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FORMULATION AND STUDY OF SOME CONTROLLED RELEASE TABLETS WITH PENTOXIFYLLINE BASED ON HYDROXYPROPYLCELLULOSE MATRIX OBTAINED BY WET GRANULATION METHOD WITH PEG 6000

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Abstract. In this work three formulations of modified release tablets containing pentoxifylline 400 mg/tablet were obtained. Hydroxypropylcellulose (HPC) in different ratios was used as hydrophilic matrix agent. The pentoxifylline inclusion in the matrix has been carried out by water granulation, using PEG 6000 as binder. Tablets were obtained with a single station tablet machine (Korsch), using standard pressure, and obtaining tablets with 13 mm diameter, 800 mg weight and 400 mg pentoxifylline per tablet.

The weight uniformity, friability, hardness, thickness and disintegration of tablets were determined according to the stipulations of the 2001 Supplement of the Romanian Pharmacopoeia Xth edition. The experimental formulations with 400 mg pentoxifylline/tablet were studied by comparing them to the industrial reference product, Trental 400 mg (Aventis Pharma) and in according to the stipulations of Romanian Pharmacopoeia X^{th} edition, USP 27 and European Pharmacopoeia 5th edition. Every determination was performed using 20 tablets.

We followed the comparison between dissolution profiles of slow release tablets containing pentoxifylline based on hydrophilic matrix. The dissolution studies were performed using the method from USP 24, using the paddle apparatus, and water as medium of dissolution at 37 $\pm$ 0,5 ^{o}C, at a rotation speed of 50 rpm. The determination was performed by spectrofotometric assay in UV at 274 nm. It was noticeable that regarding the weight uniformity, friability, hardness, thickness and disintegration the proposed formulations are comparable with the industrial reference product (Trental, 400 mg) and are in

agreement with the stipulations of the Romanian Pharmacopoeia X^{th} edition and European Pharmacopoeia 5^{th} edition. The analysis of dissolution profiles showed that all formulations exhibit slow release.

KEYWORDS: *pentoxifylline, hydrophilic matrix, hydroxypropylcellulose, controlled release, pharmaceutical forms*

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1. Introduction

Pharmaceutical forms with prolonged action often replace conventional forms, and to obtain these forms with prolonged action hydrophilic polymers are often used. After administration of controlled release pharmaceutical forms with pentoxifylline a decrease in the adverse effects of the active substance was observed especially at gastrointestinal level.

Pentoxifylline (PTX) is used in the treatment of circulatory disorders [2, 5]. Pentoxifylline was used as a model hydrophilic drug in the present study [3].

In this paper, we proposed the study of some new modified release tablets with pentoxifylline. As hydrophilic matrix formers we used hydroxypropylcellulose (HPC) in different ratios: 17%, 34%, 45%. Solubility of pentoxifylline (PTX) in water by heating [3] (77 mg/mL at 25 ^{o}C and 191 mg/mL at 37 ^{o}C) allows formulation into hydrophilic matrix [7].

2. Materials and method

2.1. Materials

The following substance were used: pentoxifylline (Terapia), Trental 400 mg (Aventis Pharma) as reference product, hydroxypropylcellulose (HPC) of Klucel EXF (Aqualon Hercules), PEG 6000 (Macrogol 6000) (Merck), vegetable magnesium stearate (Faci Spa), colloidal anhydrous silicagel (Aerosil 200) (Degussa), talc (S&D Chemicals), lactose (S&D Chemicals). All the used excipients had pharmaceutical quality and were analytically pure.

The tablets formulation:

The modified release tablets with pentoxifylline based on hydrophilic matrix with different concentration of hydroxypropylcellulose (HPC) were obtained by wet granulation, followed by compression of the dried granulate. Table 1 presents the compositions of the studied tablets.

Homogenized mixture of pentoxifylline with hydrophilic polymer trainer of matrix (HPC) was granulated by wet granulation method with a 5% aqueous solution of PEG 6000. The obtained mass was passed through the sieve III. After drying the granulate, we added magnesium stearate, aerosil, talc (lubricants) and lactose (diluent). The mixture was passed through the sieve

Table 1: The compositions of the controlled release tablets formulated with pentoxifylline incorporated into hydrophilic matrix

Ingredients (mg)	F_1	F_2	F_3
Pentoxifylline	400,00	400,00	400,00
HPC	136,00	272,00	360,00
PEG 6000	4,15	3,00	5,53
Magnesium stearate	8,00	8,00	8,00
Aerosil	80,00	80,00	
Talc	24,00	24,00	24,00
Lactose	147,85	13,00	2,47
The polymer ratio into the matrix (%)	17,00	34,00	45,00

IV and compressed. For the compression process we used a Korsch machine with eccentric having ponsons of 13 mm diameter using the same compression pressure for all formulations [4]. The tablets obtained were smooth and had a flat surface.

After formulating modified release tablets containing 400 mg of active substance (pentoxifylline) the following parameters were determined:

- friability;
- mechanic strength (diameter, height of tablets);
- mass uniformity;
- disintegration.

Determinations were performed in accordance with the stipulation of F.R. X., USP 27 and E. Ph. 5 [10, 11, 13]. All determinations were performed on 20 tablets.

For the friability tests we used a drum of 285 mm diameter and 39 mm depth, made of transparent synthetic polymer with the internal rubbed surface. Part of the drum is mobile. Tablets arrive at each sweep of the drum in a projection curve extended from the middle wall of drum. The drum is situated

in a horizontal axis of the device and rotates about 25 rpm. Each turn, tablets roll, slide and fall to about 130 mm on the drum wall or on the other tablets. For the testing a number of 20 tablets are enough, and if their weight exceed 650 mg each, even 10 tablets are sufficient.

We placed the tablets in the sieve no. 10 and removed all dust with air pressure or a soft brush. The tablets were weighted accurately sample and brought in the device. The drum was rotated by 100 rpm and then the tablets and also the formed dust, including broken tablets, were removed and then weighted. Generally, the test is performed only once. If weight lost is more than 1%, the test should be repeated another two times and the results are interpreted using the average of the three tests.

Equipment:

- Pharmatest PTF E apparatus for friability test;
- Pharmatest PTB 411 device for mechanic strength test (diameter, thickness);
- Balance Mettler - Toledo AX - 205 for mass uniformity test;
- Pharmatest PTZ E device for the disruption test.

In vitro dissolution studies:
Equipment:

- Hanson Research dissolution 0Tester SR +;
- Shimadzu UV-1650 PC 0 spectrophotometer.

Dissolution tests:

In vitro dissolution tests were performed in accordance with USP 24 [12] using the product formulated with 400 mg of pentoxifylline, in comparison with Trental, 400 mg as reference product. We used the apparatus No.2 (with paddles), and as dissolving medium 1000 ml distilled water [8], maintained at a constant temperature $37 \pm 0.5\ ^oC$. In all experiments, the rotation speed was 50 rpm. Tests were performed on six tablets of each formulation studied [1, 6, 9]. For the determination of pentoxifylline release from the pharmaceutical form in each experiment were sampled 0.2 ml at intervals of 20, 30, 60 minutes in the first hour, from 30 to 30 minutes three hours and then hourly. The

test was performed for as long as 8 hours. The loss in volume was solved by replacing the used volume with an equivalent volume of distilled water to maintain constant volume of dissolution medium. Samples (0.2 ml) were diluted with distilled water to 10 ml. Pentoxifylline was determined by UV spectrophotometric analysis at 274 nm using as blank distilled water.

2.Results and discussion

Uniformity of mass:

We weighted 20 uncovered tablets and calculated the average mass. The same tablets were weighted individually.

Compared to the average mass calculated, the individual mass may submit a small deviation: 18 tablets ± 5% and 2 tablets ±7,5% (if the tablet contain above 300 mg active substance). The values of individual and average masses are shown in the table 2.

The standard deviations calculated for each formulation are presented in the table 3.

As it results from table 3, the calculated standard deviations are below ±5%; which is according to the requirements of the monographia "Compressi" (F.R. X.).

The friability:

A loss of less than 1% is considered acceptable for most products. In the case of new formulations, a loss of initial weight of 0,8% must come up to a loss of up to 1% after packaging.

The experimental results showed that all the three formulations are appropriate regarding friability. For all studied wording, weight loss was less than 1% (table 4).

Mechanic resistance:

The results are shown in the table 5. All three formulations had mechanic strengths close to the reference product (Trental, 400 mg: 47 N) and also to the stipulated requirements (mechanic resistance must have a minimum value of 30 N).

The diameter of the tablets

The results from table 5 show that the 20 tablets of each formulation studied, have a diameter of about 13 mm.

Table 2: Uniformity of mass (mg) of the studied tablets

Nr..	Trental, 400 mg	F_1	F_2	F_3
1.	791,53	788,05	805,23	800,88
2.	792,08	803,24	806,18	805,34
3.	798,85	805,17	784,86	795,85
4.	799,42	799,12	804,30	829,63
5.	800,65	780,85	797,70	789,05
6.	806,26	803,14	818,78	798,40
7.	810,12	805,17	793,18	807,10
8.	815,10	810,23	799,45	801,60
9.	825,60	781,53	800,44	815,30
10.	830,45	814,25	802,32	800,92
11.	800,65	807,15	803,05	801,38
12.	791,53	804,20	801,45	819,23
13.	792,08	805,15	804,30	815,45
14.	799,42	807,18	805,20	824,45
15.	798,85	800,85	800,75	826,36
16.	806,26	801,75	789,40	803,33
17.	815,10	825,75	800,17	830,33
18.	825,60	790,45	799,40	802,15
19.	830,45	826,15	784,86	804,40
20.	810,12	804,25	803,25	815,25
Average	807,01	803,18	800,21	809,32
SD	12,97	11,78	7,72	11,90
RSD %	1,61	1,47	0,96	1,47

Table 3: The calculated standard deviations

Nr.	Trental, 400 mg	F_1	F_2	F_3
1.	-1,91%	-1,88%	+0,62%	-1,04%
2.	-1,85%	+0,01%	+0,74%	-0,49%
3.	-1,01%	+0,24%	-1,91%	-1,66%
4.	-0,94%	-0,50%	+0,51%	+2,50%
5.	-0,78%	-2,78%	-0,31%	-2,50%
6.	-0,09%	-0,01%	+2,32%	-1,34%
7.	+0,38%	+0,24%	-0,87%	-0,27%
8.	+1,00%	+0,87%	-0,09%	-0,95%
9.	+2,30%	-2,69%	+0,02%	+0,73%
10.	+2,90%	+1,37%	+0,26%	-1,03%
11.	-0,78%	+0,49%	+0,35%	-0,98%
12.	-1,91%	+0,12%	+0,15%	+1,22%
13.	-1,85%	+0,24%	+0,51%	+0,75%
14.	-0,94%	+0,49%	+0,62%	+1,86%
15.	-1,01%	-0,29%	+0,06%	+2,10%
16.	-0,09%	-0,17%	-1,35%	-0,74%
17.	+1,00%	+2,81%	-0,01%	+2,59%
18.	+2,30%	-1,58%	-0,10%	-0,88%
19.	+2,90%	+2,85%	-1,91%	-0,60%
20.	+0,38%	+0,13%	+0,37%	+0,73%

Table 4: The friability of the studied tablets

Nr.	F_1 (%)	F_2(%)	F_3(%)
1.	0,55	0,69	0,45
2.	0,34	0,70	0,32
3.	0,66	0,96	0,12
4.	0,78	0,45	0,27
5.	0,24	0,32	0,16
6.	0,35	0,44	0,65
7.	0,66	0,32	0,56
8.	0,41	0,26	0,41
9.	0,15	0,15	0,32
10.	0,98	0,40	0,20
11.	0,35	0,20	0,28
12.	0,40	0,30	0,43
13.	0,20	0,28	0,52
14.	0,12	0,13	0,54
15.	0,27	0,15	0,60
16.	0,60	0,26	0,35
17.	0,45	0,55	0,44
18.	0,26	0,56	0,39
19.	0,30	0,62	0,60
20.	0,15	0,43	0,40
Average	0,41	0,41	0,40

Table 5: The diameter (mm) -denoted "D", thickness (mm) -"H" and the mechanical resistance (N) - denoted "MR" of the studied formulations

Nr.	F_1	F_1	F_1	F_2	F_2	F_2	F_3	F_3	F_3
	D	H	MR	D	H	MR	D	H	MR
1.	13,13	3,26	46	13,05	3,30	44	13,13	3,25	47
2.	13,12	3,25		13,08	3,24		13,12	3,24	
3.	13,11	3,29		13,10	3,40		13,13	3,28	
4.	13,10	3,30		13,12	3,24		13,09	3,26	
5.	13,09	3,25		13,09	3,25		13,08	3,28	
6.	13,08	3,40		13,10	3,24		13,11	3,28	
7.	13,14	3,41		13,11	3,25		13,15	3,25	
8.	13,15	3,24		13,13	3,25		13,14	3,28	
9.	13,12	3,42		13,15	3,26		13,12	3,28	
10.	13,12	3,24		13,14	3,42		13,12	3,29	
11.	13,11	3,28		13,12	3,28		13,13	3,42	
12.	13,10	3,26		13,10	3,29		13,13	3,40	
13.	13,12	3,28		13,09	3,30		13,16	3,24	
14.	13,13	3,27		13,08	3,28		13,08	3,30	
15.	13,10	3,26		13,15	3,29		13,08	3,24	
16.	13,08	3,28		13,14	3,28		13,09	3,26	
17.	13,09	3,26		13,13	3,27		13,10	3,25	
18.	13,11	3,28		13,11	3,24		13,11	3,25	
19.	13,14	3,26		13,10	3,24		13,13	3,30	
20.	13,15	3,25		13,13	3,24		13,12	3,24	
Avg	13,11	3,29		13,11	3,28		13,12	3,28	
SD	0,02	0,06		0,03	0,05		0,02	0,05	
RSD%	0,16	1,69		0,20	1,53		0,18	1,50	

Table 6: Disintegration of the proposed tablets, compared with that of the industrial reference product (Trental, 400 mg); where "TM" denotes the Time of disintegration from intestinal medium pH=6,8 (min)

Nr.	Formulation	TM
1.	Trental, 400 mg	110
2.	F1	103
3.	F2	100
4.	F3	110

The thickness of tablets:

The results from table 5 show that the height of tablets is around 3,3 mm.

Time of dissolution:

In vitro dissolution tests were conducted in two different environments: artificially simulated gastric environment solution represented by an HCl 0.1 N solution (pH = 1.2) and artificially simulated intestinal medium prepared from 6.8 g KH_2PO_4, 1.12 g NaOH and distilled water to 1.000 grams (pH = 6.8).

Disintegration was verified by maintaining the samples for two hours on gastric environment and six hours in the intestinal environment. For these experiments, we have used the device Pharmatest Auto PTZ E, 500 mL artificially liquid maintaining a constant temperature of 37 $\pm$ 0,5 ^{o}C. The results are shown in the table 6.

Following the experimental determinations, it was observed that all formulations presented a disintegration time close to the reference product (Trental, 400 mg).

After keeping the tablets in acid medium for two hours, the tablets did not disintegrate.

The experimental values indicate variables that have influenced the disintegration process for each different type of used polymer.

Disintegration is deeply influenced by the mechanic resistance of tablets, and concentration of polymer matrix.

All three proposed formulations, exhibited a proper disintegration for a modified release tablets.

Table 7: The quantities of the dissolved pentoxifylline from the studied formulations)

Time (minutes)	Trental 400 mg (%)	F_1(%)	F_2 (%)	F_3(%)
20	5,16	5,41	6,18	5,79
30	8,41	10,70	10,64	8,17
60	11,14	11,21	13,24	10,76
90	23,51	29,42	28,85	24,08
120	31,18	34,86	31,83	31,24
150	39,14	40,68	40,11	39,96
180	42,86	52,73	52,60	43,94
240	54,69	58,72	57,82	51,30
360	62,99	68,82	70,57	63,42
480	80,08	83,13	85,12	80,54

In vitro dissolution studies

In table 7 are listed the quantities of the active substance (pentoxifylline) from the studied modified release tablets at different times of sampling.

Figure 1 show the dissolution profiles of pentoxifylline from tablets based on hydroxypropylcellulose (F_1, F_2, F_3) compared to the reference product Trental 400 mg while figure 2 show the dissolution profile of pentoxifylline from F_3 which have a similar dissolution profiles with the reference product, Trental 400 mg.

The analysis of dissolution profiles, shows that all the formulations have a slow release (until 8 hours), and the formulations with 45% HPC have the closest profile with the dissolution of the reference product.

Based on the results we can observe that when smaller concentrations of polymer were used (17% HPC, 34% HPC), the quantities of pentoxifylline dissolved from the matrix were bigger.

4.Conclusions

The present paper presents a pharmacotechnical study of some new modi-

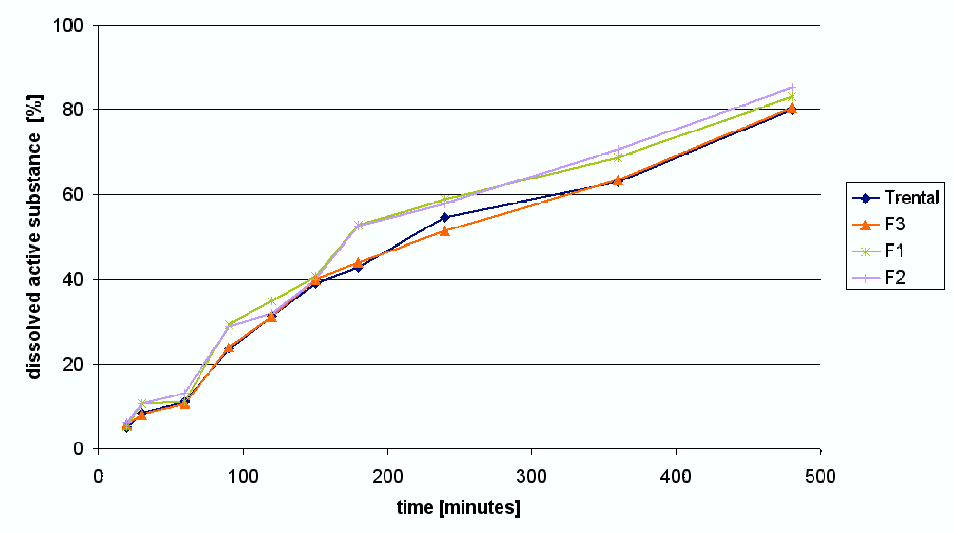

Figure 1: Dissolution profiles of pentoxifylline from the formulations with hydroxypropylcellulose (F_1, F_2, F_3) and reference product (Trental 400 mg)

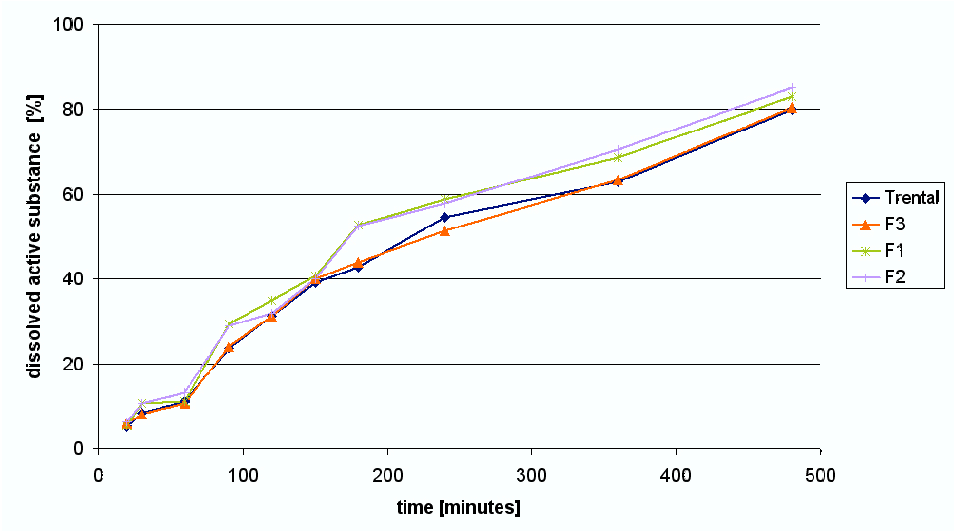

Figure 2: Dissolution profiles of pentoxifylline from the formulation with hydroxypropylcellulose (F_3) and reference product (Trental 400 mg)

fied release tablets with pentoxifylline formulated with hydroxypropylcellulose (HPC) matrix, used in different concentrations.

The tablets were obtained by applying a wet granulation method, using PEG 6000 5% aqueous solution as agglutinant; and the dried granulate were compressed with the Korsch tablet machine.

Physical examinations were performed for the three experimental formulations in comparison with the industrial reference product, Trental.

The results of the study show that disintegration of the studied formulations present the characters of a controlled release tablets (due the disintegration times).

In terms of uniformity of weight, friability, mechanical resistance, disintegration, the proposed wordings are similar to those of the reference product (Trental) and meet the requirements of F.R. X. and E. Ph. 5.

The analysis of dissolution profiles, shows that all the formulations have a slow release, and the formulations with 45% HPC have a closer profile to the dissolution of the reference product.

The differences recorded are due to technique preparation of tablets compared with the reference preparation.

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