by change in the quantity of lactose and starch, containing in the matrix.

Apart from the properties of the matrix, the rate of release also depend on the properties of the active substance (e.g. the particle size distribution of the drug particles is a critical parameter determining the rate of release of hydrogel matrix formulations). Therefore, in a validated technology regime, changing the manufacturer of the substance is always risky. At the same time, changes in the market and the drive of generic manufacturers to lower the cost of manufactured medicines require the inclusion of active substances from new manufacturers. It is not uncommon when, although the substance meets the specification, the release of the drug of the respective dosage form has been changed. Resolving the problem through substantial changes in composition is undesirable from a regulatory point of view, and any changes in the appearance of the drug are met with suspicion by the patient. It is preferable, where possible, to regulate the release rate by minimal changes in the technology.

The aim of the present work was to investigate the possibilities for correction of the rate of drug release rate by minimal changes in the technology process and by maintaining the quantitative and qualitative composition of the product.

Materials and methods

Pentoxifylline was purchased from Saneca Pharmaceuticals a.s. Hydroxypropyl methylcellulose K4M, hydroxypropyl methylcellulose K100M, polyethylene glycol 6000 and magnesium stearate meet the requirements of the European Pharmacopoeia (Ph.Eur.).

Granulation: fluidized bed apparatus „Huttlin Unilab“, provided with sprayer 1.2 mm.

Mixing: fast speed mixer granulator „Oystar Huttlin Mycromix“.

Drying: fluidised bed apparatus „Huttlin Unilab“. Supply air temperature: 45–55 °C. Residual moisture of the product ≤ 0.5%.

Measurement of residual moisture: Scale „Precisa XM 50“ in 105 °C.

Calibration of the finished granules: sieves with a pore size of 1.5 mm.

Characterization of the finished granules: Tapping apparatus: „Sotax TD1“, equipped with a measuring cylinder of 250 ml. Samples volume - 100 ml was used in the study. The determination was made according to the requirements of European Pharmacopoeia. The following indicators were monitored: bulk volume, volume after tapping, index of compression and Hausner's factor.

Tableting: The tablets were prepared using a rotary tablet machine „Kilian Pressima“, equipped with punches (round, biconvex, 10 mm in diameter). The mechanical strength of the tablets was within the range 120–160 N. The measurement was conducted by using the apparatus for measuring of the mechanical strength „Sotax HT1“. Ten tablets were used in the study.

Drug release study: The study was carried out by using the „Sotax AT7 Smart“, apparatus, equipped with 7 vessels (apparatus type II – Paddle method), at speed of 100 rpm. Medium – distilled water, 1000 ml. The samples were further analyzed spectrophotometrically - apparatus „Thermo Evolution 3000“, at a wavelength of 274 nm.

Results and discussion

Qualitative and quantitative composition used in the study is given in Table 1.

In preliminary studies of pentoxifylline from a new manufacturer, it was found that in standard and validated technology process, the release of extended-release tablets did not meet the pre-defined criteria (Table 2).

Table 1. Qualitative and quantitative composition of pentoxifylline extended release tablets (one tablet).

Composition	Quantity (mg)
Active substance	
pentoxifylline	400.00
Excipients (intragranular)	
Hypromellose K4M	14.00
Hypromellose K100M	30.5
Granulation solution	0.90
PEG 6000	4.0
Water purified	q.s.
Excipients (extragranular)	
Magnesium stearate	1.5
Total :	450.00

Table 2. Results from drug release study of newly developed tablets, containing pentoxifylline from new manufacturer, compared to referent product.

Time, h	Referent product, %	Newly developed tablets, %
0.5	5–16	27.2
1.0	12–25	35.1
3.0	32–50	55.5
6.0	55–80	73.7
8.0	>70	78.4

Obviously, the release of the drug from the tablets run faster than referent product, especially at the beginning of the process. These observations drive to correction in the technological regime in order pre-defined criteria for dissolution rate to be met.

Granulation was obtained under fluidized bed conditions. PEG 6000 was used as granulation agent due to its good water solubility and low viscosity of the resulting solutions. Suitable conditions for obtaining pores and channels in the matrix were obtained by the use of such granulating agents. The increased number of pores and channels would facilitate the transport of the dissolved drug and would speed up the release process. At the same time, the HPMC K4M (4000 cps) was present in the formulation as a sustained release excipient. HPMC K4M was dissolved in water and can be used as a granulating agent in a fluidized bed granulation at an appropriate viscosity.

It was decided to add a certain amount of HPMC K4M to the granulating solution of PEG and to carry out the granulation with the combined solution. Expectations were the addition of HPMC K4M to the solution to modify the matrix properties in order drug release to be delayed.

In preliminary study, the optimal process parameters of the granulation were determined, namely:

- granulating solution – 0.8% HPMC K4M dissolved in water. The required amount of PEG 6000 was dissolved in the final solution;
- Nozzles – 1.2 mm;
- spray pressure - 0.9 atm; microclimate – 0.15 atm;
- inlet – 240÷260 m³/h;
- product temperature – 29÷33 °C.

The process runs seamlessly under the conditions described above. As a first step, granules with 5% of HPMC K4M into the binding solution were prepared. As a positive effect from a technological point of view, an improvement in the parameters related to the granules flow was noted – compressibility index changed from 25 (passable) to 20 (fair)(Fig. 2). Tapped density changed from 0.71 g/ml to 0.64 g/ml (Fig. 3). Tablets with a mechanical strength of

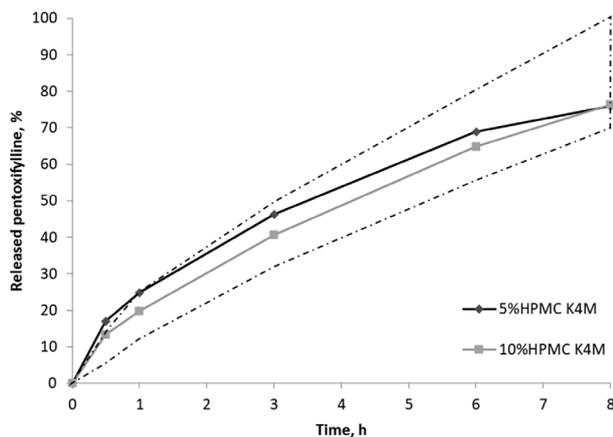


Figure 1. Drug release profiles from pentoxifylline tablets, obtained after granulation with 5% HPMC K4M (black curve) and 10% HPMC K4M (grey curve).

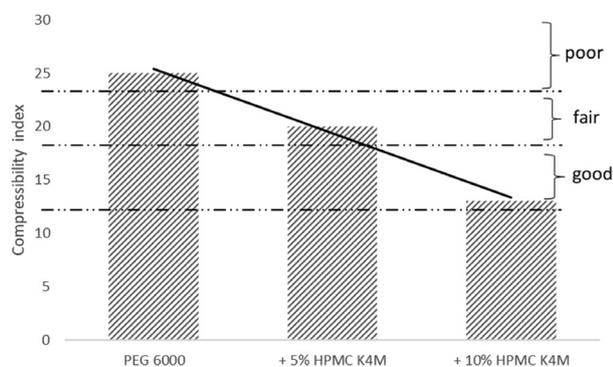


Figure 2. Change in the compressibility index of granules, obtained after granulation with PEG 6000 and after addition of 5% and 10% HPMC K4M.

Table 3. Results from drug release study of pentoxifylline tablets obtained after granulation with 5 and 10% HPMC K4M, compared to the release profile of referent product.

Time, h	Referent product, %	5% HPMC K4M	10% HPMC K4M
0.5	5–16	16.9	13.3
1.0	12–25	24.7	19.8
3.0	32–50	46.2	40.5
6.0	55–80	68.9	64.8
8.0	>70	76.0	76.3

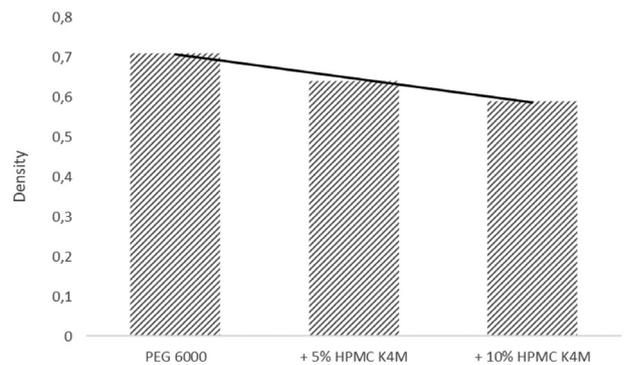


Figure 3. Change in the density of granules, obtained after granulation with PEG 6000 and after addition of 5% and 10% HPMC K4M.

140N were obtained from the resulting granules after powdering with silicon dioxide and magnesium stearate. The rate of drug release of the tablets was determined under the conditions described in materials and methods section. The results show a significant delay in the release rate (Table 3 and Fig. 1, black curve). However, the results on the 30th minute and the 1st hour were higher than the norms.

In the next series of experiments granules with 10% of HPMC K4M in the binding solution were prepared. An improvement in granule characteristics were noted (Fig. 2) – from a compressibility index 20 (fair) to a compressibility index 13 (good).

The density was varied from 0.64 g/ml to 0.59 g/ml (Fig. 3). The tableting process passed seamlessly, tablets with mechanical strength 140 N were obtained. Drug release from the tablets is shown on Fig. 1, grey curve. Delay in the release rate was achieved and the results met the predetermined criteria.

Our results show that the changes in the technological process lead to changes related mainly to the initial stages of drug release. To obtain more information on the release process, the swelling of the hydrogel tablets in water was determined. The results are presented on Figure 4.

A direct correlation between the degree of swelling and the rate of release of pentoxifylline was established, as tablets where granulation was established with PEG 6000 only released faster than tablets where PEG 6000 + HPMC was used. It is well known that there is a direct correlation between the degree of hydration of the polymer and its permeability. The degree of hydration determines the free volumes (diffusion spaces) through which the diffusion process is performed (Yasuda et al. 1968).

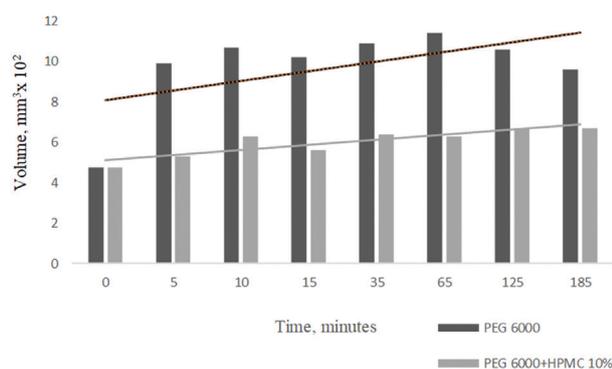


Figure 4. Swelling ($\text{mm}^3 \times 10^2$) of the hydrogel tablets containing PEG 6000 and PEG 6000 + 10% HPMC in water.

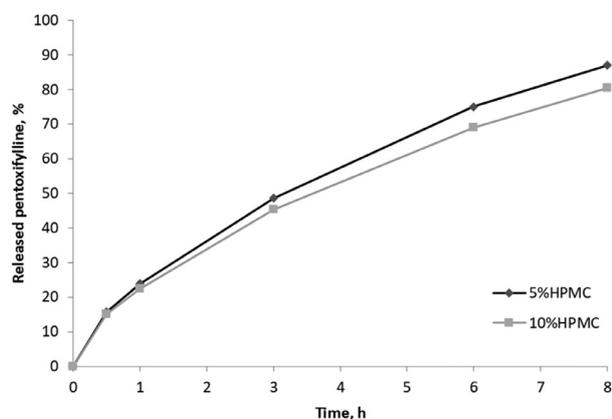


Figure 5. Drug release profiles from pentoxifylline tablets, containing 5% HPMC (black curve) and 10% HPMC (grey curve)

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Most probably, when granulation was obtained with PEG 6000, the more easily soluble and low viscosity PEG creates the ability to rapidly dissolve and allow water penetration into the depth of the matrix, especially at the beginning of the process. This allows the creation of pores and free volumes in a larger area of the matrix and which lead to faster drug release. At the same time granulation with PEG + HPMC lead to the presence of densified polymer in the pores which permeates the water in depth only after its swallowing. Indirectly, data obtained from the release of models produced after granulation with HPMC (5 and 10% without PEG addition) are also in support of this assumption. The graphs of the release are presented in Figure 5. There is a delay in the release process when the amount of the granulating agent HPMC was increased. At the same time, delay is characteristic of the entire duration of the process, not just its beginning.

Conclusion

It was found that the addition of HPMC (4000 cPs) to a granulating solution of PEG 6000 resulted in a change in the rate of release of pentoxifyllin from a hydrogel HPMC matrix. The approach allows controlling the release process. The release delay is most likely due to reduction of the possibility for formation of empty spaces and free volumes in the initial phases of the release process.

Using this approach, the release of pentoxifyllin tablets was adjusted in order to meet the preset requirements. The correction was made by minimal changes in technology and while no changes in the quantitative and qualitative composition of the product were necessary.