

INFLUENCE OF THE PHYSICOCHEMICAL FACTORS ON DISSOLUTION OF THE SUBSTANCE OF CLASS II BCS FROM SOLID DISPERSIONS WITH CHITOSAN

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Abstract

The BCS class II includes drugs with low solubility and high permeability. Fenofibrate is an example of this class drugs. The aim of the study was to investigate the effect of chitosan about average molecular weight in various formulations on the dissolution of fenofibrate incorporated into this polymer carrier. The study investigated fenofibrate in solid dispersions using a method of the solvent evaporations at the drug to polymer ratio of 1:9;3:7;5:5. The highest dissolution of fenofibrate, amounting to 72.7%, was observed after 60 minutes from solid dispersions with drug-polymer weight ratio 1:9 in the presence chitosan A and was 72 times higher in relation to the amount of added polymer in comparison to the solubility of pure drug. Investigations DSC showed that fenofibrate was remained in crystalline state in solid dispersion.

Key words: *solid dispersion prepared solvent evaporation, dissolution, fenofibrate, different molecular weights of chitosan.*

1. Introduction

The therapeutic efficacy and bioavailability of any drug depends up on the solubility of drug. Solubility of drug is one of the important parameter to attain the desired concentration of drug in systemic circulation for the pharmacological response.

Various solubility enhancement techniques are investigated such as particle size reduction pH adjustment co-solvency, complexations and solid dispersions [1, 2].

Fenofibrate is a Biopharmaceutics Classification System (BCS) Class II drug with a log P value of 5.3. Fenofibrate is a lipophilic drug with a low aqueous solubility. Thus the low oral bioavailability of Fenofibrate is due to its solubility and dissolution limitations [3, 4].

Recent research aiming at increasing drug solubility has focused on formation of solid dispersions with polymer carriers. The role of such a carrier may be performed by chitosan.

Thus a study was undertaken to investigate the effect of chitosan about different viscosity and average molecular weight on the solubility of fenofibrate incorporated into this polymer using a method of the solvent evaporation In order to determine changes in the structure, or possible drug-polymer interactions occurring in the prepared solid dispersions, thermochemical examinations were performed by means of differential scanning calorimetry (DSC).

Demonstration of the effect of chitosan about average molecular weight in various formulations or with various methods of preparation of the solid dispersions on the solubility of fenofibrate may enable development of new preparations of this drug with increased dissolution [5-7].

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 **sample S** with 92% deacetylation and viscosity average molecular weight $M_{\eta} = 1087$ kDa, intrinsic viscosity $\eta = 0.7437$ dm³ g⁻¹, **sample A** 92% deacetylation and viscosity average molecular weight $M_{\eta} = 839$ kDa, intrinsic viscosity $\eta = 0.5843$ dm³ g⁻¹, **sample B** 92% deacetylation and viscosity average molecular weight $M_{\eta} = 407$ kDa, intrinsic viscosity $\eta = 0.2986$ dm³ g⁻¹ (Chitosan Huasu p.a., Chitin, France), sodium lauryl sulfate p.a., PPH „Stanlab”, Poland, Aqua purification, acc. to FP VIII.

2.2. Methods

2.2.1. Examination of pure fenofibrate and its solid dispersions dissolution 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 [8]. 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.

Dissolution 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 μ m 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, $y = 0.0414x + 0.0153$. Quantitative drug-to-polymer ratios in which the solid dispersion had the most beneficial properties improving the drug dissolution were determined.

2.2.2. Comparison of dissolution profiles

Dissolution profiles were compared by using similarity factor (f_2), which is defined by the following equation $f_2 = 50 \log\{[1 + 1/n \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100\}$ where: n is the number of dissolution sampling time, and R_t and T_t are the percentage of tablet dissolved at each time point for the reference and test products, respectively. An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

2.2.3. Examination of samples by means of differential scanning calorimetry (DSC).

In the study the DSC analysis was performed with the use of samples prepared according to the formula presented in paragraph 2.2.3.4. A DSC 25 flow calorimeter manufactured by Mettler Toledo with integrated STAR^e program was used. The samples were heated at a rate 5 °C per minute to a range from 30 to 300 °C. Argon with 99.999% purity was passed through the measurement compartment at the flow rate 50 ml/min. The examination was carried out in 40 μ l aluminum melting pots with a cover.

2.2.3. Technology for the preparation of investigated formulations

2.2.3.1. Preparation of samples for investigation of fenofibrate dissolution

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 2 ton for 20 sec.

2.2.3.2. Preparation of fenofibrate-chitosan solid dispersions by means of solvent method

Adequate amounts of fenofibrate were weighed on a Sartorius analytical balance and dissolved in 3 ml of chlorophorm. Adequate amounts of chitosan medium and high molecular weight, weighed on an analytical balance were in chlorophorm and to obtain drug-polymer mass ratio 1:9, 3:7, 5:5 suspended. The solvent was removed using a rotary evaporator.

Table 1. The quantitative composition of solid dispersion prepared by the evaporation method of the fenofibrate onto chitosan.

Average molecular weight of chitosan	Solid dispersion	Drug/ polymer ratio	Quantity of polymer, mg	Quantity of polymer, mg	Quantity of chloroform, ml
Sample S $M_n=1087$ kDa	SDS55	5:5	500	500	5
	SDS37	3:7	300	700	3
	SDS19	1:9	100	900	1
Sample A $M_n=839$ kDa,	SDA55	5:5	500	500	5
	SDA37	3:7	300	700	3
	SDA19	1:9	100	900	1
Sample B $M_n=407$ kDa	SDB55	5:5	500	500	5
	SDB37	3:7	300	700	3
	SDB19	1:9	100	900	1

The resultant solid dispersion was transferred to an aluminum pan and allowed to dry at room temperature.

The drying was next powdered in an agate mortar for 10 minutes and passed through a sieve with 315 μm wholes. Every dispersion was prepared in the amount of 1 g (**Table 1**), placed in glass bottles sealed with cork and stored in an excicator over silica gel.

3. Results and discussion

3.1. Dissolution of fenofibrate in presence of chitosan

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

The drug dissolution was found to increase gradually with time and it was from 0.18% to 1.02% of the investigated dose.

Analysis of data from **Tables 1 - 2** and **Figure 1** revealed that the addition of chitosan has a considerable effect on fenofibrate dissolution in the range of investigated solid dispersions.

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

The presence of chitosan improved markedly the dissolution of fenofibrate, which increased with time and with amount of the chitosan in formulations. The dissolution rates presented in **Table 2** indicated that fenofibrate dissolution from solid dispersions was dependent on the molecular weight of chitosan.

The highest dissolution of fenofibrate, amounting to 72.69%, was observed after 60 minutes from solid dispersions with drug-polymer weight ratio 1:9 in the presence chitosan A.

Comparison of data from **Tables 2 - 3** demonstrates a significant increase in the drug dissolution, which in the presence of chitosan- 839 kDa (chitosan A) in dispersions was almost 15 times (for weight ratio 5:5), 50 times (for weight ratio 3:7), 72 times (for weight ratio 1:9) higher in relation to the amount of added polymer in comparison to the solubility of pure drug.

It was noticed that the dissolution rate of fenofibrate from the dispersions in the presence of chitosan - $M_n = 1087$ kDa (chitosan S) and $M_n = 407$ kDa (chitosan B) was obviously lower than that from the dispersions with chitosan - $M_n = 839$ kDa. The enhancement of drug dissolution rate is about 66-to for weight ratio 1:9 (time 60 min) solid dispersion fenofibrate in chitosan - $M_n = 1087$ kDa and chitosan $M_n = 407$ kDa respectively formulations.

In dispersions containing 10% of the drug and 90% of the chitosan S and chitosan B the dissolution of fenofibrate was at the level of 66%. The result demonstrated higher drug dissolution of the solid dispersion prepared by means of solvent method containing chitosan

Table 2. Dissolution of fenofibrate alone in 0.5% aqueous solution SLS.

Time intervals collected samples, min	5	10	15	20	25	30	35	40	50	60
Average of dissolubility, %	0.18	0.24	0.32	0.36	0.43	0.47	0.57	0.75	0.84	1.02
Standard deviation	0.01	0.01	0.05	0.05	0.06	0.04	0.07	0.12	0.11	0.14

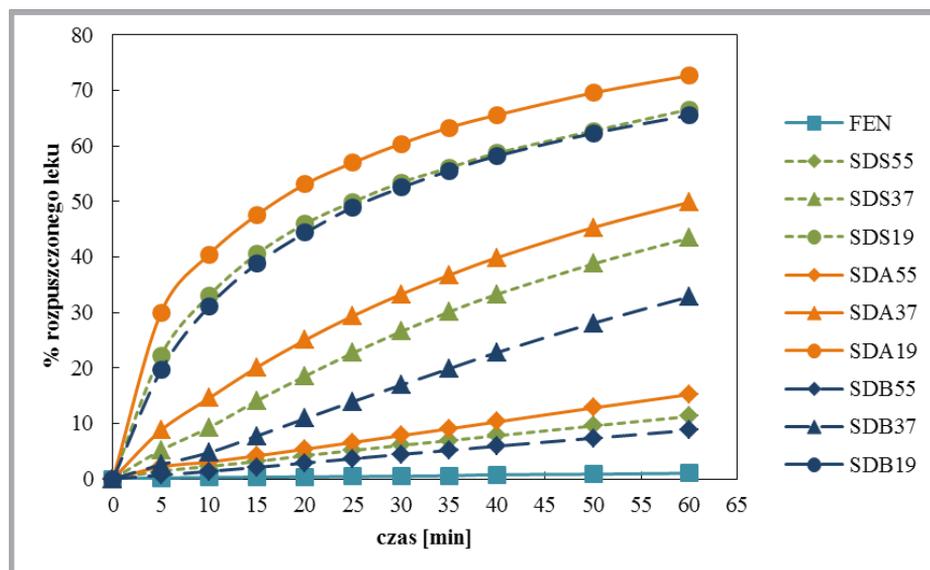


Figure 1. Dissolution profiles of Fenofibrate from solid dispersion in water 0.5% SLS medium.

Table 3. Influence of chitosan on the dissolution of fenofibrate from solid dispersion prepared by the evaporation method in 0.5% aqueous solution SLS.

	Time, min	SDS 55		SDS 37		SDS 19	
		average % dissolved of fenofibrate	standard deviation.	average % dissolved of fenofibrate	standard deviation	average % dissolved of fenofibrate	standard deviation
Fenofibrate – to – Chitosan S - weight $M_n = 1087$ kDa weight ratio of solid dispersion	5	1.41	0.19	5.15	0.47	22.25	0.38
	10	2.24	0.30	9.24	0.57	33.03	0.57
	15	3.13	0.40	14.08	0.50	40.54	0.83
	20	4.19	0.54	18.52	0.56	45.99	0.76
	25	5.13	0.63	22.70	0.52	49.94	0.81
	30	6.04	0.70	26.55	0.44	53.43	0.83
	35	6.91	0.75	30.09	0.48	56.08	1.04
	40	7.77	0.82	33.27	0.47	58.73	1.16
	50	9.54	0.95	38.74	0.36	62.73	0.83
60	11.25	1.06	43.40	0.27	66.61	0.60	
Fenofibrate – to – Chitosan A - weight $M_n = 839$ kDa weight ratio of solid dispersion	5	2.16	0.38	8.75	0.36	29.97	0.19
	10	3.04	0.57	14.54	0.42	40.45	0.05
	15	4.14	0.83	20.12	0.59	47.60	0.09
	20	5.36	0.76	25.02	0.62	53.10	0.09
	25	6.57	0.81	29.38	0.70	57.02	0.13
	30	7.80	0.83	33.28	0.74	60.42	0.16
	35	9.03	1.04	36.71	0.77	63.33	0.22
	40	10.27	1.16	39.87	0.86	65.60	0.31
	50	12.79	0.83	45.30	0.93	69.58	0.36
60	15.21	0.60	49.85	0.91	72.69	0.35	
Fenofibrate – to – Chitosan B - $M_n = 407$ kDa weight M weight ratio of solid dispersion	5	0.68	0.01	2.55	0.27	19.56	0.38
	10	1.34	0.03	4.72	0.05	31.11	0.58
	15	2.07	0.00	7.73	0.21	38.80	0.54
	20	2.85	0.03	10.85	0.48	44.36	0.54
	25	3.63	0.02	13.94	0.70	48.97	0.63
	30	4.42	0.02	16.91	0.93	52.52	0.60
	35	5.13	0.05	19.86	1.06	55.53	0.67
	40	5.90	0.03	22.77	1.15	58.20	0.76
	50	7.33	0.06	28.06	1.18	62.28	0.65
60	8.75	0.09	32.84	1.11	65.53	0.66	

Sample A than that of chitosan sample S and sample B. The difference in dissolution rate enhancement by chitosan A and chitosan S and B can be explained as, the lower the molecular weight; the faster was the drug dissolution.

This behaviour was predictable taking into account the relationship between molecular weight and viscosity of polymer solution. These results demonstrated the carrier-controlled drug dissolution in solid dispersion systems [9].

Chitosan, dispersing in water environment, causes a significant increase in the contact area of the fenofibrate with solution, increases its hydrophilic properties of drug and may affect its crystalline structure.

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

3.2. Analysis of DSC thermograms for fenofibrate, chitosan and their solid dispersions

DSC thermograms are presented in **Figure 2**, while data concerning the temperatures of the observed thermal effects are presented in **Table 4**. The fenofibrate (F) heating curve contains a sharp, single endothermic peak of melting at 79.1 °C, Peak height was ($\Delta H = 118.33$ J/g). In solid dispersions, a sharp peak as pure fenofibrate was observed at 77.10 °C. Peak height was reduced to 9.9 J/g. Sharp peak indicated that Fenofibrate was remained in crystalline state in solid dispersion.

The polymer heating curves revealed broad, endothermic heat effects accompanying melting of the drug. Chitosan heated to 180 °C did not undergo dissolution. Heated the drug to temperature 180 °C did not undergo schedule. On curve of heating chitosan in range of temperature 25 - 130 °C wide endothermic thermal answering effect was observed probably dehydration of sample Solid dispersion of fenofibrate with chitosan is characterized by thermal stability in the investigated range of temperatures.

Thermograms do not contain any new thermal effects, only overlapping of a sharp fenofibrate melting peak with a broad polymer melting peak.

The height of the melting peak for fenofibrate in solid dispersions is slightly decreased, what results from the polymer content in the mixture – in mixtures with a higher content of the polymer the decrease is more significant.

Thermograms for solid dispersions of fenofibrate with chitosan demonstrate a distinct shift of the peak corresponding to fenofibrate melting point towards lower temperatures in comparison to pure drug. For solid dispersions prepared by evaporation of the solvent in the, this temperature shift ranged to 2,0 °C. The degree of lowering of temperature and increased heat effects is correlated with increased solubility of the drug in all the formulations.

The above studies require supplementation with structural and qualitative studies of the obtained solid dispersions. Above been mentioned investigations should be confirmed investigations powder X-ray diffraction in aim of exact examining of changes of structure fenofibrate in direction of amorphous state.

Table 4. *Temperatures and heat effect (ΔH [J/g]) for the fenofibrate (F) and solid dispersions obtained by solvent evaporation with chitosan (CH) in relation to the drug/polymer ratio.*

Sample	Fenofibrate	
	Temperature at the beginning of the peak, °C	Heat effect of the drug melting in formulation ΔH , J/g
Fenofibrat pure	79.1	118.3
Solid dispersion 1:9	77.1	9.9

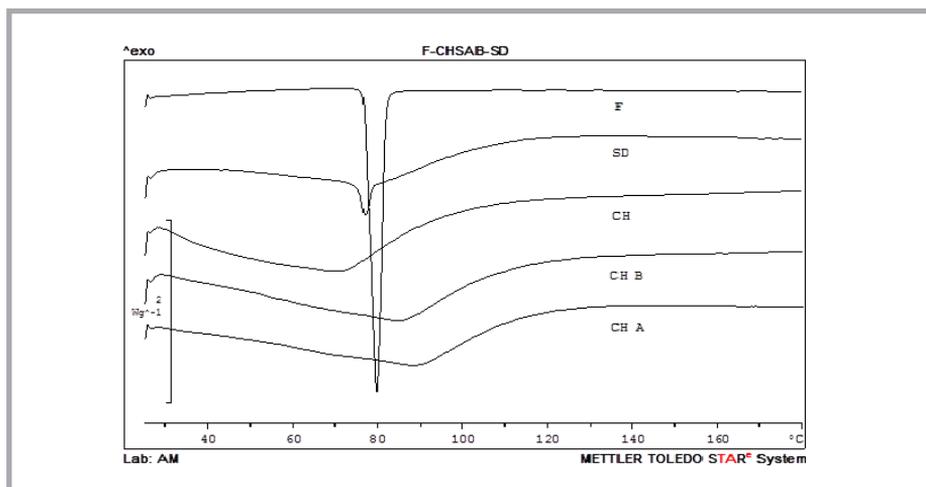


Figure 2. DSC thermogram of fenofibrate (F), chitosan S (CH S), chitosan A (CH A), chitosan B (CH B), and solid dispersion prepared (SD) drug polymer:ratio 1:9.

4. Conclusions

1. Solid dispersions prepared evaporation of solvent technique of with chitosan increased the dissolution of fenofibrate. The effect depends on the drug/polymer weight ratio and on molecular weight of chitosan.
2. Highest dissolution of fenofibrate was achieved at drug/polymer ratio 1:9 in the presence medium-molecular-weight chitosan Chitosan A
3. Investigations DSC showed that degree of lowering of temperature and increased heat effects of fenofibrate is correlated with increased dissolution of the drug in the formulation.

5. References

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