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Research Article

Study of xymedone release from hydrogels with zinc oxide nanoparticles

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Abstract

In this work the approaches to assess of the xymedone release from hydrophilic gels with zinc oxide nanoparticles were proposed using a vertical Franz diffusion cell at 37 °C. A partial validation protocol included the varying of the membrane polarity (lipophilic or hydrophilic cellulose acetate), the acceptor chamber volume (4,35 mL or 12,71 mL), the gel composition (with or without zinc oxide nanoparticles), as well as the metrological characteristics for the xymedone assay when it was released through the membrane in a Franz cell. It was estimated that the Franz cell with the volume of 12,71 mL, and the lipophilic membrane made it possible to estimate the amount of xymedone released with less error (RSD no more than 2%). We showed that the xymedone immobilization into zinc oxide nanoparticles increased the efficiency of xymedone release from the hydrophilic gel by 30%. The xymedone release through the both hydrophilic and lipophilic membranes is described by a pseudo-second-order equation that typical for desorption process from the polymer matrix. The proposed partial validation protocol to assessing the drug release using the Franz cell can be useful for selection of optimal composition of dermal topical dosage forms with hydrophilic pharmaceutical active substances.

Keywords: hydrogels, release, xymedone, zinc oxide nanoparticles, partial validation protocol

INTRODUCTION

Xymedone (1-(β-hydroxyethyl)-4,6-dimethyl-1,2-dihydropyrimidin-2-one) is an active pharmaceutical substance of pyrimidine group, which has a wide range of biological activities: regenerating, reparative, anti-inflammatory and antioxidant [1-5]. Despite of numerous effects in *in vitro*, *in vivo* experiments and according to the results of clinical practice, which proved the anti-inflammatory and wound-healing activity of topical dosage forms (DF) [3,6], only one xymedone DF is known as tablets. One of the reasons for the lack of topical dosage forms is its high solubility (up to 100 g/L) and polarity, and, accordingly, low bioavailability at administration through the lipophilic stratum corneum of the skin.

Previously, we proposed a hydrophilic gel containing xymedone with immobilized by zinc oxide nanoparticles (ZnO NPs), which showed high biological activity in relation to the healing of burn wounds (degree 2B) [7]. The wound healing effect was explained as follows. Firstly, the ability of the gel components to activate antioxidant enzymes such as SOD, catalase, LDH, GR, G6P-DG. Secondly, the antibacterial effect of ZnO NPs and zinc ions that due to the ROS generation. In addition, zinc ions can activate collagen synthesis [7]. The introduction of ZnO NPs reduced the concentration of xymedone by half, which probably can be contributed to the effective release of xymedone.

Assessing the drug release from the dosage form is one of the important criteria for the effectiveness of the drug. The study of drug release is necessary both for optimizing drug formulations, toxicity screening and quality control, and for the bioavailability predicting of transdermal delivery agents.

The drug release was studied using a solubility test (SPh of RF, XV) but it the correspondence between the drug and skin lipophilicity it is difficult to estimate in this case. The use of a vertical Franz diffusion cell makes it possible to improve the reproducibility of the results obtained by changing the membrane polarity and lipophilicity, temperature, volume and solution composition in the acceptor chamber, making it closer to physiological conditions [8-18]. In the work [19] the authors provided the protocol of incomplete validation of release methods using a Franz cell. The results of the work allowed the authors to optimize the conditions for determining drug release and the composition of the dosage form.

In this work, we proposed the approaches to assess of xymedone release from hydrophilic gels with zinc oxide nanoparticles through a membrane simulating the stratum corneum of the skin using a vertical Franz diffusion cell. We developed of the partial validation protocol, by varying the polarity of the membrane, the acceptor chamber volume, the gel composition (with and without zinc oxide nanoparticles), as

well as studing of metrological characteristics of the xymedone assay during release from membrane.

MATERIALS AND METHODS

Reagents. Xymedone (1-(β-hydroxyethyl)-4,6-dimethyl-1,2-dihydropyrimidin-2-one) (Xym) was purchased from the Institute of Organic and Physical Chemistry. Named by A.E. Arbuzov (Kazan, Russia). Carbopol 974P NF (Lubrizol, Wycliff, Ohio, USA). Ethanol (purity 95.0%, Vekos, Nizhny Novgorod, Russia). Cellulose acetate membrane (d = 0.45 μm, LenReaktiv, St. Petersburg, Russia). Sodium chloride (purity 99.9%, LenReaktiv, St. Petersburg, Russia). Potassium phosphate trihydrate (purity 99.0%, LenReaktiv, St. Petersburg, Russia), Dipotassium phosphate trihydrate (purity 99.0%, LenReaktiv, St. Petersburg, Russia). Octanol (purity 99.0%, LenReaktiv, St. Petersburg, Russia). Lipoid C-80 (Shanghai Immense Chemical Co, Ltd, China). Cholesterol (purity 99.0%, LenReaktiv, St. Petersburg, Russia).

Devices. IR spectra were obtained using an infrared spectrophotometer with a Fourier converter "IRAffinity-1S" (Shimadzu, Japan) in the region of 4000-500 cm^{-1}. UV spectra were obtained by Schimadzu UV-1800 spectrophotometer (Schimadzu, Japan).

XRD-patterns were obtained using an XRD-6000 diffractometer (Schimadzu, Japan).

A gel composition: xymedone 5,0%; zinc oxide nanoparticles 0,1%; carbopol PNF974 1,0%; distilled water to 100,0%.

Methods of the study of xymedone release using a vertical Franz diffusion cell. Figure 1 shows the schematic diagram and the photo of Franz diffusion cell. The Franz cell consists of donor chamber, receptor (acceptor) chamber, magnetic stirrer, membrane. The volume of the acceptor chamber of the Franz cell was 4,35 mL and 12,71 mL, consequently, the medium temperature was 37 °C. Stirring in the acceptor chamber was carried out using a magnetic stirrer. Sampling was carried out using a chromatographic syringe with a volume of 10 μL.

Figure 1: Photo and diagram of a Franz diffusion cell

Physiological phosphate buffer with pH 7.4 was used as an acceptor release medium. The lipid membrane was prepared as follows. Cellulose acetate membrane (LenReaktiv) (d = 0,45 μm) was immersed in a solution containing 2,1 g of cholesterol, 1,7 g of lipoid C-80, 100 g of n-octanol, and kept for 24 hours. After removing residual solvent, the membrane was dried at air for 12 hours. The mass of the analyzed gel applied to the donor zone was constant and equal to 400 mg. Taking into account swelling, the maximum amount of gel that could penetrate into the acceptor chamber corresponded to 320 ± 20 mg. The surface area occupied by the gel was constant and equal to 1,35 ± 0,05 cm^2.

RESULTS AND DISCUSSIONS

Properties of zinc oxide nanoparticles with immobilized xymedone

Zinc oxide nanoparticles (ZnO NPs) was obtained according to the method [7], they were preliminarily analyzed by the following characteristics: specific surface area (A, not less than 60-68 m^2/g); zeta potential (not less than -10 mV in a phosphate buffer solution with pH 7,4). Xymedone immobilization in ZnO NPs was carried out by two steps: 1) 10% xymedone aqueous solution (10 mL) was added to suspension of 2,0 g of ZnO NPs in 95% ethanol (10 mL) and kept for 24 hours at the stirring; 2) the precipitation was dried under vacuum to constant weight. The properties of Xym-ZnO NPs were estimated by UV-, FTIR-, AAS- data. The absorbance (A) of the exciton band at a wavelength of 360 nm in UV-spectrum of Xym-ZnO NPs suspension (C = 2,8 mg/100 mL of ethanol) decreased by almost one and a half times from 0,347 (for the original ZnO NPs) to 0,198 (for – Xym-ZnO NPs) at the same concentration, which characterizes the immobilization of xymedone in ZnO NPs. The AAS results confirmed that the zinc content (in terms of ZnO) almost doubled from 99,7% to 57,1%. FTIR-spectrum of Xym-ZnO NPs had the vibration bands of xymedone and ZnO NPs - υ, cm^{-1}: 3209 (-OH, -NH); 3100-2500 (-CH, $-CH_2$, $-CH_3$); 1606, 1659 (C=O, amide I, amide II), 3274 (-OH); 452 (Zn-O)); 34.48(002); 47.68(102); ; 19.86; 30.76;

The development of a partial validation protocol for assessing the xymedone release from hydrophilic gels through a lipid membrane using a Franz cell

To reduce variability and improve the reproducibility of the results obtained by the release of polar drug using, we have proposed the protocol for partial validation of the research method by a Franz cell (Table 1). We considered the volume of the acceptor chamber – 4,35 mL and 12,71 mL, as variation parameters as well as membranes polarity with different lipophilicity (lipid and cellulose acetate membranes), and the effect of the composition on release using the example of Xym and Xym-ZnO NPs gels.

The carbopol gel without xymedone was chosen as placebo. The gels named a Xym, Xym-ZnO NPs, contained the same amount of carbopol as placebo, but different concentrations of the active pharmaceutical substance. Purified water and a placebo solution (carbopol gel without xymedon) were used as a comparison solution.

Table 1: Protocol for partial validation of xymedone release assessment

Gel	DS, %	Preparation day	Release rate, %	Day of analysis
Placebo(carbopol)	0	1		1
Xym	50	1		1,2,3
Xym	100	1		1,2,3
Xym-ZnO NPs	50	1		1,2,3
Xym-ZnO NPs	100	1		1,2,3

Quantitative determination of xymedone from Xym-ZnO NPs gels from the acceptor chamber was carried out by spectrophotometric analysis using 299 nm as a reference band.

The specificity of methods was determined by the correspondence of the sample absorbance from the acceptor chamber with the absorbance of the standard xymedone sample of known concentration in the presence of traces of carbopol, measured under identical conditions with the same device. The relative standard deviation (RSD, %) of an individual result did not exceed specificity parameter (Table 2). Thus, the methods satisfied the specificity criterion.

Table 2: The relative standard deviations data of absorbance of xymedone samples, xymedone standard and in the presence of impurities - zinc compounds. Cell volume was equal to 12,71 mL

Sample	Xymedone absorbance			Average value of absorbance	SD	RSD, %
Xymedone in sample	0,102	0,106	0,105	0,104	$2,12\times10^{-3}$	1,99
Xymedone standard	0,221	0,220	0,228	0,223	$3,37\times10^{-3}$	1,51
ZnO (0,001%)	0	0	0	0	0	0

Accuracy was assessed by the relative deviation RSD, % based on a comparison of the actual and specified amount of the standard. The method satisfied the criteria of correctness if the relative deviation (SD) of the measured actual value of xymedone from the true value of the xymedone standard did not exceed ±2%. Metrological characteristics in terms of accuracy were also carried out using one-sample Student's t-test.

The linearity of the method was determined for a series of xymedone solutions (with concentrations in the linearity range from 0,01 to 0,5 mg/mL). The dependence of absorption intensity on concentration had the form Y=aX+b (Figure 2), correlation coefficient R^2=0,9984, which confirms the linearity of the method. The limit detection of xymedone was 0,05 mg/mL.

Solutions were analyzed over 1-8 hours and remained stable during this time.

To determine **precision** (Table 3) (repeatability and reproducibility), we performed multiple tests under the following conditions. When determining **repeatability**, the amount of xymedone was measured within a short period of time in the same laboratory using the same instrument in the laboratory of the Research Institute of Chemistry of Lobachevsky University. The precision of methods was confirmed, since the coefficient of variation was no more than 2%.

Figure 2: Calibration dependence of A=f(C xymedone)

Table 3: The precision of the methods based on experimental data

Concentration of xymedone		Experiment day	Absorbance (n=3)	SD	RSD, %
C, %	C, μg/mL				
5,0	500	1	0,102 0,104 0,105	$1,58\times10^{-3}$	1,51
5,0	500	2	0,109 0,111 0,107	$2,08\times10^{-3}$	1,83
5,0	500	3	0,105 0,106 0,104	$1,87\times10^{-3}$	1,78

The study of the xymedone release from the hydrophilic gels on the Franz cell

Figures 3 (a, b) show the amount of xymedone dependence (Q, μg/cm2) released on time (t, min) when Xym was released from the Xym-ZnO NPs gel into an acceptor chamber with a volume of 4,35 and 12,71 mL: through hydrophilic cellulose acetate membrane (1,1`), through the lipid membrane (curves 2,2`) as well as curve reflecting the release of xymedone from the Xym gel without ZnO NPs (curve 3). The kinetic curves of xymedone release through lipid membrane simulating the stratum corneum of the skin reached a plateau over the studied period of time (8 hours). The xymedone release through a hydrophilic cellulose acetate membrane did not lead to xymedone plateau on the curve. The maximum amount of xymedone that passed into the acceptor chamber through the lipid membrane from Xym-ZnO NPs gels with a volume of 4,35 mL was equal to 9100 μg/cm², which was almost 30% lower than the amount of xymedone released through the hydrophilic membrane (Q = 12400 μg/cm²). This value was almost twice the amount of xymedone released from Xym gels without ZnO NPs through the lipid membrane (Q = 6300 μg/cm²). Further, the kinetic curves data obtained using only the lipid membrane and cell volumes of 4,35 and 12,71 mL were compared by the relative standard deviation (RSD, %) values.

Figure 3. Xymedone release dependences (Qτ) on time (τ) obtained with the cellulose acetate membrane (1,1`) and the lipid membrane (2,2`,3). Curves 1,1`, 2, 2` were given for xymedone release from gel Xym-ZnONPs, and from Xym gel (curve 3): a) cell volume was 4,35 mL; b) cell volume was 12,71 mL, n = 3

Comparison of the amount of xymedone released into cells of different volumes showed that the relative standard deviation determination of the amount of xymedone did not exceed 2,0% with a confidence probability of 95% when using a cell with a volume of 12,71 mL (Table 4 (a, b))

Table 4. Metrological characteristics of xymedone assay for comparison of xymedone release from cells of various volumes through the lipid membrane

a) V = 4,35 mL (n=7; f = 6; P,% = 95)

τ, min	$X_{cp.}$ μg	S^2	S	t (P, f)	ΔX	RSD,%
80	4564	26829	164	2,45	±154,5	3,6
140	6110	26603	154	2,45	±144,7	2,5
200	7996	22991	152	2,45	±142,9	1,9
320	8663	119764	346	2,45	±325,2	3,9
440	9127	24907	158	2,45	±148,5	1,7

b) V = 12,71 mL (n=7; f = 6; P,% = 95)

τ, min	$X_{cp.}$ μg	S^2	S	t (P, f)	ΔX	RSD,%
80	4765	8848	94	2,45	±88,4	1,9
140	5784	12763	113	2,45	±105,3	1,9
200	7938	25536	160	2,45	±149,5	1,9
320	8113	28023	167	2,45	±156,9	1,9
440	8596	29412	172	2,45	±161,7	1,9

The comparison of these results on the xymedone release from Xym gels without ZnO NPs (curve 3, Figure 2a) and Xym-ZnO NPs gels (curve 1,1`,2,2`) indicated more efficient xymedone release through the lipid membrane. This result is probably due to the possible formation of lipophilic chelate complexes of xymedone with zinc ions but also the role of ZnO NPs as a delivery vector for xymedone (Figure 4).

Figure 4. Possible structures of chelate complexes of xymedone with Zn^{2+} on the surface of zinc oxide nanoparticles. pKa values for N^+ (8,39) and H^+ of the OH-group (15,62) were presented

Thus, in *in vitro* studies the release of polar xymedone from hydrophilic gels, it is advisable to use lipid membranes that more adequately reflect the stratum corneum of the skin and cells with a volume of 12,71 mL.

Mathematical modeling of the kinetics of xymedone release from hydrophilic Xym-ZnO NPs gels

Kinetic of xymedone release from hydrophilic gels of Xym-ZnO NPs (volume 4,35 and 12,71 mL) through the lipid membrane was studied using mathematical modeling. Xymedone release models based on adsorption-desorption equations, Higuchi and Korsmeyer-Peppas polynomial models using the correlation coefficient (R^2) were used. The graphical illustration of these equations was shown in Figures 5 (a, b, c, d).

Figure 5. Graphical solution of the equations in accordance with various models of xymedone release from Xym-ZnONPs gel: a) Korsmeyer-Peppas; b) Higuchi; c), d) pseudo-second order reactions. a, b, d) release through the lipid membrane; c) – through a hydrophilic cellulose acetate membrane

The kinetics of xymedone release through both hydrophilic and lipophilic membranes corresponds to a pseudo-second-order reaction equation considering the correlation coefficient (R^2 = 0,9961 for a hydrophilic cellulose acetate membrane and R^2 = 0,9984 for a lipid membrane correspodently,. The calculated values of xymedone release constants corresponded to K(xymedone) = $1,5\times10^{-8}$ $cm^2/\mu g\times min$ for the cellulose acetate membrane and K(xymedone) = $1,6\times10^{-8}$ $cm^2/\mu g\times min$ for the lipid membrane. Pseudo-second order equation characterizes the release of substances from a polymer matrix according to the mechanism of adsorption-desorption which is limited by diffusion in sorbent granules [20].

The middle section of the kinetic curve Q = f(τ) (after two hours of xymedone release) can be described by the process corresponding to the Korsmeyer-Peppas mathematical polynomial model in accordance with the equation:

$$\frac{Q_\tau}{Q_e} = k_{KP}\tau^n \quad 21$$

The solution of this equation allows us to calculate the dimensionless release rate constant KKP equal to 11.18. The calculated release exponent n = 0.45, reflecting the transport mechanism of xymedone, may characterize the release process in a period of two to four hours as a process of controlled diffusion according to Fick.

CONCLUSION

In this work we investigated hydrophilic xymedone gels with zinc oxide nanoparticles as an element of pharmaceutical development by the biopharmaceutical indicator - xymedone release. We have proposed approaches to assess the release of hydrophilic substances such as of xymedone from hydrophilic gels using a vertical Franz diffusion cell in accordance with the "Dissolution" test. The partial validation protocol included the

following parameters: membrane polarity, volume of the acceptor chamber, gel composition, metrological characteristics of the quantitative determination of xymedone.

Quantitative xymedone determination by the spectrophotometric method used in assessing release corresponded to the indicator - linearity (R^2 = 0,9984), accuracy (90-110%), precision - (RSD, % not more than 2,0).

It has been shown that the release of xymedone immobilized in zinc oxide nanoparticles (Q = 9100 μg/cm^2) through a lipid membrane simulating the stratum corneum of the skin was 31% greater than from hydrophilic xymedone gels without nanoparticles. This result is likely due to a change in the lipophilicity of xymedone complexes with zinc ions compared to the lipophilicity of xymedone, and better permeability of zinc oxide nanoparticles. The use of a 12,71 mL cell and a lipophilic membrane allows for higher accuracy and precision and is therefore preferable for assessing the release of hydrophilic drugs through the lipophilic stratum corneum of the skin.

Mathematical modeling of the xymedone release kinetics from the hydrophilic gels of xymedone immobilized in zinc oxide nanoparticles characterizes the process of xymedone release as similar to the desorption of a drug from a polymer matrix.

Thus, our proposed approaches to the validation protocol for release can be useful for assessing the release of hydrophilic drugs from dermal hydrophilic gels through the lipophilic stratum corneum and correction of the gel composition.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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