THE STUDY OF PHYSICOCHEMICAL PROPERTIES OF SOLID DISPERSIONS OF IBUPROFEN IN THE PRESENCE OF CHITOSAN

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Abstract

The aim of the present study was to increase the solubility of ibuprofen. Among the methods to increase the solubility selected solid dispersions of the drug with the polymer. Chitosan was used as the polymer. Solid dispersion obtained. Ibuprofen was incorporated into the chitosan type 652 with molar masse chitosan Mη = 429 kDa. Solid dispersions were prepared by using different ratios of ibuprofen and chitosan (1:9. 3:7 and 5:5). Formulations were tested dissolution rate of the ibuprofen.

The highest dissolution of ibuprofen, amounting to 12.59%, was observed after 60 minutes from solid dispersion prepared by the evaporation method and 12.18% from physical mixtures with drug-polymer weight ratio 1:9 in the presence chitosan. The solubility of the drug improved more than 60-fold. XRPD analysis indicates the presence of the ibuprofen in amorphous form in the solid dispersion obtained by the modified solvent evaporation.

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Key words: *solid dispersion, dissolution, chitosan, ibuprofen*

Receive: 03.05.2015
Accepted: 15.06.2015

1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSDAID) with analgesic, antipyretic and anti-inflammatory. This drug belongs to class II in The Biopharmaceutical Classification System, which means that despite the good permeability, this drug has poor solubility [1]. This is a lipophilic drug with a low aqueous solubility. Thus the low oral bioavailability of Ibuprofen is due to its solubility and dissolution limitations [2].

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

Recent research aiming at increasing drug solubility has focused on formation of solid dispersions with polymer carriers. In the previous literature, various solid dispersions of ibuprofen are reported for improving its dissolution using various carriers [3-4]. 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. Chitosan in dispersions may prevent agglomeration of ibuprofen molecules and increase wettability of the drug molecules, thus intensifying the drug solubility [5-6].

Thus a study was undertaken to investigate the effect of chitosan on the solubility of ibuprofen incorporated into this polymer carrier. Solid dispersions were prepared by using different ratios of ibuprofen and chitosan (1:9. 3:7 and 5:5).

Demonstration of the effect of chitosan in various formulations or with various methods of preparation of the solid dispersions on the solubility of ibuprofen may enable development of new preparations of this drug with increased dissolution.

2. Materials and methods

2.1. Materials

The study was performed with the use of ibuprofen (Ibuprofen p.a.≥. 98%, Pfizer) incorporated into natural, highly purified chitosan with 95% deacetylation and viscosity average molecular weight M_η=429, intrisic viscosity $\eta[dm^3\ g^{-1}]$ =0,3132 (Chitozan 652 p.a., Chitine, France), Aqua purification, acc. to FP X.

2.2. Methods

2.2.1. Examination of pure ibuprofen and its solid dispersions dissolution rate.

The examination of solubility was carried out in a tablet dissolution apparatus according to FP X, which determines the active substance dissolution rate from solid drug forms. The studies were performed in a VanKel VK 7025 dissolution apparatus, which was connected to a fraction collector Varian Inc. 1000 ml of phosphoric buffer at pH 6.8 was used as releasing medium.

Dissolution was evaluated after compressing 100 mg of samples, which were placed in each of the six chambers of the apparatus at 37°C +/- 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 10μm 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 λ=222 nm.

The drug concentration in samples and an average percentage of dissolved ibuprofen were calculated using linear regression equation for ibuprofen y=97.103x + 0.0183. Quantitative drug-to-polymer ratios in which the solid dispersion had the most beneficial properties improving the drug dissolution were determined.

2.2.2. Examination of samples by means of X-ray diffraction (XRD)

Powder X-ray diffraction patterns for solid dispersions containing ibuprofen and Chitosan and pure substances were recorded on an X-diffractometer (Bruker D2 Phaser, detector LynxEye, USA), employing CuK∞ radiation source operating at 30 mA and 40 kV. Samples were scanned from 4 to 50° 2θ at a scanning rate of 0.02° 2θ s^{-1}.

2.2.3. Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of ibuprofen and chitosan and its solid dispersions were obtained by using a spectrometer UART FT/IR, Perkin Elmer, USA . In order to measure this, a suitable amount of the sample was applied on the crystal plate surface of the device so that it covered the entire surface of the prism. The sample was then pressed against the head to the point of transition of the radiation beam. Spectra were recorded in the range 4000 to 400 cm^{-1} using a resolution of 2 cm^{-1} and 64 co-added scans.

2.2.4. Technology for the preparation of investigated formulations

2.2.4.1. Preparation of samples for investigation of ibuprofen dissolution

The solubility of ibuprofen 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.

2.2.4.2. Preparation of ibuprofen and polymer physical mixtures

Physical mixtures were prepared by grinding in an agate mortar for 10 minutes of adequate amounts of chitosan 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 315μm 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).

DOI: 10.15259/PCACD.20.06

2.2.4.3. Preparation of ibuprofen-chitosan solid dispersions by means of solvent method

Adequate amounts of ibuprofen were weighed on a Sartorius analytical balance and dissolved in proper amount of ethanol. Adequate amounts of chitosan about molecular weight M_η=429 weighed on an analytical balance were in ethanol 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 (Table 1).

The drying was next powdered in an agate mortar for 20 minutes and passed through a sieve with 315μm wholes. Every dispersion was prepared in the amount of 1 g (table 1), placed in glass bottles sealed with cork and stored in an exicator over silica gel.

2.2.4. Statistical analysis

Statistical analysis was performed for maximum percentage values of ibuprofen 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.

Table 1. The quantitative composition of solid dispersion prepared by the evaporation method and physical mixtures of the ibuprofen onto chitosan.

Solid dispersion	Drug/ polymer ratio	Quantity of drug [mg]	Quantity of polymer [mg]	Quantity of ethanol [ml]
SD5+5	5:5	500	500	5
SD3+7	3:7	300	700	3
SD1+9	1:9	100	900	1
MF5+5	5:5	500	500	5
MF3+7	3:7	300	700	3
MF1+9	1:9	100	900	1

SD - the solid dispersion, MF - the physical mixture

3. Results and Discussion

3.1. Dissolution of ibuprofen in presence of chitosan

Table 2 presents the solubility of pure ibuprofen without chitosan. The dissolution findings of pure ibuprofen in phosphate buffer at pH 6.8 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 0.01% to 0.2 % of the investigated dose.

Analysis of data from Tables 3-4 and Fig.1 revealed that the addition of chitosan has a considerable effect on ibuprofen dissolution in the range of investigated solid dispersions.

The results of the demonstrated that all the investigated solid dispersions of ibuprofen with chitosan increased of the solubility of ibuprofen. The presence of chitosan improved markedly the dissolution of ibuprofen, which increased with time with amount of the chitosan in formulations.

The highest dissolution of ibuprofen, amounting to 12.59%, was observed after 60 minutes from solid dispersion prepared by the evaporation method and 12.18% from physical mixtures with drug-polymer weight ratio 1:9 in the presence chitosan. In dispersions containing 30% of the drug and of the polymer, the solubility of ibuprofen from solid dispersion prepared by the evaporation method was at the level of 3.7% and from physical mixtures was 5.74%.

Table 2. Dissolution of ibuprofen pure in phosphate buffer at pH 6.7.

time intervals collected samples [min]	the average of dissolubility [%]	standard deviation
5	0.010	0.002
10	0.023	0.006
15	0.037	0.015
20	0.052	0.025
25	0.067	0.032
30	0.080	0.036
35	0.097	0.015
40	0.117	0.015
50	0.153	0.015
60	0.203	0.067

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 3.3% and 3.6% depending on the prepared dispersion.
Comparing data from Tables 1 and 2-3, we can notice a significant increase in the drug solubility, which in the presence of chitosan increased 60 times, 25 times and almost 18 times in relation to the amount of added polymer in comparison to the solubility of pure drug.

When the course of ibuprofen solubility curves in the presence of chitosan is observed, it becomes apparent that they are situated in the field above the ibuprofen solubility curve without polymer. The solubility curve for ibuprofen mixed with chitosan at 1:9 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 6.19% to 12.59% from solid dispersion and 7.44% to 12.18%, i.e. it increases with time.

The solubility line of pure ibuprofen is characterized by a low inclination angle to the time axis, and the drug solubility in time increases slightly and is from 0.01% to 0.2%.

Table 3. Influence of chitosan on the dissolution of ibuprofen from solid dispersion prepared by the evaporation method in phosphate buffer at 6.8.

Ibuprofen– to – Chitosan (weight M_η= 429 kDa) weight ratio of solid dispersion						
time intervals collected samples	**SD 5+5**		**SD 3+7**		**SD 1+9**	
	average % dissolved of ibuprofen	standard deviation	average % dissolved of ibuprofen	standard deviation	average % dissolved of ibuprofen	standard deviation
5	0.41	0.3723	0.68	0.5806	6.19	0.4311
10	0.58	0.1647	1.16	0.9276	7.68	0.1609
15	1.11	0.2754	1.38	0.7147	9.09	1.7316
20	1.38	0.5288	1.67	0.7102	10.02	0.9146
25	1.86	0.3289	2.01	0.7485	10.64	0.6327
30	2.27	0.1140	2.28	0.7871	11.19	0.7423
35	2.53	0.2835	2.59	0.5640	11.57	0.7511
40	2.76	0.2435	3.02	0.5372	12.17	0.7436
50	3.01	0.1930	3.38	0.4598	12.28	0.7223
60	3.29	0.2168	3.69	0.4854	12.59	0.8036

Increased solubility of ibuprofen 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 ibuprofen molecules and increase wettability of the drug molecules, thus intensifying the drug solubility.

3.2. Analysis X-ray diffractograms (XRD) of ibuprofen, chitosan and their solid dispersions.

The X-ray diffractograms of pure components and solid dispersions of ibuprofen with chitosan are shown in Fig 2.

Analysis of the spectra in the physical mixtures of ibuprofen, obtained by kneading in the presence of chitosan, revealed the presence of peaks and a decrease in crystallinity of the dispersed phase of the drug, in the case of the smallest physical mixture of ibuprofen content. This was confirmed by analysis of the rate of drug dissolution studies, which showed the best solubility of a physical mixture of ibuprofen in a ratio of 1:9. Analysis of diffraction patterns of solid dispersions obtained by evaporation of the modified exposure showed a diffuse peaks, irrespective of the quantitative share of drug to polymer in the solid dispersions. This may be explained by the presence of the drug in amorphous form, which is confirmed by testing the rate of dissolution of ibuprofen in those formulations which exhibits the greatest solubility.

Table 4. Influence of chitosan on the dissolution of ibuprofen from physical mixtures prepared by grinding method in phosphate buffer at 6.8.

Ibuprofen– to – Chitosan (weight M_η= 429 kDa) weight ratio of solid dispersion						
time intervals collected samples	**MF 5+5**		**MF 3+7**		**MF 1+9**	
	average % dissolved of ibuprofen	standard deviation	average % dissolved of ibuprofen	standard deviation	average % dissolved of ibuprofen	standard deviation
5	1.24	0.3627	2.66	0.5708	7.44	0.4321
10	1.76	0.1454	3.11	0.9324	8.01	0.1508
15	2.28	0.2635	3.69	0.7126	8.76	1.7215
20	2.54	0.5128	4.14	0.7104	9.29	0.9226
25	2.82	0.3212	4.55	0.7285	9.84	0.6436
30	3.13	0.1140	4.81	0.7621	10.27	0.7528
35	3.27	0.2835	5.11	0.5345	10.85	0.7413
40	3.43	0.2428	5.34	0.5280	11.24	0.7356
50	3.58	0.1917	5.52	0.4690	11.79	0.7218
60	3.64	0.2154	5.74	0.4721	12.18	0.8126

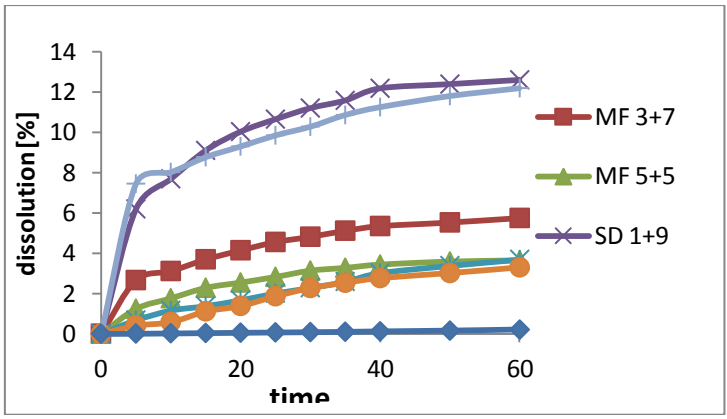

Figure 1. Dissolution profiles of ibuprofen from solid dispersion in phosphate buffer at pH 6.7.

DOI: 10.15259/PCACD.20.06

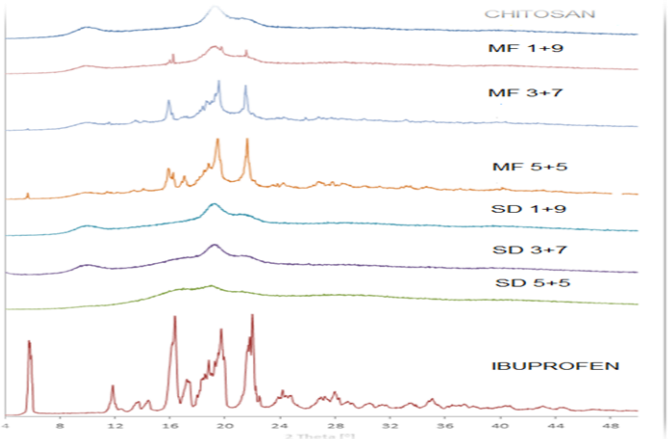

Figure 2. XRPD paterns of ibuprofen, chitosan and their solid dispersions.

3.3. Analysis Fourier Transform Infrared Spectroscopy spectra of ibuprofen, chitosan and their solid dispersions

The FTIR spectra of ibuprofen and solid dispersions of ibuprofen with chitosan are shown in Fig.3.

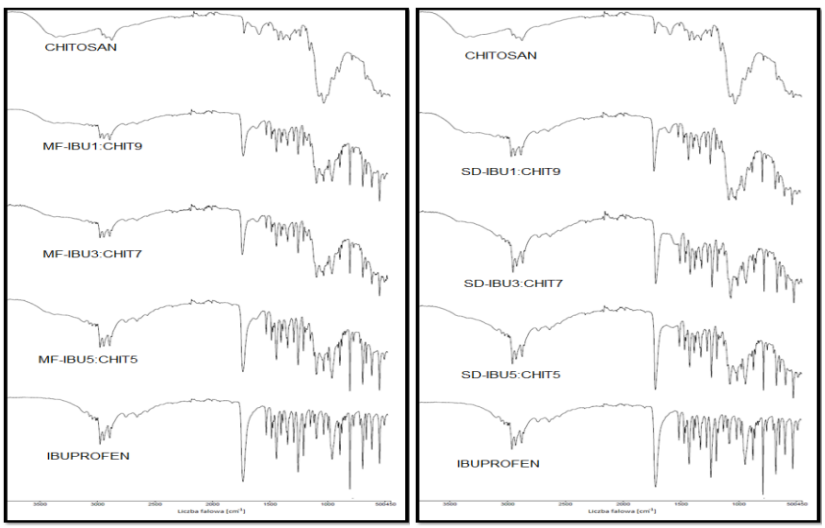

Figure 3. Infrared spectra of: ibuprofen, chitosan , solid dispersion (MF and SD) drug polymer ratio 1:9.3:7.5:5.

In the FTIR analysis, the spectrum of pure ibuprofen shoved an intense band at around 1721 cm^{-1}(carbonyl-stretching of isopropionic acid group), characteristic bands at 3000 cm^{-1}-hydroxyl group of carboxylic acid, and a band at around 942 cm^{-1}. Fourier Transform Infrared Spectroscopy FTIR showed that no chemical interaction between the drug and chitosan. The only noticeable difference is the height of the peaks occur, which decreases with the change in the phase composition of the polymer added relative to ibuprofen. These differences arise from the different drug content in the formulations.

4. Conclusions

1. Solid dispersions prepared evaporation of solvent technique and grinding method with chitosan increased the dissolution of ibuprofen. The effect depends on the drug/polymer weight ratio.
2. Highest dissolution of ibuprofen was achieved at drug/polymer ratio 1:9 in the presence solid dispersion prepared evaporation of solvent technique.
3. The results of FTIR spectroscopy reveal that there was no chemical interaction between drug and the polymer. X-ray analysis of solid dispersions studies showed the amorphous character of the drug/polymer.
4. Chitosan has been proposed as a useful excipient for enhancing the bioavailability of poorly water-soluble compounds.

5. References

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