NEW MODIFIED RELEASE TABLETS WITH PENTOXIFYLLINE BASED ON LIPOPHILIC MATRIX. NOTE 1. FORMULATION, PHYSICAL STUDY AND DETERMINATION OF DISSOLUTION PROFILES OF THE ACTIVE SUBSTANCE FROM THE PROPOSED FORMULATIONS

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Abstract

The objective of this study is to test new formulations, regarding modified release tablets containing pentoxifylline, obtained by technological modulation of the drug release from tablets. Precirol AT 05 in different ratios was used as a lipophilic matrix agent; pentoxifylline incorporation in the matrix has been carried out by granulation followed by compression of granulates in tablets.

The weight uniformity, friability, hardness, thickness and the disintegration of the tablets were determined according to the stipulations of the 2001 Supplement of the Romanian Pharmacopoeia Xth edition, the United States Pharmacopeia (USP) 27 and the European Pharmacopoeia (EPh) 5.

The dissolution studies were performed using the official method in USP 24, using the paddle apparatus, and water as medium of dissolution at 37±0.5ºC, at a rotation speed of 50 rpm. The determination was performed by spectrophotometric assay in UV at 274 nm. The study of experimental formulations with 400 mg pentoxifylline/tablet was performed in comparison with an industrial reference product, Trental SR® 400 mg.

The prepared tablets were found to comply with the stipulations of the 2001 Supplement of the Romanian Pharmacopoeia Xth edition, USP 27 and EPh 5 regarding the weight uniformity, friability, hardness, thickness and disintegration time.

The study results show that the proposed formulations present the specific characteristics of controlled release tablets. The studied tablets presented dissolution

profiles close to that of the reference product (Trental SR® 400 mg), over a period of eight hours, with the exception of the formulation without Precirol AT 05.

Rezumat

Obiectivul acestui studiu îl constituie testarea unor noi formulări cu cedare prelungită cu pentoxifilină, obţinute prin modelarea tehnologică a eliberării substanţei medicamentoase din comprimate. Ca formator de matriţă lipofilă s-a utilizat Precirol AT 05 în diferite proporţii; încorporarea pentoxifilinei în matriţă s-a realizat prin granulare şi granulatele au fost supuse procesului de comprimare.

S-au determinat: uniformitatea masei comprimatelor, friabilitatea, rezistenţa mecanică, diametrul, grosimea tabletelor şi dezagregarea acestora, conform datelor din Suplimentul 2001 al FR X, Farmacopeia Statelor Unite (USP) 27 şi Pharmacopeia Europeana (EPh) 5.

Studiul de dizolvare s-a efectuat după metoda oficinală în USP 24, utilizând aparatul cu palete, la o rotaţie de 50 rpm şi apă distilată la 37±0,5ºC ca mediu de dizolvare. Determinarea s-a efectuat prin analiză spectrofotometrică în UV la 274 nm. Studiul formulărilor obţinute experimental cu 400 mg pentoxifilină/comprimat, s-a efectuat comparativ cu produsul industrial de referinţă Trental SR® 400 mg.

Pe baza rezultatelor obţinute, s-a observat că din punct de vedere al uniformităţii masei, friabilităţii, rezistenţei mecanice, diametrului, grosimii tabletelor şi a timpului de dezagregare, formulările obţinute corespund cerinţelor Suplimentului din 2001 al FRX, USP 27 şi EPh 5.

Rezultatele obţinute demonstrează faptul că formulările propuse prezintă caracteristicile unor forme farmaceutice cu cedare prelungită. Profilurile de dizolvare ale formulărilor studiate sunt apropiate de cele ale produsului de referinţă (Trental SR® 400 mg), pe o perioadă de analiză de opt ore, cu excepţia formulării fără Precirol AT 05.

Keywords: pentoxifylline, lipophilic matrix, dissolution profiles

Introduction

Investigation of polymers has drawn considerable attention in the development of modified release pharmaceutical matrix products. The drug release depends on the interactions between water (from gastrointestinal fluids), polymer and drug [8].

Pentoxifylline is used for the treatment of peripheral vascular and cerebrovascular diseases. After administration of modified release pharmaceutical forms with pentoxifylline a decrease in adverse effects such as gastrointestinal ones was observed [2,5,7].

The main goal of this study was to prepare pentoxifylline matrix tablets containing different concentrations of Precirol AT 05 in order to reduce the daily intake and to compare the rate of drug release of this new formulations with the ones of a commercial product Trental SR® 400 mg (Aventis Pharma) [6].

Materials and Methods

The following substances were used: Pentoxifylline pure substance (Merck), Precirol AT 05 (glyceryl palmitostearate) (Gattefossé S.A.), Compritol 888 AT0 (glyceryl behenate) (Gattefossé S.A.), lactose (Meggle). All the used excipients were of analytical grade.

The tablets formulation and preparation

The modified release tablets with pentoxifylline based on lipophilic matrix with different concentrations of Precirol AT 05 were obtained by granulation, followed by granulates compression [1,4]. We also prepared a blank formulation without Precirol, in order to evaluate whether the lipid excipient is able to form a lipophilic matrix using a concentration range between 10-30% and also for a better assessment of pentoxifylline release from the studied formulations. The amount of Compritol incorporated in all studied formulations has been constant because in the applied concentration it has no ability to form lipophilic matrix. In table I the compositions of the studied formulations are shown.

Each formulation was prepared using the same protocol. The lipophilic matrix used for the granulation was obtained by melting the lipid excipient at 60 ± 2˚C (maintaining a constant temperature in the granulator) [1,6]. Pentoxifylline was incorporated in this melted mass (through suspension). The homogenized mass containing pentoxifylline was solidified at room temperature and was granulated using an oscillant granulator (Erweka, GmbH, Germany). The granules were then mixed with Compritol 888 AT0 [3] and lactose (used as lubricant and diluent). The mixture homogenized in the mixer/stirrer (UMC 12, Stephan, Hameln), was then compressed. The compression was performed using a tablet machine with eccentric (Korsch EKO, Germany) with a single 13 mm ponson, using the same compressing pressure (30 N) for all formulations.

Table I

The compositions of the formulations with pentoxifylline incorporated into lipophilic matrix

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Pentoxifylline	400.00	400.00	400.00	400.00	400.00	400.00
Precirol AT 05	80.00	120.00	160.00	200.00	240.00	-
Compritol	50.00	50.00	50.00	50.00	50.00	50.00
Lactose	270.00	230.00	190.00	150.00	110.00	350.00
Precirol ratio into the matrix (%)	10.00	15.00	20.00	25.00	30.00	0

After preparing the modified release tablets containing 400 mg pentoxifylline, the following parameters were determined: friability, mechanical strength, diameter, dimensions of tablets, uniformity of mass and disintegration.

20 uncovered tablets were weighed and the average mass was calculated. The same tablets were weighed individually. Compared with the calculated average mass, the individual mass may submit a small deviation: 18 tablets ± 5% and only 2 tablets ± 7.5% (if the tablets contain above 300 mg active substance).

Determinations were performed in accordance to FR X, USP 27 and EPh 5 [10,11,13].

The following apparatus were used: Pharmatest PTF E for friability test, Pharmatest PTB 411 device for diameter, dimensions of tablets, Balance Mettler – Toledo AX – 205 for uniformity of mass, Pharmatest PTZ E device for the test of mechanical strength.

The test was conducted in two different environments: artificially simulated gastric medium represented by a solution of HCl 0.1 N (pH = 1.2) and artificially simulated intestinal medium prepared from 6.8 g KH_2PO_4, 1.12g NaOH and distilled water to 1.00 grams (pH = 6.8).

The tests were performed by maintaining the samples for two hours on gastric medium and six hours in the intestinal medium. In order to achieve this, we have used the device Pharmatest Auto PTZ E, 500 mL artificially liquid and maintained a constant temperature of 37 ± 0.5ºC.

All determinations were performed on 20 tablets.

***In vitro* dissolution studies**

Dissolution tests

In vitro dissolution tests were performed according to USP 24 [12] from the product formulated with 400 mg of pentoxifylline, and then compared with Trental SR® 400 mg. The apparatus No.2 was used (with paddles), 1000 mL of distilled water as dissolution medium [9], and the temperature was maintained constant at 37 ± 0.5°C. In all experiments, the rotation speed was 50 rpm. Tests were performed on six tablets of each studied formulation [4]. To determine pentoxifylline release from the pharmaceutical form in each experiment, 0.2 mL were sampled at intervals of 20, 30, 60 minutes in the first hour, from 30 to 30 minutes in the next three hours and then hourly. The tests were performed for a period of 8 hours. The volume of solution taken was replaced with an equivalent volume of distilled water to maintain a constant volume of the dissolution medium. Samples (0.2mL) were diluted with distilled water to 10mL.

Pentoxifylline was determined by UV spectrophotometric analysis at 274nm using as blank distilled water.

The following equipment was used: Hanson Research dissolution Tester SR +, Shimadzu UV-1650 PC spectrophotometer.

Results and Discussion

Uniformity of mass

The obtained values showed that the percentage deviations calculated falls within ± 5%; which complies with the requirements of the monograph "Compressi" (FR X).

The diameter of the tablets

Table II shows that all the 20 tablets of each studied formulation have a diameter around 13 mm.

The thickness of tablets

Table II shows that the height of tablets is around 3.3 mm.

Mechanical resistance and friability

The experimental results show (table III**)** that all the formulations fit the requirements regarding friability. For all the studied tablets, the weight loss was less than 1%.

The formulations F_1, F_2, F_3, F_4, F_5 have a mechanical strength (table III) close to the reference product (Trental SR® 400 mg: 47 N) and also fit the monographic stipulated requirements (mechanical resistance must have a minimum value of 30 N).

Table II

The medium values of the diameter (mm) and height (mm) of the studied formulations

No.	Formulation	d (mm)	SD	RSD%	h (mm)	SD	RSD%
1.	F_1	13.09	0.03	0.21	3.30	0.06	1.72
2.	F_2	13.10	0.03	0.30	3.29	0.04	1.31
3.	F_3	13.10	0.03	0.30	3.28	0.04	1.14
4.	F_4	13.11	0.04	0.30	3.29	0.05	1.63
5.	F_5	13.09	0.03	0.21	3.30	0.06	1.72
6.	F_6	13.10	0.03	0.21	3.28	0.03	1.04

Table III

The medium values of the mechanical strength (N) and the friability (%) of the studied formulations

No.	Formulation	Mechanical strength (N)	*SD*	Friability (%)	*SD*
1.	F_1	50	1.06	0.45	0.03
2.	F_2	50	1.11	0.51	0.03
3.	F_3	49	1.23	0.56	0.05
4.	F_4	49	1.27	0.46	0.01
5.	F_5	47	1.59	0.40	0.02
6.	F_6	30	1.61	0.60	0.01

SD = standard deviation - n = 6

Disintegration time

Following experimental determinations, it was observed that all formulations presented a disintegration time close to that of the reference product (Trental SR® 400 mg), with the exception of formulation F_6 (Table IV).

Experimental values obtained indicated that disintegration of the studied formulations was influenced by the mechanical strength of tablets and the concentration of Precirol in the matrix.

A higher mechanical strength of the tablets extended their disintegration time.

The proposed formulations (F_1 - F_5), submit a proper disintegration to the one of a modified release tablet.

In the case of the formulation without Precirol, disintegration occurred rapidly because the small amount of Compritol from the matrix is unable to provide the characteristics of a modified release formulation.

Table IV

Disintegration of proposed tablets, compared with that of the industrial reference product (Trental SR® 400 mg)

No.	Formulation	Time of disintegration from intestinal medium pH=6.8 (minutes)
1.	Trental SR® 400 mg	110
2.	F_1	116
3.	F_2	118
4.	F_3	112
5.	F_4	114
6.	F_5	110
7.	F_6	40

In vitro dissolution studies

In this part of the study, we tested the influence of excipients on the dissolution profiles. Precirol AT 05 which was used as lipophilic matrix agent (through varying the concentration of the lipophilic excipient into matrix) and Compritol 888 ATO, which was used as lipophilic diluent. In table V the quantities of the active substance (pentoxifylline) from the studied modified release tablets at different time of sampling are listed.

Table V

The quantities (%) of pentoxifylline dissolved from the studied formulations

No.	Time (minutes)	Trental SR® 400 mg	F_1	F_2	F_3	F_4	F_5	F_6
1.	20	5.16	5.01	5.12	5.09	5.03	5.54	42.52
2.	30	8.41	9.80	9.70	9.65	9.42	8.92	56.25
3.	60	11.14	14.60	15.30	15.90	13.05	12.98	80.13
4.	90	23.51	26.30	28.25	25.30	20.85	19.30	90.10
5.	120	31.18	31.12	32.12	33.20	31.56	30.01	97.13
6.	150	39.14	44.20	42.20	41.30	39.83	38.05	98.90
7.	180	42.86	48.30	48.02	47.90	47.28	45.21	99.92
8.	240	54.69	59.22	58.15	57.25	50.80	48.31	99.93
9.	360	62.99	69.50	64.13	65.10	66.07	60.12	99.98
10.	480	80.08	70.25	70.80	71.35	72.51	78.22	99.99

The dissolution profiles (figure 1) shows that all the studied tablets release constantly the active substance (pentoxifylline) over a period of eight hours and exhibit dissolution profiles close to the reference product. Depending on the concentration of the lipophilic polymer in the matrix, Precirol AT 05, in which pentoxifylline was incorporated, the results showed variations between the studied formulations. The slightly different values of pentoxyfilline at different sampling times in comparison with the ones obtained with the reference product Trental SR® 400, can be explained by taking into consideration the different nature of the lipid excipients. Precirol AT 05 is a substance with hydrophobic characteristics, which in high concentrations slows down the dissolution of pentoxifylline, in comparison with hydrophilic excipients.

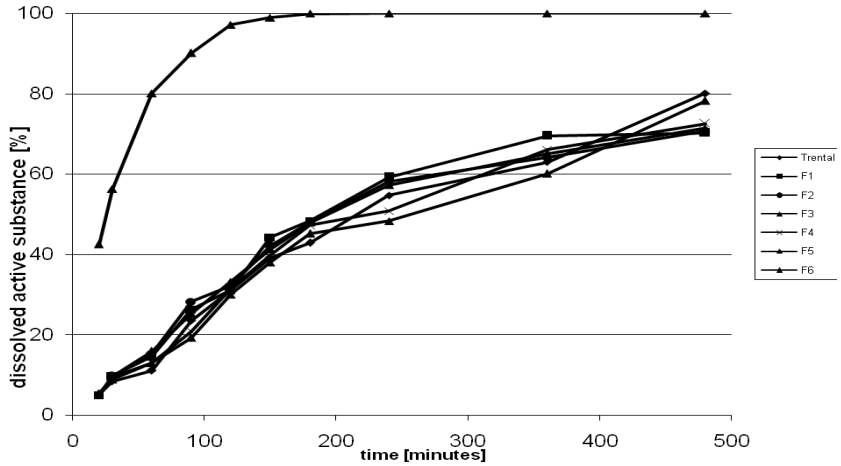

Figure 1

The dissolution profiles of pentoxifylline from the formulations with Precirol AT 05 (F_1, F_2, F_3, F_4, F_5), from the blank formulation (F_6) and from the reference product (Trental SR® 400 mg)

Experimental values have shown that in order to obtain a similar dissolution profile to the reference product, a concentration of around 10-30% Precirol in the lipophilic matrix is necessary.

The increase of Precirol concentration led to formulations with a dissolution profile close to the reference product.

Regarding the comparison formulation F_6 without Precirol, the experimental values show the rapid dissolution of pentoxifylline from this formulation, which can be explained by the absence of Precirol and the incapacity of Compritol to form a lipophilic matrix.

Conclusions

Six different formulations containing pentoxifylline were prepared using different concentrations of Precirol and then evaluated according to the stipulations of several modern Pharmacopoeias. The proposed formulations were compared with the industrial reference product, Trental SR® 400 mg.

All the tablets were found to comply with the stipulation of USP 27, F.R. X. and EPh 5 regarding weight variation, friability, hardness, thickness and disintegration.

It was observed that all the studied formulations presented a disintegration time close to that of the reference product, with the exception of formulation F_6, which didn't contain Precirol AT 05.

Depending on the concentration of the lipophilic polymer in the matrix, Precirol AT 05, in which pentoxifylline was incorporated, the results showed variation between the studied formulations, the dissolution profile evolving differently.

The differences are due to different preparation techniques of the studied formulations compared with the reference product Trental SR® 400mg.

In the case of the studied formulations, the only variable that influenced the dissolution of the active substance is the different amount of Precirol from each formulation.

Based on the experimental results, it appears that the lipid excipient used (Precirol AT 05) is capable to form lipophilic matrix. Concentrations ranging from 10-30% of lipid excipient provide dissolution profiles close to the reference product Trental SR® 400 mg and exhibit features of modified release formulations.

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