INVESTIGATION OF FENOFIBRATE SOLUBILITY IN THE PRESENCE OF CHITOSAN

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Abstract
Fenofibrate is an active substance which is well absorbed from the gastrointestinal tract, but it is characterized by limited solubility. Due to a wide spectrum of its pharmacological activity, it would be beneficial to improve its solubility, and thus increase the drug absorption capability. The aim of the study was to investigate the effect of chitosan on the solubility of fenofibrate incorporated into this polymer carrier. The study investigated fenofibrate in solid dispersions at the drug to polymer ratio of 3:7,5:5,7:3. The solubility investigation was performed by means of a dynamic method in a dissolution apparatus; mean amount of dissolved fenofibrate and the drug to polymer quantitative ratio in which the solid dispersion possessed the most beneficial properties improving the drug solubility were calculated. The study revealed a multi-fold increase (from 33 to 50 times) in fenofibrat solubility in the presence of chitosan, which increased with duration of the study and with increasing percentage of the polymer in formulations. The obtained results may help develop new technologies for fenofibrate preparations with chitosan, with better solubility characteristics, and thus increased bioavailability of the drug.

Key words: *solid state, dissolution, fenofibrate, chitosan.*

1. Introduction

An oral drug form is a convenient and simple dosage form. However an orally administered drug undergoes a number of complex and differentiated individually phenomena. Among them, the effect of intaken food, pH of the gastric content, intestinal passage, the presence of endogenous surfactants, as well as the character of the active substance itself should be considered [1]. The drug, in order to be absorbed into the bloodstream, has to be present in the form of solution at the site of absorption. For this reason the degree of the drug absorption from the gastrointestinal tract may be limited by its poor solubility [2].

Majority of currently used drugs are characterized by poor solubility in water. Active substances which are well absorbed from the gastrointestinal tract, but are characterized by limited solubility, constitute a special case. Fenofibrate is one of these drugs; it reveals a broad spectrum of pharmacological activity. It decreases the levels of LDL-c cholesterol and triglycerides, and increases the level of the HDL-c fraction. In studies involving diabetic patients it increased insulin sensitivity of cells, as well as improved the vasodilating effect of vascular endothelial cells. In future this drug may play an important role in the therapy of metabolic syndrome [3].

Recent reports have demonstrated that the use of solid dispersions in order to increase drugs solubility is a highly effective method. Solid dispersions with the use of polymers, especially chitosan, as a carrier, play an exceptional role. Chitosan, dispersing in water environment, causes a significant increase in the contact area of the drug with solution, increases its hydrophilic properties and may affect its crystalline structure. All these factors lead to increased solubility of the drug [4 - 6].

Thus a study was undertaken to investigate the effect of chitosan on the solubility of fenofibrate incorporated into this polymer carrier.

2. Materials and methods

2.1. Materials

The study was performed with the use of fenofibrate (Fenofibrat p.a. min. 99%, SIGMA, Italy) incorporated into natural, highly purified chitosan with 95% deacetylation and viscosity average molecular weight $M_\eta = 429$, intrisic viscosity η in $dm^3\ g^{-1} = 0{,}3132$ (Chitozan 652 p.a., Chitine, France), sodium lauryl sulfate p.a., PPH 'Stanlab', Poland, Aqua purificata, acc. to FP VIII.

2.2.Methods

2.2.1. Examination of pure fenofibrate and its solid dispersions solubility rate

Evaluation of solubility was performed in a dissolution apparatus according to FPVII, which describes investigation of active substance solubility rate from solid drug forms [7]. The examination was performed in a VanKel VK 7025 dissolution apparatus, to which Varian Inc. fraction collector was attached. 1000 ml of 0.5% solution of sodium lauryl sulfate (SLS) at pH 6.8 was used as a release medium.

Solubility was evaluated after compressing 100 mg of samples, which were placed in each of the six chambers of the apparatus at 37 ± 0.5 °C, with velocity of 100 rotations per minute. The trial was continued for 1 hour, 5 ml samples were collected in 10 time intervals, i.e. after 5, 10, 15, 20, 25, 30, 35, 40, 50 and 60 minutes. Collected samples were filtered on filters with 10 μm pore size.

The collected samples were diluted and next their content was evaluated with the use of JASCO V650 spectrophotometer with the use of 1 cm cuvette at wavelength $\lambda = 290$ nm.

The drug concentration in samples and an average percentage of dissolved fenofibrate were calculated using linear regression equation for fenofibrate, $y = 0.439 x + 0.0172$. Quantitative drug-to-polymer ratios in which the solid dispersion had the most beneficial properties improving the drug solubility were determined.

2.2.2. Technology for the preparation of investigated formulations

2.2.2.1. Preparation of samples for investigation of fenofibrate solubility

The solubility of fenofibrate was investigated immediately after compressing the powders in a Specac hydraulic press. The prepared 100 mg samples weighed on a Mettler balance were pressed on a punch die with a diameter of 13 mm. The pure drug and physical mixtures were pressed at a pressure of 5 ton for 20 sec.

2.2.2.2. Preparation of fenofibrate and polymer physical mixtures

Physical mixtures were prepared by grinding in an agate mortar for 10 minutes of adequate amounts of fenofibrate with chitosan at drug-to-polymer weight ratios 3:7,5:5,7:3 weighed on a Sartorius analytical balance. The prepared physical mixtures were passed through a sieve with 315 μm wholes, and next placed in glass bottles sealed with cork and stored in an exicator over silica gel. Every sample was prepared in 1 g amount.

2.2.3. Statistical analysis

Statistical analysis was performed for maximum percentage values of fenofibrate solubility (in 60 minutes) from dispersions containing chitosan. The effects of chitosan as well as the effect of the dispersion preparation method on the drug solubility were analyzed. In order to check the normality of variables distribution, the following tests were performed: the Kolmogorov-Smirnov, the Lilliefors, as well as the Shapiro-Wilk tests. Next the variance homogeneity was checked by means of the Brown-Forsythe's test at significance level $p < 0.50$ as well as ANOVA variance analysis was performed.

3. Results and discussion

Fenofibrate is a BCS class II drug (Biopharmaceutical Classification System); it is practically insoluble, with solubility in water less than 0.5 mg/l [8].

Table 1 presents the solubility of pure fenofibrate without the presence of chitosan prepared according to p. 2.2.3.1. The solubility findings of pure fenofibrate in 0.5% SLS were used as reference to compare the solubility of the drug incorporated into chitosan.

Table 1. *Dissolution of fenofibrate alone in 0.5 % aqueous solution SLS.*

time, min	concetration, mg/100 ml	average of dissolubility, %	standard deviation
5	0.0710	0.57	0.0600
10	0.0781	0.63	0.0551
15	0.0878	0.70	0.1050
20	0.0998	0.80	0.0751
25	0.1256	1.01	0.0300
30	0.1306	1.05	0.0400
35	0.1418	1.15	0.0058
40	0.1483	1.20	0.0058
50	0.1747	1.41	0.0700
60	0.1920	1.55	0.0950

Table 2. *Influence of chitosan on dissolution of fenofibrate from physical mixture in 0.5% aqueous solution SLS.*

Drug / polimer ratio	time, min	average percentage of dissolved fenofibrate	standard deviation
3/7	5	18.99	0.0500
	10	30.51	0.1100
	15	38.86	0.0000
	20	45.60	0.0950
	25	50.98	0.0551
	30	55.64	0.0651
	35	59.62	0.0300
	40	63.30	0.2150
	50	68.69	0.0451
	60	73.05	0.0600
5/5	5	13.68	0.2750
	10	22.93	0.2700
	15	30.42	0.2950
	20	36.61	0.2200
	25	41.88	0.2200
	30	46.46	0.2100
	35	50.54	0.1750
	40	54.09	0.1450
	50	59.99	0.1800
	60	64.88	0.1350
7/3	5	8.41	0.0551
	10	14.70	0.0500
	15	20.22	0.1000
	20	25.02	0.0351
	25	29.22	0.0500
	30	33.17	0.0351
	35	36.47	0.0500
	40	39.80	0.0153
	50	45.28	0.0300
	60	50.04	0.0600

The drug solubility was found to increase gradually and it was from 0.57% to 1.55% of the investigated dose.

Analysis of data included in ***Table 2*** and plotted solubility curves presented in Figure 1 revealed that the addition of chitosan had a beneficial effect on the fenofibrate solubility profile in the investigated solid dispersions.

The results of the study demonstrated that all the investigated physical dispersions of fenofibrate with chitosan increased the solubility of fenofibrate.

The presence of chitosan increased significantly the solubility of fenofibrate, which increased with duration of the trial and with increasing percentage of polymer in the formulations.

The highest solubility of fenofibrate, amounting to 73%, was observed after 60 minutes from physical mixtures containing the drug-to-polymer weight ratio 3:7. In dispersions containing 50% of the drug and of the polymer, the solubility of fenofibrate was at the level of 65%. The lowest solubility was observed in dispersions in which the drug-to-polymer weight ratio was 7:3, in which case the drug solubility was slightly above 50%.

Comparing data from Tables 1 and 2, we can notice a significant increase in the drug solubililty, which in the presence of chitosan increased 33 times, 43 times and almost 50 times in relation to the amount of added polymer in comparison to the solubility of pure drug.

When the course of fenofibrate solubility curves in the presence of chitosan is observed, it becomes apparent that they are situated in the field above the fenofibrate solubility curve without polymer.

The solubility curve for fenofibrate mixed with chitosan at 3:7 ratio assumes the highest position in the field, also the inclination angle of the straight line to time axis is significant, and the drug solubility in relation to time is from 30.51% to 73.05%, i.e. it increases with time.

The solubility line of pure fenofibrate is characterized by a low inclination angle to the time axis, and the drug solubility in time increases slightly and is from 0.57% to 1.55%.

Increased solubility of fenofibrate in solid dispersion with chitosan may be explained by numerous factors. Decreased size of the molecules may be the first of them. Chitosan, when dispersing in water, may cause molecular dispersion of the drug by increasing the surface of the drug solubility [4, 5].

Chitosan in dispersions may prevent agglomeration of fenofibrate molecules and increase wettability of the drug molecules, thus intensifying the drug solubility.

The above findings were supported by statistical analysis of the investigated samples.

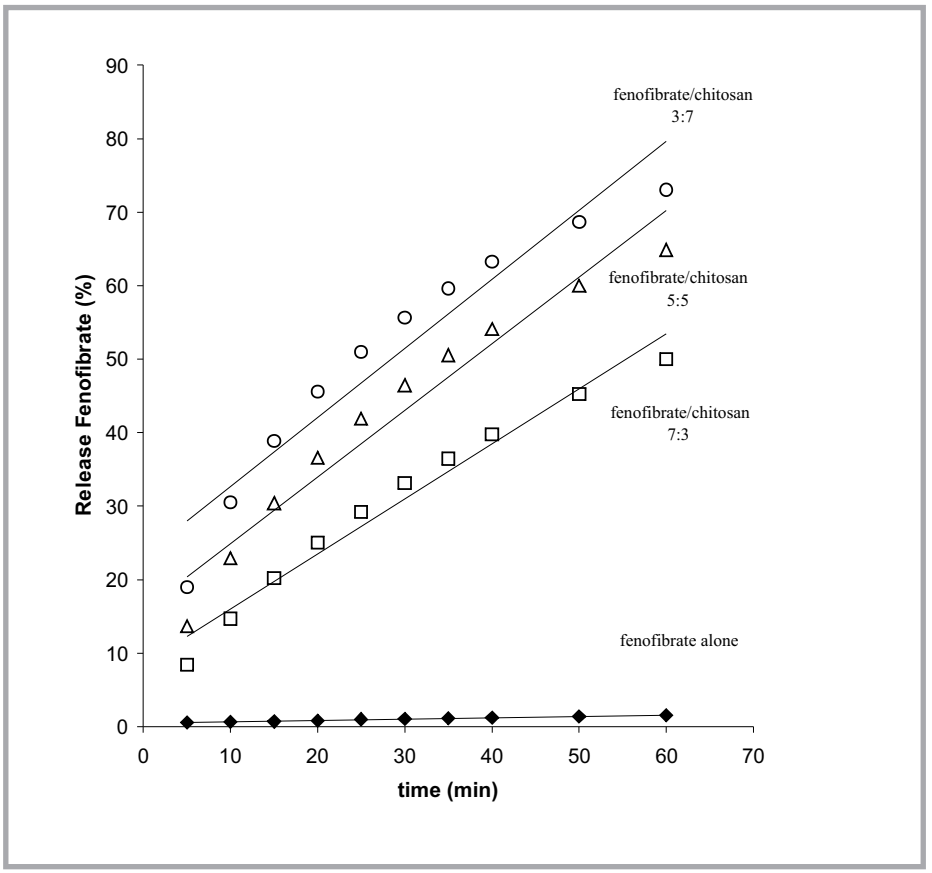

Figure 1. *Dissolution profiles of Fenofibrate from physical mixture in water 0.5% SLS medium.*

Normality tests performed for the percentage amount of dissolved fenofibrate after 60 minutes in relation to the drug-to-polymer weight ratio revealed normal distribution of data. Variance analysis demonstrated statistically significant differences in the findings in relation to the applied composition of physical mixtures. Value $p<0.05$ was assumed as statistically significant.

4. Conclusions

Chitosan demonstrated a significant effect on the solubility of fenofibrate. The effect depends on the drug-to-polymer quantitative ratio. The highest solubility of fenofibrate was achieved in the presence of chitosan at the drug-to-polymer weight ratio 3/7 (30% of the drug and 70% of the polymer).

The above results may enable development of new technologies for fenofibrate formulations with the use of chitosan, which would be characterized by better solubility and thus increased bioavailability of the drug.

5. References

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