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INFLUENCE OF MICROENCAPSULATION PROCESS PARAMETERS ON NALTREXONE PROLONGED-RELEASE DOSAGE FORM

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The quality parameters of naltrexone microspheres based on the copolymer of lactic and glycolic acids (PLGA) were established as a function of the microencapsulation process parameters. The release profile of the developed naltrexone dosage form was found to coincide with that of the reference drug Vivitrol. The results were interesting scientifically and could be used to develop technology for producing generic Vivitrol.

Keywords: naltrexone, microspheres, copolymer of lactic and glycolic acids (PLGA).

Alcohol-dependence therapy is currently a critical problem of the utmost importance due to the rampant abuse of alcohol and alcohol dependence in Russia. Current approaches to the treatment of alcohol dependency are based on the principles of complexity, differentiation, and the pathogenetic justification of using some drugs or others [1].

In this respect, a group of opiate receptor blockers is most interesting. Naltrexone (Fig. 1) is a representative of this group.

Naltrexone is a narcotic analgesic antagonist and has the greatest affinity for the μ- and κ-receptors. It binds to opioid receptors and blocks the effects of endorphins in the presence of alcoholism. Its clinical use is limited despite the existence of a rather large amount of data on its effectiveness. In particular, this is due to the unpredictability of its effect. One reason for the unpredictability of the effect of naltrexone is the inability of patients to observe the treatment regime, which requires daily use. This problem is typical also for other drugs taken according to a similar regime [2].

A prolonged-release dosage form of naltrexone, Vivitrol, was developed to solve this problem. Polymer microspheres are used as the delivery system and enable the therapeutic concentration of naltrexone to be maintained in blood at a certain level, avoiding concentration variations that diminish the therapeutic activity and generate undesirable effects.

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The drug is injected once per month. The pharmacological effect persists for four weeks. Vivitrol has a relatively smooth pharmacokinetic profile with or without small fluctuations during the day. Vivitrol was approved in 2006 for clinical use by the US Food and Drug Administration (FDA) for treatment of alcohol dependency [3].

The goal of the present work was to study naltrexone microencapsulation process parameters during production of the prolonged-release generic drug form.

EXPERIMENTAL PART

We used naltrexone drug substance (Cilag AG, Switzerland); copolymer of lactic and glycolic acids (PLGA, 75:25, Evonik Industries, Germany); microsphere stabilizers water-soluble methylcellulose (MC, SM-100, Shin-Etsu, Japan) and polyvinyl alcohol (PVA, MW = 40,000, Chang Chun Petrochemical Co. Ltd., Taiwan); and solvents CH_2Cl_2 (Komponent-Reaktiv, Russia), benzyl alcohol (Aldrich, USA), EtOAc (Aldrich, USA), and Me_2CO (Aldrich, USA).

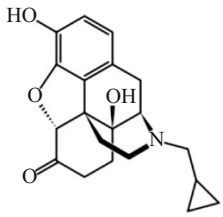

Fig. 1. Structural formula of naltrexone.

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TABLE 1. Critical Parameters Determining Microsphere Characteristics

Particle characteristic	Critical parameters affecting microsphere characteristics
Size	Polymer concentration in organic phase, organic phase composition, phase ratio, stabilizer type and concentration, temperature regime, type and duration of mechanical action
Degree of inclusion	Drug release from microspheres
Amount of loaded drug, organic phase composition	Polymer molecular weight, polymer concentration in organic phase, amount of loaded drug, organic phase composition, phase ratio, stabilizer type and concentration, temperature regime, type and duration of mechanical action

TABLE 2. Effect of Process Parameters on Naltrexone Microsphere Characteristics

Microsphere characteristics	Process parameters
Particle size	Type of mechanical action, external phase volume, organic phase copolymer concentration, stabilizer type and concentration
Effectiveness of substance inclusion	Amount of loaded naltrexone, type of organic solvent and its removal method

TABLE 3. Naltrexone Microsphere Size as a Function of Type of Mechanical Action on Emulsion

Parameter	Mixing type		
	Homogenizer	Ultrasonic disperser	Paddle stirrer
Rotation rate, rpm	6500	-	400
Power, %	-	60	-
Treatment time, min	3	3	3
Particle size, μm	10 ± 1	5 ± 1	61 ± 2

TABLE 4. Naltrexone Microsphere Size as a Function of Inner Phase Volume

Inner phase volume, %, v/v	Particle size, μm
33.0	16 ± 1
66.5	21 ± 2
86.9	38 ± 2
96.7	57 ± 2
98.3	70 ± 2

TABLE 5. Naltrexone Microsphere Size as a Function of Copolymer Concentration

PLGA concentration, mass%/v	Particle size, μm
2.14	3.96 ± 1
4.16	7 ± 1
13.27	22.8 ± 2
22.39	50 ± 2
34.1	65.8 ± 2

An Ultrasonic Processor (Cole-Parmer Instruments 750 W, USA), DIAX 900 homogenizer (Heidolph, Germany), and paddle stirrer (Ekros, Russia) were used as the mixing devices.

The dosage form was characterized by the microsphere size (laser diffraction method), effectiveness of naltrexone inclusion into the polymer microspheres (HPLC method), residual organic solvent content (GC method), and release parameters (UV spectrophotometric method).

Naltrexone drug substance was very soluble in $CHCl_3$ and practically insoluble in H_2O. The most effective method for microencapsulation of hydrophobic drugs into polymer particles is one-step emulsification by forming an oil/water emulsion.

PLGA and naltrexone base were dissolved in an organic solvent. In parallel, an outer aqueous phase containing MC and PVA was prepared. The main process step was preparation of the oil/water emulsion. The organic phase was emulsified in the aqueous stabilizer solution.

TABLE 6. Naltrexone Microsphere Size as a Function of Particle Stabilizer Type and Concentration

Stabilizer concentration, %	Stabilizer			
	PVA	MC	Lutrol F68, μm	PVA and MC, μm
0.5	Agglomeration	Agglomeration	30 ± 2	80 ± 3, agglomeration
1	75 ± 3 μm, agglomeration	Agglomeration	20 ± 1	75 ± 3 μm, agglomeration
2	60 ± 2 μm, agglomeration	39.1 ± 2 μm	15 ± 1	50 ± 2

TABLE 7. Degree of Inclusion as a Function of Amount of Added Naltrexone Base

Naltrexone:PLGA ratio	Degree of inclusion, %
1:2	73.8 ± 5
1:1.5	50 ± 2
1:1.2	56 ± 2
1:1	81 ± 5
1:0.75	58.1 ± 2

TABLE 8. Degree of Inclusion as a Function of Organic Solvent

Organic solvent	Degree of inclusion, %
CH_2Cl_2	81 ± 5
Benzyl alcohol	60 ± 2
EtOAc	60 ± 2
Me_2CO	40 ± 2

TABLE 9. Degree of Inclusion as a Function of Organic Solvent Removal Method

Removal method	Evaporation	Extraction
Degree of inclusion, %	70 ± 5	81 ± 5
Residual organic solvent content, %	2	1.5

TABLE 10. Prolonged-Release Naltrexone

Compound	Amount, g
Naltrexone	0.380
PLGA (75:25)	0.620
Polyvinyl alcohol	0.009
Methylcellulose	0.015

The organic solvent was removed from the emulsion by either evaporation at elevated temperatures or extraction into a large amount of H_2O, which formed dense microspheres. The solvent removal rate affected the final microsphere morphology. Changing the solution temperature and the copolymer and solvent solubility parameters changed the solvent removal rate.

Next, microspheres were rinsed and separated from the rinsings by centrifugation. The resulting solid was lyophilized (condenser temperature 50°C, vacuum 0.1 mbar, drying time 5 d).

The microencapsulation parameters affected the morphology of the resulting microspheres and; therefore, the drug release rate and the duration of their prolonged-release.

Table 1 presents the parameters that affected the microsphere morphology and nature of the release.

RESULTS AND DISCUSSION

Specific procedures for estimating the overall pharmacopoeial quality parameters of the drug substance and microsphere parameters including the particle size and drug release were developed in order to characterize naltrexone microencapsulated into polymer microspheres.

The influences of various factors on parameters such as the particle size and effectiveness of drug substance inclusion were studied (Table 2).

Factors influencing naltrexone microsphere size. The size of naltrexone microspheres was one of the principal quality parameters of the dosage form because a suspension of the drug should pass smoothly through a needle with little resistance or without it.

The size of microspheres obtained by the aforementioned technology was studied as a function of the type of mechanical action on the emulsion (with otherwise equal conditions) in order to produce a form that satisfied the aforementioned requirement.

Table 3 shows that the microsphere size and stirring rate were inversely dependent. Larger microspheres could be produced through mechanical action of a paddle stirrer on the emulsion; the smallest, by using an ultrasonic processor.

The next factor determining the microsphere size was the external phase volume (Table 4).

An increase of the external phase volume led to decreased disintegration of inner phase drops. This resulted in an increase of the average sphere size.

We also studied the microsphere size as a function of PLGA solution concentration (Table 5).

The microsphere size increased with increasing solution copolymer concentration. The optimum PLGA concentration was 22.39% (mass/vol), for which the microspheres had a size of 50 μm.

Table 6 presents results for the influence of the type of stabilizer and its concentration on the particle size.

The presence of surfactant (SA) molecules stabilized the microdrop emulsion and prevented them from coalescing

TABLE 11. Naltrexone Release Profiles from Microspheres

Day	Release, %		
	Reference values (Vivitrol)	Vivitrol	Developed naltrexone dosage form
1	≤ 3.5%	3.33 ± 1	2.7 ± 1
7	≥ 14% and ≤ 42%	40.6 ± 2	25.6 ± 1
14	≥ 35% and ≤ 65%	55.2 ± 2	43.4 ± 2
28	≥ 65% and ≤ 95%	65.5 ± 3	69.7 ± 3

with each other. The SA molecules should cover the whole interface between the organic and aqueous phases for effective stabilization.

A hydrophilic colloid tends to aggregate and is thermodynamically active. Its dispersed phase binds significant amounts of H_2O and forms around the particles a distinct solvation (hydration) shell. The stability of the emulsion depends on the solvation shell and the particle surface charge.

TABLE 6 shows that the sphere size decreased as the stabilizer concentration was increased because of enhanced stabilization at the interface.

Insufficiently stable particles formed and aggregated if PVA was used as the stabilizer. This problem was solved by using MC instead of PVA as the mixture stabilizer. This resulted in the formation of particles of the required size that were stable to aggregation.

Factors influencing the degree of naltrexone inclusion into polymer microspheres. Table 7 presents results from a study of the amount of added naltrexone base on the incorporation effectiveness.

The maximum degree of incorporation was achieved for a 1:1 naltrexone:PLGA ratio. The degree of incorporation did not increase if the concentration of incorporated drug relative to that of the copolymer was increased.

Tables 8 and 9 present the degree of inclusion as functions of the type of organic solvent and its removal method.

Judging from the physicochemical properties of naltrexone (solubility in organic solvents), the degree of incorporation was optimal if CH_2Cl_2 was used as the organic solvent.

Judging from the results, extraction was the most effective method for removing the organic solvent.

A microsphere formulation based on PLGA (75:25) with particle size 40 – 60 μm and degree of naltrexone incorporation 85 ± 5% was proposed taking into account the aforementioned functions (Table 10).

A composition and production technology for naltrexone microspheres were selected using the experimental results. CH_2Cl_2 was proposed as the optimal solvent because the highest degree of naltrexone incorporation was attained if it was used. Microspheres with the optimal characteristics were produced for a PLGA:drug ratio of 1:1.

An important parameter that confirmed that the dosage form produced by us was similar to Vivitrol was the naltrexone release profile [4]. The release profiles of one of the produced batches of naltrexone microspheres and Vivitrol were compared (Table 11).

Table 11 shows that the release parameters of the original reference drug and the developed generic were in agreement.

Thus, the influence of the type of mechanical action, external phase volume, copolymer concentration in the organic phase, stabilizer type and concentration, amount of loaded naltrexone, and type of organic solvent and its removal method on the quality parameters of naltrexone microspheres based on PLGA copolymer (75:25) was studied.

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