THE INFLUENCE EXCIPIENTS ON THE DISSOLUTION PROFILES OF NIFEDIPINE TABLETS

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ABSTRACT

PURPOSE: Study of dissolution profiles of nifedipine tablets from different manufacturers to further assess of their equivalence *in vitro*, as well as study of the dependence of the dissolution profile on the adjuvants composition.

MATERIAL AND METHODS: 3 buffer media with pH 1.2 (hydrochloric acid buffer); 4.5 (acetate buffer); 6.8 (phosphate buffer) was used. The absorptions were observed at 343.

RESULTS: The dissolution profiles of nifedipine tablets from different manufacturers have been studied and have been founded that the percentage of nifedipine release from the sample B is higher than from "Corinfar", and the percentage of nifedipine release from "Corinfar" is higher than from the sample A. Adjuvants composition of nifedipine tablets have been studied. It is founded that the inclusion of surfactants, solubilizers and emulsifiers into tablets contribute to increasing of active substance release from the dosage form.

CONCLUSIONS: Found that the introduction of surfactants into tablets, solubilizers and emulsifiers help to increase the release of active substance from the dosage form.

Key words: *bioequivalence, adjuvants, BCS, generic medicines, nifedipine*

INTRODUCTION

Currently a large number of generic drugs are registered in Ukraine for medical use. The advantage of generic drugs is the relatively cheapness compared to innovative medicines, because the creation and registration of generic drugs require less research and, consequently, less material costs, which are necessary in the development, research and market introduction of a new original drugs (6-9).

The equivalence of the efficacy and safety of innovative and generic drugs ensures their therapeutic equivalence (11). Currently abroad for some generic drugs estimate of interchangeability may be set on the basis of comparative tests *in vitro*, which includes the study of biopharmaceutical properties of medicinal substances, examination of adjuvants composition, determining the dissolution rate and evaluation of dissolution profiles equivalence (1-4,13,14).

Aim of the work. Study of dissolution profiles of nifedipine tablets from different manufacturers to further assess of their equivalence *in vitro*, as well as study of the dependence of the dissolution profile on the adjuvants composition.

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MATERIAL AND METHODS

The study included two samples of selected drugs nifedipine of different composition from Ukrainian producers, sample A and sample B, 10 mg tablets. As a reference drug used "Corinfar" 10 mg tablets. Selecting of the reference product was conducted in accordance with the requirements of the WHO recommend primarily used as a comparator the original drugs (4,14).

Comparative study of the kinetics of dissolution was carried out in accordance with the WHO's requirements using 3 buffer media with pH 1.2 (hydrochloric acid buffer); 4.5 (acetate buffer); 6.8 (phosphate buffer) and in accordance with the requirements of the Manual of Clinical Trials "Investigation of Bioavailability and Bioequivalence" (5). All buffer solutions were prepared in accordance with SPhU (12). pH of the solution was measured by pH meter pH 150MI, if necessary the pH was adjusted to the desired value. Test "Dissolution" was performed in the apparatus by Pharma Test (Germany) "Device with basket" (temperature - 37 °C, the rate of rotation of the vane - 75 rev/min, the volume of dissolution medium - 900 ml).

In the glasses 1 tablet of each of the nifedipine medicines respectively were placed for dissolving. Sequential sampling was performed at 15, 30, 45 min in the volume of 10 ml, same volume of buffer solution was added to the dissolution medium for maintaining of volume. Obtained samples were allowed to stand at room temperature in a dark place for 20-30 min, then filtered through a paper filter. To obtain statistically reliable results, the study was carried out by 6 times for each drug.

The content of extracted active substance was determined by UV spectrophotometry. The absorbance of samples was measured with a spectrophotometer Evolution 60S at a wavelength of 343 nm in a cuvette with a layer thickness of 10 mm. Simultaneously, the absorbance of standard solution of nifedipine at a concentration of 0.02 mg/ml in an appropriate buffer was measured. As the comparison solution served the same buffer solution, which was used as dissolution medium.

RESULTS

To determine the character of the absorption spectrum were removed ultraviolet spectra of the standard sample (SS) of nifedipine in all buffer media at a concentration of active substance of 0.02 mg/ml. Fig. 1 shows an absorption spectrum in hydrochloric acid , acetate and phosphate buffer solutions, peaks are observed at the wavelengths 239 nm and 343 nm. The absorption spectra of the extracts of the investigational drugs tablet mass in the same buffer solutions were identical.

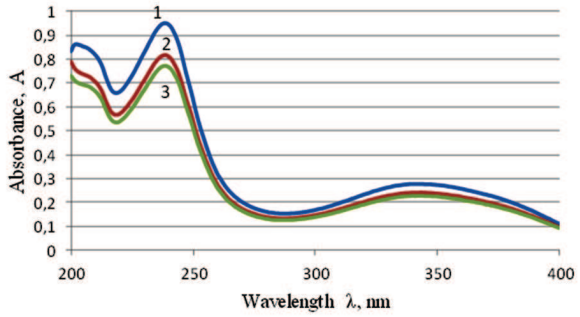

Fig. 1. Ultraviolet absorption spectrum of nifedipine SS in hydrochloric buffer (1), acetate buffer (2) and phosphate buffer (3)

As a result of this experiment releasing profiles of nifedipine tablets of samples A and B, and of the original drug "Corinfar" were obtained. According to the analysis of obtained data (Fig. 2-4), nifedipine sufficiently rapidly goes into solution: after 15 minutes released not less than 70% of the active substance, then the dissolution process was dramatically slowed. As it often happens, the most significant differences between the release profiles were observed at the beginning of the test after 15 minutes. The dependence of release rate on pH of dissolution medium was observed: the release rate increased with increasing of pH.

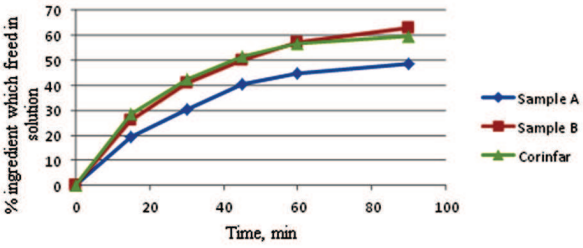

Fig. 2. Profiles of comparative dissolution kinetics of nifedipine medicines in hydrochloric acid buffer (pH 1.2)

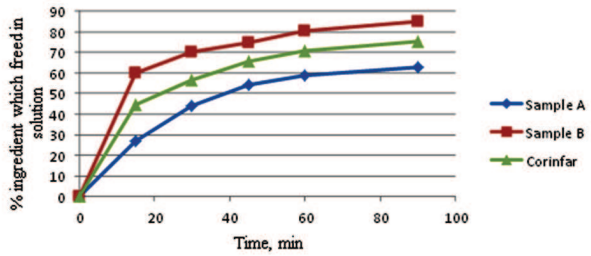

Fig. 3. Profiles of comparative dissolution kinetics of nifedipine medicines in acetate buffer (pH 4.5)

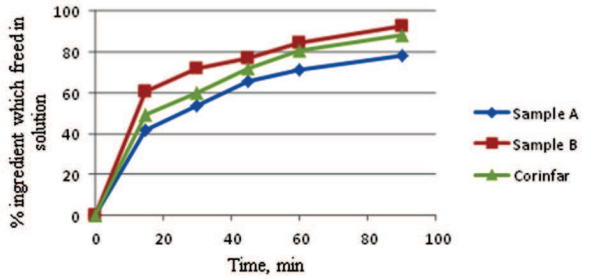

Fig. 4. Profiles of comparative dissolution kinetics of nifedipine medicines in phosphate buffer (pH 6.8)

DISCUSSION

From the data obtained by the dissolution profiles (Figs. 2-4) it is evident that at pH =1.2, sample B and "Corinfar" have identical dissolution profiles. The percentage of maximum release of nifedipine for 90 minutes was about 60%, while the percentage of nifedipine release from sample A was very low – 48.74%. With increasing pH values to 4.5 the percentage of nifedipine released from the sample B was increased to 85%, releasing from "Corinfar" was somewhat worse – 75%, and from the sample A – 63%. In phosphate buffer solution, there was a noticeable increasing of the release of nifedipine from all three samples: the sample B – 92%, "Corinfar" – 88%, the sample A – 78%.

Seeing that the dissolution profile of sample B is better than the original drug "Corinfar" and the dissolution profile of the sample A is significantly worse, we decided to study the tablet composition in order to find the dependence of the dissolution profiles on the adjuvants composition. In the table 1 set the composition of adjuvants of samples A, B and "Corinfar" tablets. From table 1 shows that the compositions of sample B and "Corinfar" are similar, except that the composition of sample B includes a combination of Tween-80 with sodium laurylsulfate, and "Corinfar" - Macrogol 35000. Sodium laurylsulfate is anionic surfactant which in combination with emulsifier Tween-80 promotes the dissolution of poorly soluble in water nifedipine. Therefore, releasing of nifedipine from the sample B passes noticeably better. The composition of "Corinfar" includes a combination of film formers Macrogol 6000 and Macrogol 35000, which are polyethyleneglycols (non-aqueous solvent, a solubilizer) and during the dissolution process they increase the solubility and the percentage of nifedipine release, so the release profile of "Corinfar" is better than the profile of sample A.

Table 1. Adjuvants composition of nifedipine tablets

Sample A	Sample B	"Corinfar"
	Lactose monohydrate	
	Potato starch	
Refined sugar		Cellulose
Polysorbate -80		Valium
		Magnesium stearate
		Povidone 25
		Macrogol 6000
		Talc
Calcium stearate		Titanium dioxide (E171)
		Quinoline yellow (E104)
	Sodium laurylsulfate	
	Twin-80	Macrogol 35000

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CONCLUSIONS

The dissolution profiles of nifedipine tablets from different manufacturers have been studied and have been founded that the percentage of nifedipine release from the sample B is higher than from "Corinfar", and the percentage of nifedipine release from "Corinfar" is higher than from the sample A.

Adjuvants composition of nifedipine tablets have been studied. It is founded that the inclusion of surfactants, solubilizers and emulsifiers into tablets contribute to increasing of active substance release from the dosage form.

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