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DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

EFFECT OF CRYSTALLINE AND AMORPHOUS FORMS OF *N*-BUTYL-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL ON TECHNOLOGICAL PROCESSES IN PRODUCTION OF THE FINISHED DOSAGE FORM

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The bioequivalence of finished dosage forms obtained from pharmaceutical compositions containing amorphous and crystalline forms of *N*-butyl-1,5-dideoxy-1,5-imino-D-glucitol as the active ingredient was demonstrated. Pharmaceutical compositions based on different aggregate forms of the active ingredient were shown to have different abilities to accumulate electrical charge. The use of an amorphous form was a possible solution to reduce technological losses in the production of a finished medicinal product based on *N*-butyl-1,5-dideoxy-1,5-imino-D-glucitol because of the lower electrification of the amorphous form of the main substance.

Keywords: amorphous form, crystalline form, electrification, static electricity, technological losses.

The manufacturing of finished dosage forms (FDFs) is fraught with several difficulties of a multistage manufacturing process. Mechanical losses in various manufacturing stages are some of them [1] and may be related to the ability of chemical substances that are a component part of an FDF to become electrified.

Losses due to electrification can arise in sieving and mixing stages during drug manufacturing. This occurs because of static electricity, which can accumulate on powder particles. As a result, the particles can agglomerate because of their surface charge, which reduces the efficiency in sieving and mixing stages and increases material losses.

Agglomeration can change the physicochemical properties of chemical substances themselves and FDFs. For example, an increase in particle size leads to a change in the solubility of a drug and; therefore, a change in the release profile of the active ingredient [2].

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Also, charging of particles can lead to their settling on equipment surfaces, cause deviations from production regulations, and eventually rejection of whole batches of drugs.

Various methods such as addition of antistatic additives, improvement of storage and transportation conditions of a material, and the use of special devices to eliminate static electricity can be used to decrease these losses.

Another solution is to convert a substance into an aggregate state in which the possibility of generating static electricity is reduced, e.g., from a crystalline form to an amorphous one.

The present research showed the effect of the physical state of the active ingredient *N*-butyl-1,5-dideoxy-1,5-imino-D-glucitol (BDIG), also known as miglustat, on technological losses during production of an FDF based on it.

BDIG is a glycosyl transferase inhibitor and is used mainly to treat Gaucher disease and Niemann-Pick disease (Fig. 1).

Significant mass losses were observed during manufacturing of an FDF based on BDIG during sieving of the starting material and mixing of the components. These mani-

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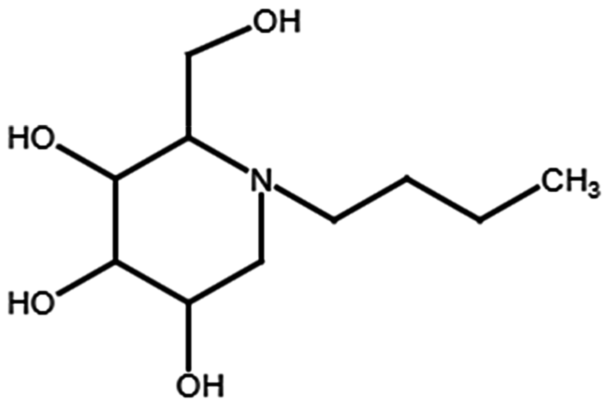

Fig. 1. Structural formula of *N*-butyl-1,5-dideoxy-1,5-imino-D-glucitol.

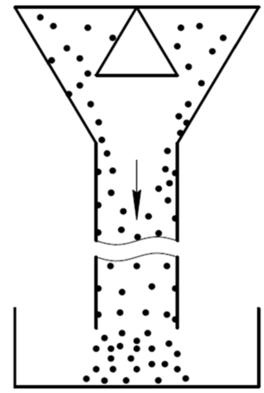

Fig. 2. Experimental setup for indirect measurement of electrostatic charge.

fested as decreased yields of both BDIG and a granulate in these stages because of settling of particles on equipment surfaces. The reason for this phenomenon may have been the ability of BDIG to accumulate static electricity, which led not only to agglomeration of the particles but also to their interaction with the equipment material. All this had a negative effect on the FDF manufacturing.

The crystalline form of a substance is known to affect its electrical properties. This occurs because various solid polymorphous forms of a single chemical substance can exhibit different properties upon transferring charge. This is explained by their different crystal structures, surface energies, surface work functions, moisture contents, and other factors [3]. Also, most charges on irregularly shaped crystalline particles can concentrate on their vertices and ridges [4].

However, charge on the surface of amorphous particles is distributed faster than on the surface of crystalline particles. In this case, molecules are more mobile in an amorphous substance than in a crystal lattice. As a result, electrical charges can be evenly distributed over the surface of spherical amorphous particles [4].

Besides electrification of a substance itself, contact electrification can appear. This is the generation of electrical charge on two identical or two different materials during their contact and separation [5]. Charge accumulation on the surfaces leads to electrical discharges and the formation of agglomerates of the substances (sticking of one material to another) that cause losses during technological processes.

Therefore, the use of an amorphous form of BDIG could solve the problem of technological losses during manufacturing of an FDF based on it.

EXPERIMENTAL PART

An amorphous form of BDIG was prepared by the literature method [6].

The crystalline form was prepared by direct alkylation of 1-deoxynojirimycin [7]. 1-Deoxynojirimycin is a polyhydroxylated piperidine alkaloid produced from D-glucose in various plants such as *Commelina communis* and in *Streptomyces* and *Bacillus* bacteria [8, 9].

The FDF based on BDIG consisted of 90% active ingredient. According to the literature [10], the excipients in the FDF could be capable of accumulating electrical charge.

A finished mixture of a composition analogous to the original drug Zavesca, capsules 100 mg, was used for the present research. Data from the experiments were used to study the ability of BDIG to accumulate electrical charge.

Wet granulation was used to prepare the finished mixture of composition:

Amorphous form of BDIG, 67.2 wt%,
Sodium carboxymethyl starch, 3.72 wt%,
Povidone K-30, 2.92 wt%,
Magnesium stearate, 0.56 wt%.

A finished mixture including the crystalline form of BDIG as the active ingredient was prepared analogously.

Electrification of the amorphous form of BDIG was studied indirectly by measuring the electrostatic charge of the finished mixtures based on the amorphous and crystalline forms of it. The experimental setup used a closed contact system consisting of a hollow vertical cylinder of height 250 mm and diameter 20 mm with a conical funnel in the upper part. The cylinder and funnel were made of 08X18X10 stainless steel. A flow divider for the loose substance was built into the mouth of the funnel to direct the falling flow to the inner wall of the cylinder, thereby creating a trickling effect of the substance over the cylinder surface. Figure 2 shows a diagram of the setup.

The studied mixtures were passed through the upper part of the cylinder during the experiment. The amount of substance reaching the cylinder base was determined. The amount of material settled on the walls was determined and possible mechanical losses of the mixture were estimated from the difference in the weights of the starting portion of substance and the substance reaching the cylinder base.

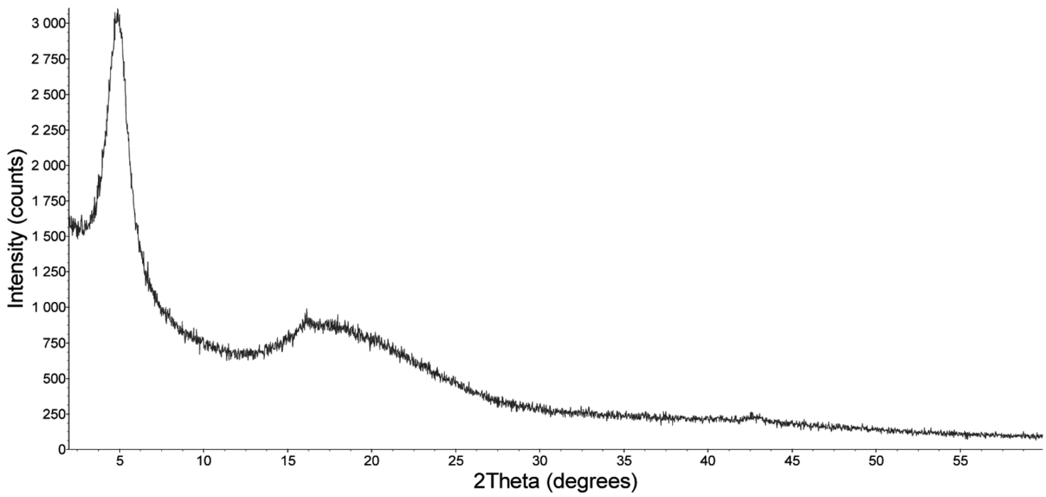

Fig. 3. Diffraction pattern of amorphous form of BDIG.

Experimental results were obtained for three successive tests. The average was calculated. The mass of a portion of substance in the experiments was 1 g; duration of one test, 15 min.

Blank tests without the active ingredient were performed by the above method to exclude an effect of the properties of the excipients (10%), despite their insignificant amount.

RESULTS AND DISCUSSION

According to the literature, the rates of surface charge distribution on amorphous and crystalline forms of the same chemical substance are different. This is explained by the greater mobility of molecules in an amorphous compound as compared to that of molecules in a crystalline compound [4].

Based on these data, the crystalline form of BDIG was hypothesized to tend to accumulate static electricity, whereas the amorphous form did not. Two forms of BDIG were produced during the work to check this hypothesis. The electrification of the finished mixtures containing the obtained forms were compared.

The structure of the amorphous form of BDIG was proved using x-ray phase analysis.

Figure 3 shows the diffraction pattern of a sample of the amorphous form of BDIG.

Two broad peaks at 2θ angles 5° and 17° characteristic of an amorphous substance were observed in the diffraction pattern of amorphous BDIG.

Electrification of the particles during friction was studied indirectly by measuring the electrostatic charges of the different forms of the substance. The method consisted of determining the amount of the finished mixture containing BDIG settled on the walls. The reason for the retention may have been the formation of electrical charge because of friction of the substance against the walls of the cylinder itself and between the falling particles. A comparison of the gravimetric density of the mixtures containing amorphous and crystalline BDIG as a factor capable of introducing uncertainty showed a slight difference of 0.40 and 0.38 g/cm^3, respectively. Based on this result, it was concluded that the effect of the gravimetric density could be ignored. The gravimetric densities of the mixtures were determined according to the method described in GPM.1.4.2.0016.15, Degree of flowability of powders.

The average mass of the substance remaining on the inner surface of the cylinder was 0.03 wt% for the finished mixture with amorphous BDIG and 0.07 wt% for the mixture with the crystalline form (Table 1). The settled mass of the mixture with the crystalline form was more than twice that of the mixture with the amorphous form. Only 0.01 wt% of the mixture with the excipients settled despite the excipients

TABLE 1. Amount of Settled Material as a Function of BDIG Form

Substance form	Average substance mass reaching cylinder base, g	Confidence interval ($P \geq 95$)	Substance mass remaining on cylinder inner surface	
			g	wt%
Amorphous	0.9997	± 0.0001	0.0003	0.03
Crystalline	0.9993	± 0.0001	0.0007	0.07
Placebo	0.9999	± 0.0001	0.0001	0.01

TABLE 2. Bioequivalence Analysis Results of Test and Reference Drug*

Parameter	Average (±standard deviation)		90% confidence intervals	Allowed values
	Test drug	Reference drug		
$AUC_{0\text{-t}}$	9665.17 ± 2766.022 ng·h/mL	9428.21 ± 2920.323 ng·h/mL	96.12 – 110.58 %	80 – 125 %
C_{max}	1073.94 ± 331.518 ng/mL	1110.57 ± 338.409 ng/mL	91.79 – 101.13%	80 – 125%
$C_{max}/AUC_{0\text{-t}}$	0.114 ± 0.033 h^{-1}	0.120 ± 0.028 h^{-1}	87.54 – 99.77%	80 – 125%

* Experiments and processing of results were performed at Belgorod State National Research University, Institute for the Pharmacology of Living Systems.

used in the FDF being capable of accumulating electrical charge. This suggested that the main factor affecting the electrification of the finished mixture was the physical properties of the form of the active ingredient. Therefore, it could be concluded that the amorphous form of BDIG was less electrified than the crystalline form.

The effect of the electrification of the different forms of BDIG on the technological manufacturing process of the FDF based on it was confirmed by producing drugs in No. 4 solid gelatin capsules containing granulate with granule size 1.0 mm, corresponding to 110.803 mg. As it turned out, the losses during manufacturing of 100 capsules were 8% for the crystalline form and 5% for the amorphous form. The results could indicate that electrification of the physical forms of BDIG was different and affected the technological parameters.

The bioequivalence of the drug prepared from the pharmaceutical composition containing amorphous BDIG as the active ingredient (test drug) and Zavesca® capsules, 100 mg (Actelion Pharmaceuticals Ltd., Switzerland) (reference drug) was studied to prove that the amorphous form of BDIG could be used in the FDF.

The composition of the test drug (per single capsule) was miglustat active ingredient 100.00 mg; excipients sodium carboxymethyl starch, 5.540 mg; povidone-K30, 4.432 mg; magnesium stearate, 0.831 mg; No. 4 solid gelatin capsule (body/cap), 38.0 mg.

The composition of the reference drug (per single capsule) was miglustat active ingredient 100.00 mg; excipients sodium carboxymethyl starch, 5.54 mg; povidone-K30, 4.432 mg; magnesium stearate, 0.831 mg; titanium dioxide, 0.76 mg; and gelatin, 37.24 mg.

The study was conducted according to conditions approved in the legally established protocol for clinical trials MG-04-2019, version 1.0 of Apr. 11, 2019. The study was approved by the Ethics Council, Ministry of Health of the RF (Extract from Ethics Council Protocol No. 193 of Jun. 4, 2019).

The trial included 24 volunteers (healthy males and females from 18 to 45 years old) that were divided into two groups and consisted of several periods, i.e., screening, randomization, and administration of the drugs. Volunteers of the first group (11 people) took the reference drug once during the administration period; of the second group (11 people), the test drug once.

Each volunteer was hospitalized in a clinical center to perform the first stage of the trial for at least 12 h before taking the drug (the hospitalization lasted ~36 h). Each volunteer was sent home before outpatient visits after 36 and 48 h if no indications for continued hospitalization were presented.

The BDIG blood plasma concentration of the volunteers was determined at discrete time intervals (0 and 30 min, 1 h, 1 h 20 min, 1 h 40 min, 2 h, 2 h 20 min, 2 h 40 min, 3 h, 3 h 30 min, 4 h, 4 h 30 min, 5, 6, 8, 10, 12, 24, 36, and 48 h) to plot pharmacokinetic concentration-time curves for the test and reference drugs. The BDIG blood plasma concentration was determined by HPLC with tandem mass spectrometry on an UltiMate 3000 RSLC liquid chromatograph (Thermo Fisher Scientific) with a Velos Pro mass spectrometric detector (Thermo Fisher Scientific).

TABLE 2 presents the analytical results for the bioequivalence of the drugs.

It could be concluded based on the results that the compared drugs were bioequivalent.

Thus, use of the amorphous form was a possible solution for reducing technological losses during manufacturing of the FDF based on BDIG, the cause of which could be electrification of the substance itself.

Conflict of interest

We declare no conflict of interest.

Financing

The studies were performed using internal resources.

Contributions of authors

AVV, LMG, and KDCh analyzed the literature, performed the experiments, and statistically processed the data; ETZh and EAV formulated the idea and provided scientific direction. All authors discussed the results. AVV wrote the manuscript.

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