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Development of Tablet Medical Form Containing Substance FS-1.

A.S. Kalykova[a,c]*, D. Vetchy[b], and Z.B. Sakipova[a].

[a] S.D. Asfendiyarov Kazakh National Medical university, Almaty, Tole by str. 94, Republic of Kazakhstan
[b] University of Veterinary and Pharmaceutical Science Brno, Palackeho tr. 1/3, 612 42 Brno, Czech Republic
[c] Scientific Center for Anti-infectious Drugs, Almaty, al-Pharaby av. 74 B, Republic of Kazakhstan

ABSTRACT

The original substance of the FS-1 is a nano-ion complex with bactericidal and virucidal activity which was developed in Scientific Center for Anti-infectious Drugs (Almaty, RK) and is intended for the treatment of tuberculosis. The purpose of presented work was to develop a rational and optimum technology for preparing of tablets based on the substance of FS-1, and to evaluate the effect of the time of hydrolysis on quality of the developed medical form. For this, 2 batches of FS-1 substance with time of hydrolysis 17 min and 20 min were synthesized. The aim was to obtain tablets with suitable mechanical properties (friability below 1%) and a suitable disintegration time (up to 15 min), as is required by the Ph.Eur. Optimal formulation and process parameters for the preparation of tablets containing FS-1, under which tablets met the requirements for tablet disintegration time, tablet friability, and tablet mass and content uniformity, were identified within presented work. Longer time of hydrolysis of FS-1 substance probably led to unsuitable conversion of iodine into iodide form.

Keywords: tablets containing FS-1, tablets with model drug lactose, treatment of tuberculosis.

Corresponding author

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INTRODUCTION

The development of drugs based on the original substances involves the use of an integrated approach to the creation of tablet forms by modern technological methods in a systematic study of the properties, the technological characteristics of substances, and excipients and their rational choice.

Because infectious agents are sensitive to iodine-containing drugs and formation of acquired resistance to them is not typical, iodine preparations are still in the leading position among modern antiseptics. However, low molecular weight solutions of iodine can cause poisoning when molecular iodine oxidizes native proteins as with oral iodine tinctures containing about 40 mg/ml of iodine. Iodine single lethal dose is 1200-9500 mg or 17-120 mg/kg [1]. Iodophors, in which iodine is immobilized on polymers or solubilized using surface active agents, can eliminate adverse effects of iodine and increase the stability of the drug during its long-term storage while retaining its antimicrobial properties [2]. By us presented medicinal product FS-1 also belongs to iodophors, because the active drug substance is iodine in polymer complex of variable structure that acts as a matrix from which the active molecule iodine is slowly released. The proposed product is based on the optimally combined antimicrobial and immune-stimulating components. Due to the wide antimicrobial spectrum of polymer complexes of iodine, it is not necessary to pre-determine the type of pathogen. This great convenience in the clinical use allows start the treatment immediately. This convenience and the rapid onset of action makes possible to treat in a short time without the adaptation of bacteria to the drug and the emergence of resistant forms among them. Furthermore, prolonged action is characterized for drugs and medicinal compositions based on these complexes. The unique biological activity of these complexes is presumably associated with the presence of ions I_3^-.

At present, special attention on the formulation of drugs based on the original substances is given in the drug development. These include medicinal product FS-1, which was developed in Scientific Center for Anti-infectious Drugs (Almaty, RK) and is intended for the treatment of tuberculosis [3-4]. Currently is completed Phase II of clinical trials of the oral form of FS-1 - the study of the efficacy and safety, the determination of effective dose and mode of application (on a sample of patients with multi-drug resistant tuberculosis of the lungs).

The original substance of the FS-1 is a nano-ion complex with bactericidal and virucidal activity [3]. The substance FS-1 is safe and effective agent with broad spectrum of antibacterial action including actions against human pathogens of tuberculosis, also bovine and avian species according to *in vitro* and *in vivo* tests [5-7]. The complexation reactions of low- and high-molecular compounds with iodine and metal halogenides are the essence of the chemical synthesis of the FS-1 preparation. Technology for producing a liquid substance FS-1 is carried out in accordance with the development industry regulations. Liquid substance FS-1 is developed pursuant to the Rules of the manufacture regulations of medicines produced by pharmaceutical manufacturing companies of Kazakhstan and approved by the company JSC “Scientific Centre for Anti-infectious Drugs” [8]. The finally active substance is prepared using the freeze-drying technique (lyophilization).

The purpose of presented work was to develop a rational and optimum technology for preparing of tablets based on the substance of FS-1, and to evaluate the effect of the time of hydrolysis on quality of the developed medical form. For this, 2 batches of FS-1 substance with time of hydrolysis 17 min and 20 min were synthesized.

MATERIAL AND METHODS

FS-1 substance samples with different time of hydrolysis were synthetized in Scientific Centre for Anti-Infectious Drugs (Almaty, Republic of Kazakhstan). Two batches FS-1-17 and FS-1-20 with time of hydrolysis 17 min and 20 min were used in the experiment. Directly compressible lactose monohydrate (Pharmatose DCL 11, DMV Internationalbv., Veghel, The Netherlands) was selected as the model drug with similar solubility in water and particle size as FS-1 substance. The prepared tablets contained microcrystalline cellulose (MCC, type Avicel® PH 112, FMC Biopolymers, Rockland, United States of America) as an insoluble filler and different amounts of disintegrating agent croscarmellose sodium (Ac-Di-Sol, FMC Biopolymers, Rockland, United States of America). Magnesium stearate (Peter Greven, Bad Münstereifel, Germany) and colloidal silicon dioxide

(Degussa, Vicenza, Italy) were used to improve the flow properties of used powders. All materials were of the European Pharmacopoeia (Ph. Eur.) quality [9].

Preparation of tablet samples

MCC, croscarmellose sodium, and the FS-1 or lactose monohydrate were mixed for 5 min in a 3-axial homogenizer Turbula (T2C WAB, Basel, Switzerland) to homogenize the powder mixture. Magnesium stearate and colloidal silicon dioxide were added to the homogenized powder mixture by a mixing procedure using a homogenizer Turbula for another 5 minutes.

Tablets of same weights (approximately 500 mg) were compressed from prepared tablet masses using 12-mm diameter lenticular punches (Korsch, EK 0, Korsch Pressen, Berlin, Germany). The composition of the tablets is shown in Tables 1 and 2. The compression force used to produce tablets was monitored to prepare tablets with required hardness.

Table 1: Composition of prepared tablets with lactose monohydrate

Composition \ Sample	L1a	L1b	L2a	L2b	L3a	L3b
lactose monohydrate	15%	15%	15%	15%	15%	15%
croscarmellose sodium	2%	2%	1%	1%	0.4%	0.4%
microcrystalline cellulose	81%	81%	82%	82%	82.6%	82.6%
magnesium stearate	1%	1%	1%	1%	1%	1%
colloidal silicon dioxide	1%	1%	1%	1%	1%	1%

Hardness of samples *a* was approximately 100 N, samples *b* approximately 200 N.

Table 2: Composition of prepared tablets with FS-1

Composition \ Sample	FS-1-a	FS-1-b
FS-1-17	15%	-
FS-1-20	-	15%
croscarmellose sodium	1%	1%
microcrystalline cellulose	82%	82%
magnesium stearate	1%	1%
colloidal silicon dioxide	1%	1%

Determination of tablet mass properties

For each tablet mass pycnometric density was measured according to Ph. Eur. [9] using a helium pycnometer (Pycnomatic - ATC, Porotec GmbH., Germany). The test is intended to determine the volume occupied by a known mass of powder (7.5-10.5 g depending on the volume; the cell no. 30) by measuring the volume of gas displaced under defined conditions. The sample volume is determined after degassing the examined powder mass and its pressurization using the following formula:

$$V_s = V_c - \frac{V_r}{\frac{P_i - P_r}{P_f - P_r} - 1} \qquad (1)$$

where V_s is the sample volume, V_c is the cell volume, V_r is the reference volume, P_i is the initial pressure, P_r is the reference pressure, and P_f is the final pressure. The density of the tablet mass ρ is given by the equation:

$$\rho = m/V_s \qquad (2)$$

Pellet flow properties were evaluated by the measurement of bulk and tapped densities according to Ph. Eur. using a tapped density tester (Erweka, SVM 102, Germany). The bulk density was determined by measuring of the volume occupied by 50 g of sample filled into a 100-ml graduated cylinder of the density tester. The tapped density was determined from the volume of pellets after 1 250 taps of the cylinder. The values of densities were calculated from the measured volume and its weight according to equation 2. Achieved values of densities were used for calculating the Hausner ratio (HR) according to Ph. Eur. [9]:

$$HR = \rho_{bulk} / \rho_{tapped} \quad (3)$$

Determination of tablet properties

Mechanical properties were characterized as the tablet hardness and friability. The tablet hardness was tested on the C 50 Tablet Hardness & Compression Tester (Engineering Systems, Nottingham, England). The average hardness of 10 single tablets was calculated. For friability testing, 30 tablets of dust free particles was put into the friabilator Roche (type TAR 10, Erweka, Heusenstamm, Germany) and rotated for 4 min at 25 rpm (according to Ph. Eur.). The friability was expressed as a percentage of the weight loss of 30 evaluated tablets of each batch (according to Ph. Eur.) after agitation. The measurement was repeated three times.

Tablet weight was determined from 20 tablets by their weighting.

Tablet disintegration was performed according to Ph. Eur. 6 tablets were placed into each of the six tubes of the basket in disintegrator Erweka, type ZT 501, Germany. The disintegration test was performed in distilled water at 37 °C. The measurement was repeated three times.

Iodine and potassium iodide content in tablets were measured by titration with 0.1M sodium thiosulphate in the presence indicator (starch) followed argentometry determination of iodide content in the potassium iodide solution (according SP RK I, v.1, 2.2.20) [10]. 10 tablets were titrated with 0.05 N silver nitrate by potentiometric titration using pH-meter PP-50, Hanna Instruments. Iodine content (I) in g per 1 kg of the sample was calculated as follows:

$$C_{I_2} = \frac{V_1 \times K_1 \times 12{,}69}{m_0} \quad (4)$$

where V1 - volume of 0.05 N sodium thiosulfate used in the sample titration under the qualitative iodine determination, ml; K_1 is correction factor for molar concentration of 0.05 N sodium thiosulfate solution; 12.69 - 1 ml of 0.1 N sodium thiosulfate solution is adequate to 12.69 mg of iodine; m_o - sample weight used for analysis, g.

Potassium iodide content (KI) in g per 1 kg of sample was calculated according formula:

$$C_{KI} = \frac{(V_2 \times K_2 - V_1 \times K_1) \times 16{,}60}{m_0} \quad (5)$$

where V1 - volume of 0.05 N sodium thiosulfate used in the sample titration under the qualitative iodine determination, ml; V2 – volume of 0.05 N silver nitrate in equivalence point under the qualitative potassium iodide determination, ml; K_1 is correction factor for molar concentration of 0.05 N sodium thiosulfate solution; K_2 is correction factor for molar concentration of 0.05 N silver nitrate solution; 16.60 – 1 ml of 0.1 N silver nitrate solution is adequate to 16.60 mg of potassium iodide; m_o - sample weight used for analysis, g.

The iodine content in the tablet ranges from 3.0 to 3,375 mg and content of potassium iodide ranges from 5.1 to 7.5 mg.

The content uniformity was calculated from 10 tablets according to Ph. Eur. [9].

RESULTS AND DISCUSSION

Firstly, tablets with model drug lactose monohydrate were prepared to determine the optimum tablet composition and tablet technology. The aim was to obtain tablets with suitable mechanical properties (friability below 1%) and a suitable disintegration time (up to 15 min), as is required by the Ph.Eur. Therefore, tablet masses with different amount of disintegrating agent croscarmellose sodium and two batches of tablets

with tablet strength of approximately 100N and 200N from each proposed tablet mass composition were prepared (Table 1).

All proposed tablet masses had suitable flow properties according to Ph. Eur. (Table 3). Hausner ratios of prepared tablet masses were in the interval of 1.18-1.26, thus had good (HR = 1.12-1.18), fair (HR = 1.19-1.25) and passable (HR = 1.26-1.34) flow properties according to Ph. Eur. (Table 3). Appropriate flow properties of tablet masses are important for subsequent transformation into tablets.

Table 3: Tablet mass properties

Property \ Sample	L1	L2	L3	FS-1-a	FS-1-b
pycnometric density (g/cm^3)	1.56435 ± 0.00193	1,55659 ±0,00147	1.54179±0.00109	1.56885± 0.00265	1.56107±0.00211
volume density (kg/m^3)	488.97 ± 11.11	515.86± 12.34	502.89± 6.04	488.97± 10.87	502.52± 2.50
tapped density (kg/m^3)	614.04 ± 5.81	618.91± 5.87	593.12± 3.26	600.98± 8.88	592.99± 1.80
Hausner ratio	1.26 ± 0.03	1.20± 0.02	1.18± 0.02	1.23± 0.01	1.18± 0.00

Table 4 shows the properties of tablets with model drug lactose monohydrate. Obtained results showed that content of disintegrating agent croscarmellose sodium 2% led to inappropriate, too rapid tablet disintegration. On the other hand, content of disintegrating agent croscarmellose sodium 0.4% led to in appropriate, too slow tablet disintegration. All prepared tablet batches with lactose monohydrate had suitable friability below 1%. With increasing tablet hardness decreases the tablet friability and increases tablet disintegration time as was expected. From mentioned reasons, tablet composition with 1% of disintegrating agent croscarmellose sodium and tablet strength of approximately 100 N were chosen as the formulation and process characteristics for the preparation of finally tablets containing FS-1.

Table 4: Properties of tablets with model drug lactose monohydrate

Property \ Sample	L1a	L1b	L2a	L2b	L3a	L3b
hardness (N)	77.3 ± 17.9	203.2± 7.7	90.4± 5.3	180.9± 4.8	75.9± 5.4	173.9± 5.0
friability (%)	0.122± 0.065	0.058± 0.009	0.105± 0.076	0.016± 0.006	0.214± 0.093	0.038± 0.011
tablet weight (mg)	503.8± 7.3	504.5± 2.5	496.5± 4.1	495.2± 1.2	484.8± 3.3	479.4± 2.1
disintegration time (min)	0.2± 0.0	0.6± 0.1	6.9± 1.2	8.2± 0.6	17.1± 7.1	> 60

The properties of finally tablets containing FS-1 are showed in the table 5. Both batches had required characteristics for tablet medical form: friability below 1%, disintegration time up to 15 min, weight variation of tablets no more than ±5%, and drug content 85-115%. Unacceptable amount of iodine was determined in tablets containing FS-1 with longer time of hydrolysis probably because of its conversion into iodide form during hydrolysis process. From the obtained data result that presence of FS-1 with longer time of hydrolysis led to tablet with decreased friability and disintegration time.

Table 5: Properties of tablets with FS-1

Property \ Sample	FS-1-a	FS-1-b
Hardness (N)	99.9± 7.0	87.0± 6.1
Friability (%)	0.148±0.071	0.015± 0.004
tablet weight (mg)	513.9± 8.3	509.5± 3.3
disintegration time (min)	7.3± 2.0	6.4± 0.9
iodine content (mg)	3.07± 1.17	2.33± 0.32
potassium iodide content (mg)	6.12± 0.75	7.47± 0.59

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CONCLUSION

Optimal formulation and process parameters for the preparation of tablets containing FS-1, under which tablets met the requirements for tablet disintegration time, tablet friability, and tablet mass and content uniformity, were identified within presented work. Longer time of hydrolysis of FS-1 substance probably led to unsuitable conversion of iodine into iodide form.

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