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IN VITRO DISSOLUTION PROFILE OF TRANSDERMAL MATRIX IBUPROFEN PATCHES USING PADDLE METHOD

PROFILUL DE DISOLUȚIE IN VITRO AL MATRICELOR TRANSDERMALE EMPLASTURI CU IBUPROFEN UTILIZÂND METODA PADEL

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Rezumat. Hidrogelul de poli(vinil pirolidonă) cu greutate moleculară mare (PVP) și poli(etilen glicol) 400 cu greutate moleculară mică (PEG 400) a fost utilizat ca matrice adezivă a sistemului de livrare transdermică a foribuprofenului. Au fost elaborate cinci plasturi, fiecare conținând 0,2 ibuprofen. Testul de dizolvare a plasturilor transdermici a confirmat eliberarea ibuprofenului din matricea tuturor plasturilor și a determinat fluxul de ibuprofen. Fluxul mediu constant de ibuprofen a fost de 1,4 μg/cm²h pentru doi plasturi, 1,5 μg/cm²h pentru doi plasturi și 1,3 μg/cm²h pentru un plasture.
Cuvinte cheie: ibuprofen, plasture transdermic, PVP: hidrogel PEG.
Abstract. The hydrogel ofhigh molecular weight poly(vinyl pyrrolidone) (PVP) and low molecular weight poly(ethylene glycol) 400 (PEG 400) was used as adhesive matrix foribuprofen transdermal delivery system. Five patches were made, each containing 0,2 ibuprofen. The dissolution test for transdermal patches confirmed the release of ibuprofen from the matrix of all patches and determined the ibuprofen flux. The average constant ibuprofen flux was 1.4 μg / cm² h for two patches, 1.5 μg/cm² h for two patches, and 1.3 μg/cm² h for one patch.
Keywords: ibuprofen, transdermal patch, PVP: PEG hydrogel.

INTRODUCTION

Transdermal drug delivery systems (TDDS) serve to deliver active pharmaceutical ingredients through intact skin into the bloodstream.Non-steroidal anti-inflammatory drug (NSAID) patches are used to create concentrations of NSAIDs in the local circulation. Modern TDDS with ibuprofen (Voltaren), ketoprofen (Ketoplastin), diclofenac (Flector) are matrix systems. The matrix consists of one or a mixture of polymers with a dissolved or dispersed active substance [1, 2]. Polymer matrix (acrylic, silicone, rubber, block copolymer, etc.) has the property of the pressure-sensitive adhesive for which the skin is a substrate [3]. The hydrogel, which is formed by mixing high molecular weight PVP and PEG 400, also has persistent adhesive properties, although individually these polymers are not tacky. The composition with 36% PEG shows the best adhesion properties.In a PVP: PEG 400 gel, PEG 400 oligomeric chains crosslink PVP strands. The terminal hydroxyls of PEG 400 form hydrogen bonds with the carbonyl groups of PVP [4].

The difference in the concentration of a substance between the matrix of the patch and the skin forms a transdermal flow described by Fick's first law for the diffusion of substances through a semipermeable membrane [5]. The skin is presented in the form of a semi-permeable membrane, which in laboratory conditions can be imitated by an artificial semi-permeable film. In accordance with the State Pharmacopoeia of the Republic of Belarus, the "Dissolution" test for transdermal patches is carried out to confirm the release of the active substance. The use of a semi-permeable membrane is allowed [6].

Thepurpose – confirm the release of ibuprofen from the PVP: PEG 400 matrix and determine its in vitro flux.

MATERIALS AND METHODS.

*Preparation of transdermal ibuprofen patches.*Ibuprofen patches were made using the irrigation-drying method. The backing for the plaster was Dupont (China) polyester fiber with a moisture-proof coating. Composition for adhesive base TTS with ibuprofen per patch:

Ibuprofen – 0,20
PEG 400– 0,36
PVP – 0,64
Ethanol 96% - 7,00 ml

Ibuprofen was mixed in a 7 ml Ethanol 96%. PVP was poured with this solution and left for 12 hours to swell and dissolve. Then PEG 400 was added. The mass was stirred and left for 2-3 hours to naturally remove air bubbles.PEG 400 was then added. The adhesive mixture was poured onto a 25 cm² nonwoven baking and left to dry for 48 hours.

*Apparatusandsoftware.*The dissolution test was carried out in an automatic dissolution tester Erweka, DH 2000, Germany. Since a hydrophilic base was used for the manufacture of TTS with ibuprofen, for the dissolution test, a semipermeable cellulose membrane Visking dialysis tubing, MWCO 12000-14000 with a pore diameter of 25 Å (Serva, Germany) was applied to each patch from the side of the removed film and was attached to the patch with the reverse sides with waterproof tape. The dissolution medium is a mixture of phosphate buffered saline

solution pH 7.4 and alcohol 96% in a 1: 1 ratio, 250 ml, T 32 ± 0.5 ° C. Samples with a volume of 5 ml were taken every hour with the return of the sampled volume to the tester's workstation. The dissolution test lasted 8 hours.

The amount of released ibuprofen was determined by UV spectrophotometry at a wavelength of λ 264 nm on a UV-Visible Spectrophotometer, Varian, Cary 50. The data were processed using the Cary WinUV computer program, Scan Application, 5.0.0.999.

To calculate the concentration of ibuprofen in the dissolution medium, a calibration graph of the dependence of optical density on the concentration of ibuprofen was constructed (Figure 1). So a series of solutions with a concentration of ibuprofen from 40 μg / ml to 360 μg / ml was obtained, for each of which the optical density was measured.

RESULTS AND DISKUSSIONS

Analysis of the data reveals that the lag teim of ibuprofen for four of the five patches was 2 hours, for one the flow of ibuprofen was recorded already in the second hour of the test (Figure 2).

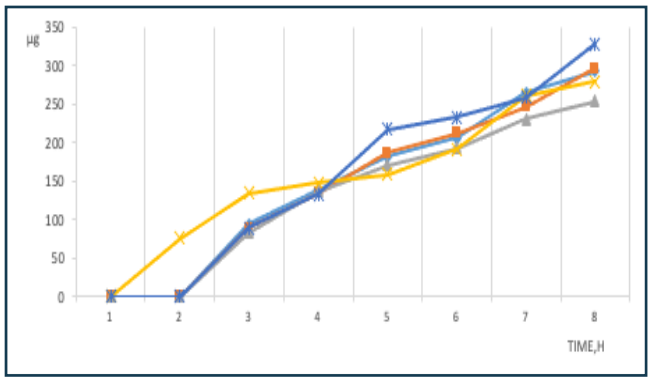

Figure 1. The calibration curve of the absorbance of the concentration of ibuprofen

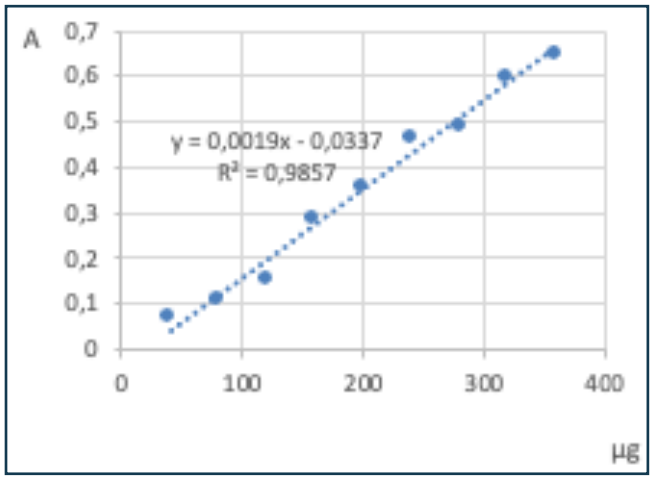

Figure 2. In vitro release profiles of ibuprofen from patches 1-5

For each patch, an average of 148.1 μg of ibuprofen was released during the 8 hours of the test (Table 1).

Table 1. In vitro ibuprofen release from patches 1-5 (μg)

Time (h)	Patches				
	1	2	3	4	5
1	-	-	-	-	-
2	-	-	-	75,60	-
3	94,10	89,80	83,50	134,1	88,80
4	138,3	134,1	137,2	148,3	133,5
5	181,9	186,7	170,4	159,3	217,7
6	206,7	213,0	193,0	191,4	233,5
7	264,6	246,2	230,4	260,9	258,3
8	293,0	296,2	254,1	279,8	328,3
Mean	147,3	145,6	133,6	156,2	157,5

On average, the transfer of ibuprofen through the semipermeable membrane increased at each hour of the test by 37.3 μg (Table 2).

Table 2. In vitro ibuprofen release from patches for each hour of the test 1-5 (μg)

Time (h)	Patches				
	1	2	3	4	5
1	-	-	-	-	-
2	-	-	-	75,6	-
3	94,1	89,8	83,5	58,5	88,8
4	44,2	44,3	53,7	58,5	44,7
5	43,6	52,6	33,2	14,2	84,2
6	24,8	26,3	22,6	11,0	15,8
7	57,9	33,2	37,4	32,1	24,8
8	28,4	50,0	23,7	69,5	70,0
Mean	36,6	37,0	31,8	39,9	41,0

The advantage of transdermal systems is their ability to form a constant flow of the active substance, which means that during the period when TTS is on the skin, the blood plasma maintains a constant level of the drug [7]. The flux (μg / cm² h), that is, the mass of ibuprofen released per unit area of the patch 1 cm² per unit time (1 hour) was calculated by the formula: J = m / St, where m is the mass of ibuprofen (μg) released from the patch area S (25

cm²) for time t (h). On average, 1 cm² of a patch through a semipermeable membrane is 1.4 μg of ibuprofen per hour (Table 3).

Table 3. In vitro ibuprofen fluxfrom patches 1-5 (μg / cm2 h)

Time (h)	Patches				
	1	2	3	4	5
1	-	-	-	-	-
2	-	-	-	1,5	-
3	1,3	1,2	1,1	1,8	1,2
4	1,4	1,3	1,4	1,5	1,3
5	1,5	1,5	1,4	1,3	1,7
6	1,4	1,4	1,3	1,3	1,6
7	1,5	1,4	1,3	1,5	1,5
8	1,5	1,5	1,3	1,4	1,6
Mean	1,4	1,4	1,3	1,5	1,5

CONCLU SIONS

The hydrogel based on high molecular weight PVP and oligomeric PEG 400 is capable of releasing active substances and can serve as a basis for matrix of transdermal systems.The properties of the membrane can possibly influence the flux rate of ibuprofen.Despite the fact that the semipermeable membrane does not fully mimic the skin, it can still be considered as the same barrier to the release of ibuprofen as human skin. The *in vitro*release profile of ibuprofen shows that the increase in the amount of ibuprofen in the dissolution medium was more or less uniform, which indicates a plateau of ibuprofen. The ibuprofen flux for each of the five patches differed slightly and averaged 1.4 μg / cm² h.

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