INVESTIGATION OF PHYSICOCHEMICAL PROPERTIES OF THE SOLID DISPERSIONS IN THE PRESENCE POLYMERIC CARRIER-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 on the saturation solubility of fenofibrate incorporated into this polymer carrier. The study investigated fenofibrate in solid dispersions using a method of the solvent evaporation and physical mixtures at the drug to polymer ratio of 1:9, 3:7, 5:5. Solid dispersion of fenofibrate containing different ratio of medium and high molecular weight chitosan showed high saturation solubility compared to pure sample of drug. IR spectroscopy reveals that there was no chemical interaction between drug and the polymer. DSC studies showed that there is no change in the crystal structure of drug during the solid dispersion technique. Chitosan has been proposed as a useful excipient for enhancing the bioavailability of poorly water-soluble compounds.

Key words: *solid dispersions, physical mixtures, saturation solubility, fenofibrate, chitosan, DSC, IR studies.*

1. Introduction

The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes according to their solubility and permeability. The BCS II class of compounds exhibit high permeability and low solubility relative to the administered dose. Solubility. one of the key parameters in BCS. as well as dissolution rate is the most essential factors controlling the rate and extent of drug absorption. One way to increase the solubility of poorly soluble drugs is through the formation of solid dispersion [**1, 2**].

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. 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 [**3 - 6**]. The range of chitosan molecular weight is extensive and is thus divided into three categories: low-molecular-weight chitosan (LMWC). medium-molecular-weight chitosan (MMWC) and high-molecular-weight chitosan (HMWC) [**7, 8**].

As a consequence of increasing molecular weight. some physicochemical and biological properties of chitosan and its solutions change. which determines the bioactivity of the material.

Fenofibrate`s clinical profile of significantly reducing total cholesterol .low-density lipoprotein cholesterol and triglycerides while significantly increasing high-density lipoprotein cholesterol .is well recognised. In aqueous media. fenofibrate exhibits very poor solubility at 37 °C ≤ 0.0002912 mg/ml...

Thus a study was undertaken to investigate the effect of chitosan on the saturation solubility of fenofibrate incorporated into this polymer carrier using a method of the solvent evaporation in the temperature room and physical mixture. 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) and Infrared Spectroscopy (IR).

Demonstration of the effect of chitosan 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 solubility.

2. Materials and methods

2.1. Materials

The study was performed with the use of fenofibrate (Fenofibrat p.a. min. 99%. SIGMA. Italy) chitosan **high molecular weight - sample S** with 92% deacetylation and viscosity average molecular weight M_η = 1087 kDa. intrinsic viscosity η = 0.7437 dm3 g^{-1}.

medium molecular weight - sample A 92% deacetylation and viscosity average molecular weight M_η = 839 kDa. intrinsic viscosity η = 0.5843 $dm^3\ g^{-1}$ **and sample B** 92% deacetylation and viscosity average molecular weight M_η = 407 kDa. intrinsic viscosity η = 0.2986 $dm^3\ g^{-1}$ (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. Saturation solubility studies of pure fenofibrate and its solid dispersions.

The saturation solubility of fenofibrate was determined in 0.5% aqueous concentrations of Sodium Laurel Sulphate- SLS pH 7.6 as a solvent. Each excessive quantity 10 mg of fenofibrate and equivalent prepared physical mixtures and solid state using a method of the solvent evaporation in the temperature room we take in screws capped test tubes with fixed volume 10 ml of 0.5% solutions SLS. The resultant suspension was treated at 37 °C with 100 r.p.m. in incubator shaker. After 24 h so that the equilibrium could be achieved .the samples were withdrawn and filtered through Whatman filter paper and the filtrate was assayed spectrophotometrically (JASCO V 650) at 290 nm. The concentration of fenofibrate was calculated by reference to predetermined standard curves. All solubility were measured in triplicate and reported as the mean the standard deviation of the mean.

2.2.2. 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 2.2.4.1. and 2.2.4.2. A DSC 25 flow calorimeter manufactured by Mettler Toledo with integrated STARe program was used. The samples were heated at a rate 5 °C per minute to a range from 30 °C 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 40µl aluminum melting pots with a cover. The samples were of 5 - 10 mg in weight.

2.2.3. Statistical analysis

Statistical analysis was performed for maximum percentage values of fenofibrate saturation solubility 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 Levene`a and Scheffe`a 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.

2.2.4. Technology for the preparation of investigated formulations

2.2.4.1. 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 **a**nd 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. 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. placed in glass bottles sealed with cork and stored in an exicator over silica gel (***Table 1***).

2.2.4.2. Preparation of fenofibrate-chitosan physical mixtures

Physical mixtures were prepared by grinding in an agate mortar for 10 minutes of adequate amounts of fenofibrate with chitosan about average molecular weight: Mη = 1087 kDa, Mη = 839 kDa, Mη = 407 kDa at drug-to-polymer weight ratios 1:9, 3:7, 5:5 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 (***Table 1***).

3. Results and discussion

3.1. Effect of chitosan on saturation solubility

Table 1 presents the experimentally determined solubility of fenofibrate in 0.5% solution SLS. The prepared physical mixture and solid dispersion with different chitosan's were show significantly higher solubility compared to drug alone. It is to be expected that fenofibrate would be solubilised well in solid dispersed form due to adsorption of polymers and surfactants. The solubility of fenofibrate is therefore expected to limit its absorption from the gastrointestinal tract.

Analysis of data from ***Table 1*** revealed that the addition of chitosan has a beneficial effect on fenofibrate saturation solubility in the range of investigated solid dispersions. The solubility of fenofibrate in 0.5% SLS in 37 °C was found to be 4.7 mg/100 ml.

The highest saturation solubility of fenofibrate. amounting to 13.89 and 13. 78 mg/ml was observed from physical mixtures with drug-polymer weight ratio 1:9 in the presence of chitosan S and chitosan A. The mechanism for solubility enhancement by solid dispersions

Table 1. *Solubility of fenofibrate. physical mixtures and solid dispersion depending on chitosan about different molecular weight; * Each value represents mean ± S.D. (n = 3).*

Average molecular weight of chitosan	Drug/ polymer ratio	Physical mixtures	Solubility*. %	Solubility. mg/100 ml	Solid dispersions	Solubility*. %	Solubility. mg/100 ml
Sample S Mη = 1087 kDa	5:5	MFS55	17.95 ± 0.48	8.97	SDS55	15.48 ± 0.47	7.74
	3:7	MFS37	22.98 ± 0.69	11.49	SDS37	18.89 ± 0.21	9.45
	1:9	MFS19	27.56 ± 0.77	13.78	SDS19	24.66 ± 0.48	12.33
Sample A Mη = 839 kDa.	5:5	MFA55	18.14 ± 0.57	9.07	SDA55	17.05 ± 0.20	8.53
	3:7	MFA37	24.74 ± 0.62	12.37	SDA37	30.32 ± 0.50	10.16
	1:9	MFA19	27.47 ± 0.45	13.89	SDA19	25.08 ± 0.11	12.54
Sample B Mη = 407 kDa	5:5	MFB55	16.34 ± 0.06	8.17	SDB55	12.50 ± 0.13	6.25
	3:7	MFB37	21.14 ± 0.42	10.57	SDB37	14.67 ± 0.33	7.33
	1:9	MFB19	24.82 ± 0.13	12.41	SDB19	20.48 ± 0.36	10.24
Fenofibrate			9.50 ± 0.1				4.75

is reported to be due to increased surface area due to reduction in particle size of drug and wetting and solubilizing effect of the chitosan.

The solubility of fenofibrate from the physical mixtures with chitosan was higher and significantly higher than from the solid dispersions and pure drug.

Solid dispersions prepared by means of solvent method with chitosan showed solubility enhancement up to 6.25 mg/100 ml while that prepared by physical mixtures by grinding technique showed solubility enhancement up to 13.89 mg/100 ml.

The solubility of fenofibrate was found to increase from 6.25 mg/100 ml to about 13.84 μg/ml i.e. 2 times higher than that of pure drug in 0.5% SLS.

Summing up. the above analysis indicates that the polymer has significantly increased the solubility of fenofibrate in all the investigated solid dispersions. The best results were obtained for the weight ratios in which the content of fenofibrate was 30%. and of polymer 70% in presence of chitosan high molecular weight – sample S in physical mixtures.

3.2. Analysis of Infrared Spectroscopy

State of drug molecule with the polymer was determined using IR. The interaction between the drug and the polymer often leads to identifiable changes in the IR profile of solid dispersion.

The IR spectra of physical mixtures and solid dispersion were compared with the standard spectrum of Fenofibrate.

Figure 1 shows IR spectra of Fenofibrate. physical mixtures MF and solid dispersion SD formulation of fenofibrat-chitosan weight ratios 1:9.

IR-spectra of drug and formulations fenofibrat-chitosan are exactly same. There is no change in chemical structure of drug after incorporated of drug onto polymer.

The characteristic peaks of pure Fenofibrate peaks are observed at 2990 cm^{-1} indicated the presence of aromatic C-H bond, 1740 cm^{-1} indicated the presence of carbonyl group. 1660 and 1600 cm^{-1}. Peaks in the range of 1100 - 1000 cm^{-1} confirms C-O stretching. IR spectra in the range of 900 - 600 cm^{-1} indicate presence of aromatic rings: aromatic C-Cl and O-H stretching. Specific for fenofibrate peaks are observed in prepared physical mixtures and solid dispersions formulation.

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

Figure 2 represents the DSC study of Fenofibrate .Chitosan and Fenofibrate solid dispersions The fenofibrate (F) heating curve contains a sharp. single endothermic peak of melting at 79.1 ºC (ΔH = 118.33 J/g). On curve of heating chitosan in range of temperature 25 - 180 °C wide endothermic thermal answering effect was observed probably dehydration of sample.

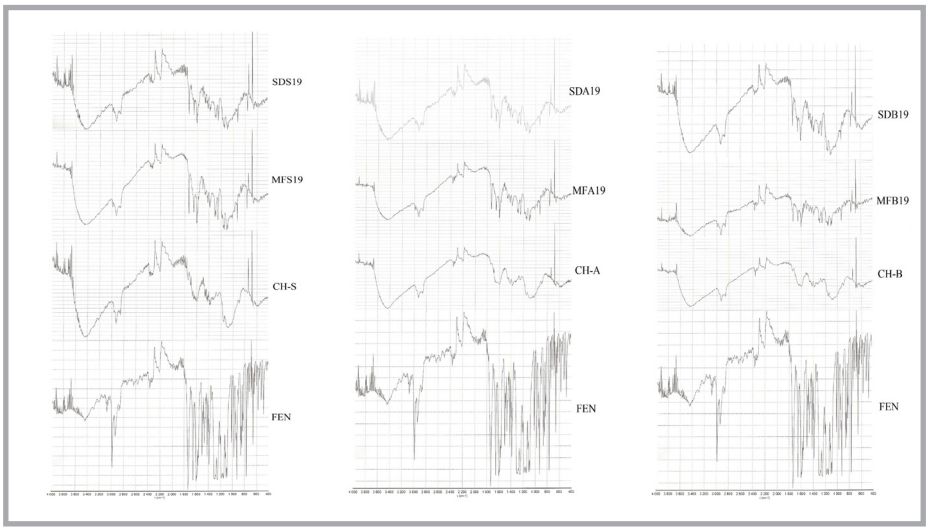

Figure 1. *Infrared spectra of: fenofibrate (FEN). chitosan (CH). physical mixtures (MF19) and solid dispersion (SD19) drug polimer:ratio 1:9 chitosan S (a), chitosan A (b), chitosan B (c).*

There was no appreciable change in the melting endotherms of the physical mixture (melting point 76. 9 ºC) and of solid dispersions (melting point 77. 1 ºC) as compared to pure drug. However there was slight decrease in the melting point of drug when prepared in the form of crystals

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 (1:9). The degree of lowering of temperature and increased heat effects is correlated with increased solubility of the drug in all the formulations.

4. Conclusions

1. Solid dispersion of fenofibrate containing different ratio of medium and high molecular weight chitosan showed high saturation solubility compared to pure sample of drug.

2. The results of IR spectroscopy reveal that there was no chemical interaction between drug and the polymer. DSC studies showed that there is no change in the crystal structure of drug during the solid dispersion technique.

3. Chitosan has been proposed as a useful excipient for enhancing the bioavailability of poorly water-soluble compounds.

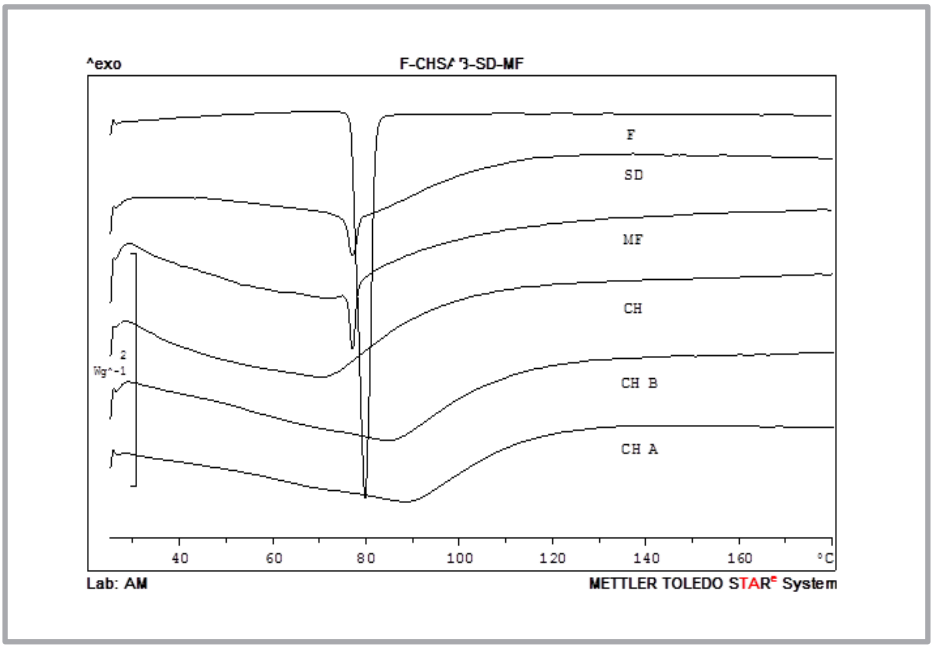

Figure 2. *DSC thermogram of fenofibrate (F).chitosan S (CHS).chitosan A(CHA).chitosan B(CHB). physical mixtures (MF) and solid dispersion (SD) drug polimer:ratio 1:9.*

5. References

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