# CHARACTERISATION AND DISSOLUTION PROPERTIES OF KETOPROFEN IN BINARY SOLID DISPERSION WITH CHITOSAN

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**Abstract**
*BCS class II includes drugs with low solubility and high permeability. Ketoprofen is an example of this class of drugs. The aim of the study was to investigate the effect of chitosan with average molecular weights in various formulations on the dissolution of ketoprofen incorporated into this polymer carrier. The study investigated ketoprofen in solid dispersions using a method of the solvent evaporations at the drug to polymer ratios of 1:9. 3:7, and 5:5. The highest dissolution of fenofibrate, amounting to 98.8%, was observed after 60 minutes from solid dispersions with a drug-polymer weight ratio 1:9 in the presence of chitosan B and was 32-times higher in relation to the amount of added polymer in comparison to the solubility of pure drug. DSC and IR investigations showed that ketoprofen remained in its crystalline state in solid dispersion. There was no change in the chemical structure of the drug after the incorporation of the drug onto the polymer. Chitosan has been proposed as a useful excipient for enhancing the bioavailability of poorly water-soluble compounds.*

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


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## 1. Introduction

Ketoprofen, a potent non-steroidal anti-inflammatory drug (NSAID), is a preferential inhibitor of cyclooxygenase-2 and its anti-inflammatory and analgesic activity is used in the treatment of rheumatoid activity. The poor aqueous dissolution and wettability of the drug leads to difficulty in formulating oral and topical states. Ketoprofen belongs to Class II of the Biopharmaceutical Classification System (BCS). This is a lipophilic drug with a low aqueous solubility. Thus, the low oral bioavailability of Ketoprofen is due to its solubility and dissolution limitations [1, 2].

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

Recent research aimed at increasing drug solubility has focused on the formation of solid dispersions with polymer carriers. Chitosan in dispersions may prevent the agglomeration of ketoprofen molecules and increase the wettability of drug molecules, thus intensifying the drug solubility [3, 4].

As a result, a study was undertaken to investigate the effect of with about different viscosity and average molecular weights on the solubility of ketoprofen incorporated into this polymer using the solvent evaporation method in the temperature room.

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 Fourier transform infrared spectroscopy (FTIR) [5, 6].

Demonstration of the effect of chitosan with average molecular weights in various formulations or with various methods of preparation of the solid dispersions on the solubility of ketoprofen may enable the 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 ketoprofen (Ketoprofen p.a. min. 99%, Zhejiang Chemicals) incorporated into a natural, highly purified chitosan **sample S** with 92% deacetylation and viscosity average molecular weight $M_\eta$=1087 kDa, intrinsic viscosity $\eta = 0.7437$ [$dm^3\ g^{-1}$], **sample A** 92% deacetylation and viscosity average molecular weight $M_\eta = 839$ kDa, intrinsic viscosity $\eta = 0.5843$ [$dm^3\ g^{-1}$], **sample B** 92% deacetylation and viscosity average molecular weight $M_\eta = 407$ kDa, intrinsic viscosity $\eta = 0.2986$ [$dm^3\ g^{-1}$] (Chitosan Huasu p.a., Chitin, France), sodium lauryl sulphate p.a., PPH "Stanlab", Poland, Aqua purification, acc. to FP IX.

## 2.2. Methods

### *2.2.1. Examination of pure ketoprofen and its solid dispersion dissolution rate*

Evaluation of solubility was performed in a dissolution apparatus according to FP IX, which describes the investigation of active substance solubility rate from solid drug forms [7]. The examination was performed in a VanKel VK 7025 dissolution apparatus, to which a Varian Inc. fraction collector was attached. Here, 1000 ml of 0.1 M solution of hydrochloric acid at pH 1.5 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, with 5 ml samples collected at 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 a pore size of 10 μm.

The collected samples were diluted and their content was then evaluated with the use of JASCO V650 spectrophotometer with a 1 cm cuvette at a wavelength of $\lambda = 260$ nm.

The drug concentration in samples and an average percentage of dissolved ketoprofen were calculated using linear regression equation for ketoprofen $y = 0.06028x + 0.0321$. 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 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 2.2.3.1. - 2.2.3.2. A DSC 25 flow calorimeter manufactured by Mettler Toledo with an integrated STARe program was used. The samples were heated at a rate of 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 μl aluminium melting pots with a cover. The samples weighed 5 - 10 mg.

### *2.2.3. Infrared Spectroscopy*

The IR spectra were obtained using a spectrometer-Specord M80. The samples ketoprofen or solid dispersion (ketoprofen or SDs) were previously ground and mixed thoroughly with potassium bromide, in an infrared transparent matrix, at a ratio of 1:100 (Sample:KBr), respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 2 min in a hydraulic press. Scans were obtained at a resolution of 2 $cm^{-1}$, from 4000 to 200 $cm^{-1}$.

### *2.2.4. Technology for the preparation of investigated formulations*

*2.2.4.1. Preparation of samples for investigation of ketoprofen dissolution*

The solubility of ketoprofen 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.

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

| Average molecular weight of chitosan | Solid dispersion | Drug/polymer ratio | Quantity of drug [mg] | Quantity of polymer [mg] | Quantity of ethanol [ml] |
|---|---|---|---|---|---|
| Sample S $M_\eta$ = 1087 kDa | SDS55 | 5:5 | 500 | 500 | 5 |
| | SDS37 | 3:7 | 300 | 700 | 3 |
| | SDS19 | 1:9 | 100 | 900 | 1 |
| Sample A $M_\eta$ = 839 kDa | SDA55 | 5:5 | 500 | 500 | 5 |
| | SDA37 | 3:7 | 300 | 700 | 3 |
| | SDA19 | 1:9 | 100 | 900 | 1 |
| Sample B $M_\eta$ = 407 kDa | SDB55 | 5:5 | 500 | 500 | 5 |
| | SDB37 | 3:7 | 300 | 700 | 3 |
| | SDB19 | 1:9 | 100 | 900 | 1 |

*2.2.4.2. Preparation of ketoprofen-chitosan solid dispersions by means of solvent method*

Adequate amounts of ketoprofen were weighed on a Sartorius analytical balance and dissolved in an appropriate amount of ethanol. Adequate amounts of medium and high molecular weight chitosan, weighed on an analytical balance, were placed in ethanol and suspended to obtain drug-polymer mass ratios of 1:9, 3:7 and 5:5. The solvent was removed using a rotary evaporator. The resultant solid dispersion was transferred to an aluminium pan and allowed to dry at room temperature.

The drying was next powdered in an agate mortar for 20 minutes and passed through a sieve with 315 μm holes. 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.

## 3. Results and discussion

### 3.1. Dissolution of ketoprofen in the presence of chitosan

***Table 2*** presents the solubility of pure ketoprofen without chitosan. The dissolution findings of pure ketoprofen in 0.1 M aqueous solution hydrochloric acid were used as a reference with which to compare solubility of the drug incorporated into chitosan.

The drug dissolution was found to increase gradually with time and ranged from 0.1% to 3.05% of the investigated dose.

Analysis of data from ***Tables 2 - 3*** and ***Figure 1*** revealed that the addition of chitosan has a considerable effect on ketoprofen dissolution in the range of investigated solid dispersions.

***Table 2.*** *Dissolution of pure ketoprofen in a 0.1 M aqueous solution of hydrochloric acid.*

| Time intervals collected samples [min] | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 50 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|
| The average dissolubility % | 0.10 | 0.19 | 0.28 | 0.42 | 0.56 | 0.67 | 0.89 | 1.43 | 2.09 | 3.05 |
| Standard deviation | 0.024 | 0.073 | 0.054 | 0.089 | 0.092 | 0.102 | 0.127 | 0.117 | 0.104 | 0.103 |

***Table 3.*** *Influence of chitosan on the dissolution of ketoprofen from solid dispersions prepared by the evaporation method in 0.1 M aqueous solution hydrochloric acid.*

| | Time [min] | Sds 55 | | Sds 37 | | Sds 19 | |
|---|---|---|---|---|---|---|---|
| | | Average % dissolved of Ketoprofen | Standard deviation | Average % dissolved of Ketoprofen | Standard deviation | Average % dissolved of Ketoprofen | Standard deviation |
| Ketoprofen-to-Chitosan S | 5 | 26.99 | 0.393 | 47.63 | 0.601 | 62.92 | 0.4305 |
| | 10 | 50.64 | 0.173 | 72.12 | 0.915 | 76.95 | 0.1614 |
| | 15 | 69.03 | 0.282 | 82.98 | 0.771 | 87.46 | 1.7445 |
| | 20 | 70.91 | 0.632 | 86.82 | 0.810 | 92.55 | 0.9266 |
| | 25 | 78.41 | 0.401 | 88.84 | 0.760 | 94.82 | 0.6565 |
| | 30 | 81.90 | 0.126 | 89.62 | 0.790 | 95.35 | 0.7576 |
| | 35 | 85.88 | 0.334 | 90.35 | 0.576 | 96.20 | 0.7587 |
| | 40 | 87.43 | 0.256 | 90.73 | 0.546 | 96.78 | 0.7469 |
| | 50 | 87.95 | 0.003 | 94.56 | 0.469 | 97.48 | 0.7243 |
| | 60 | 92.54 | 0.207 | 96.74 | 0.493 | 97.79 | 0.8082 |
| Ketoprofen-to-Chitosan A | 5 | 32.13 | 0.207 | 50.23 | 0.157 | 65.04 | 0.4159 |
| | 10 | 53.50 | 0.248 | 74.81 | 0.116 | 81.95 | 0.0224 |
| | 15 | 72.78 | 0.582 | 82.41 | 0.248 | 88.20 | 0.3903 |
| | 20 | 86.12 | 0.353 | 85.81 | 0.165 | 89.96 | 0.4841 |
| | 25 | 94.11 | 0.135 | 86.59 | 0.163 | 91.57 | 0.5023 |
| | 30 | 95.01 | 0.135 | 88.64 | 0.096 | 94.32 | 0.5033 |
| | 35 | 95.22 | 0.139 | 89.16 | 0.202 | 96.57 | 0.5140 |
| | 40 | 95.32 | 0.128 | 89.67 | 0.475 | 97.02 | 0.4735 |
| | 50 | 95.42 | 0.126 | 93.39 | 0.279 | 97.54 | 0.4266 |
| | 60 | 95.57 | 0.110 | 96.57 | 0.152 | 97.82 | 0.4436 |
| Ketoprofen-to-Chitosan B | 5 | 38.72 | 0.036 | 55.21 | 0.113 | 67.56 | 0.0568 |
| | 10 | 59.77 | 0.245 | 78.35 | 0.787 | 85.37 | 0.8026 |
| | 15 | 74.76 | 0.895 | 85.08 | 0.763 | 89.53 | 0.2488 |
| | 20 | 80.92 | 0.170 | 87.49 | 0.005 | 90.77 | 0.0241 |
| | 25 | 86.08 | 0.236 | 88.19 | 0.063 | 92.04 | 0.3736 |
| | 30 | 90.06 | 0.409 | 88.60 | 0.159 | 92.62 | 0.3050 |
| | 35 | 92.73 | 0.244 | 88.96 | 0.219 | 92.95 | 0.1902 |
| | 40 | 94.52 | 0.017 | 89.31 | 0.223 | 93.11 | 0.0904 |
| | 50 | 93.95 | 0.318 | 94.38 | 0.284 | 95.45 | 0.0891 |
| | 60 | 96.74 | 0.423 | 97.25 | 0.405 | 98.78 | 0.1852 |

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

The presence of chitosan markedly improved the dissolution of ketoprofen, which increased with time and with the amount of chitosan in the formulations. The dissolution rates presented in ***Table 3*** indicated that ketoprofen dissolution from solid dispersions was dependent on the molecular weight of chitosan.

The highest dissolution of ketoprofen, amounting to 98.78%, was observed after 60 minutes from solid dispersions with a drug-polymer weight ratio of 1:9 in the presence chitosan B.

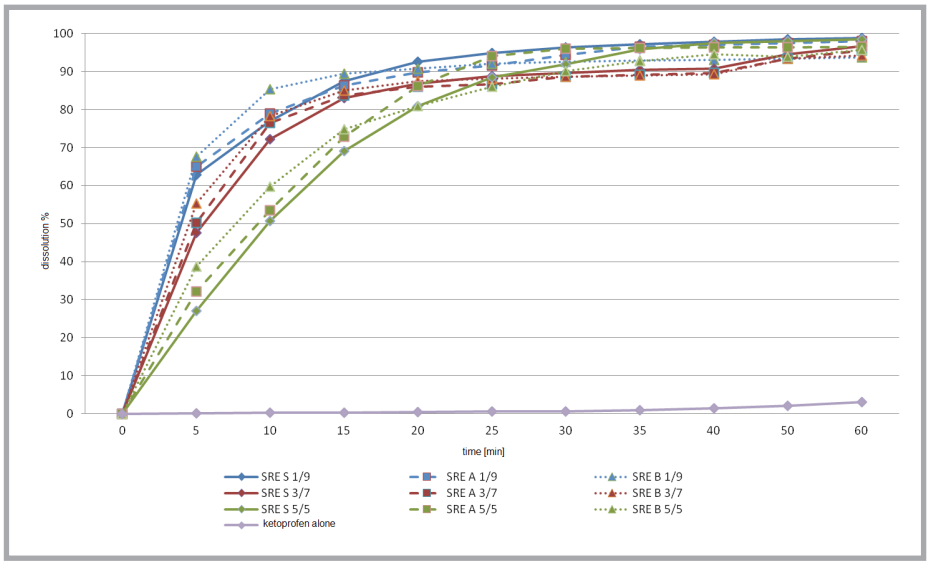


***Figure 1.*** *Dissolution profiles of ketoprofen from solid dispersion in 0,1 M aqueous solution of hydrochloric acid.*

The result demonstrated the higher drug dissolution of the solid dispersion prepared by means of solvent evaporation containing chitosan Sample B than that of chitosan sample A (Mη = 839 kDa) and sample S (Mη = 1087 kDa). The difference in dissolution rate enhancement by chitosan S and chitosan A and B can be explained by the fact that the drug dissolution was faster when the molecular weight of polymer was lower.

Solid dispersion of ketoprofen containing different ratios of drug and different molecular weight chitosan showed high dissolution compared to pure samples of the drug.

Comparison of data from ***Tables 2 - 3*** demonstrates a significant increase in the drug dissolution, within 5 minutes, which, in the presence of chitosan-407 kDa (chitosan B) in dispersions, was almost 380 times (for the weight ratio 5:5), 500 times (for the weight ratio 3:7), and 670 times (for the weight ratio 1:9) higher in relation to the amount of added polymer in comparison to the solubility of pure drug.

It was also noticed that the dissolution rate of ketoprofen from the dispersions in the presence of chitosan - Mη = 1087 kDa (chitosan S) and - Mη = 839kDa (chitosan A) was lower than that from the dispersions with chitosan - Mη = 407 kDa (chitosan B).

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

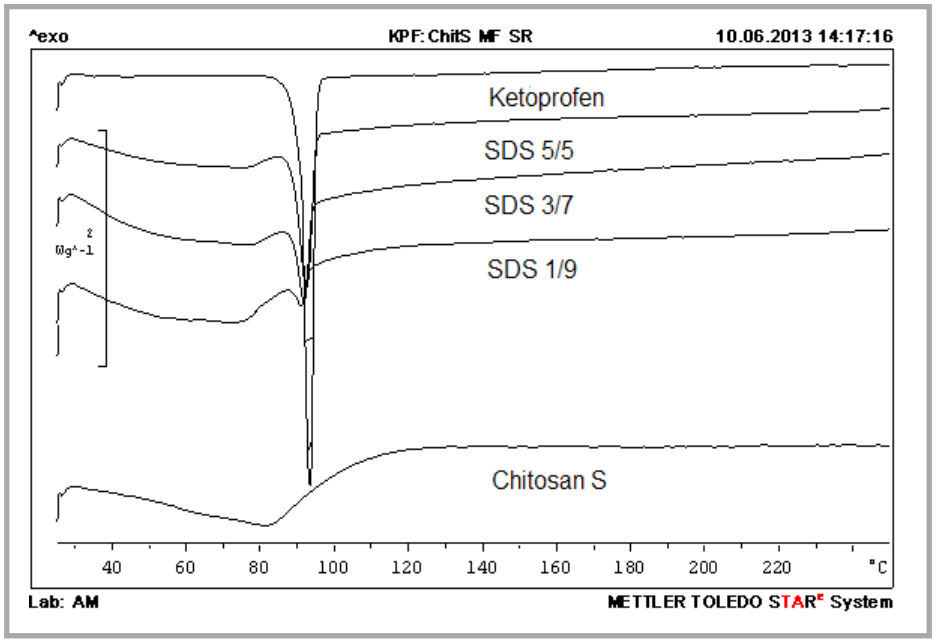


***Figure 2.*** *DSC thermogram of ketoprofen, chitosan S and solid dispersion prepared (SDS) drug-polymer ratios of 1:9, 3:7 and 5:5.*

Chitosan, dispersing in water environments, causes a significant increase in the contact area of the ketoprofen with solution, increases the hydrophilic properties of drugs and may affect its crystalline structure. Chitosan in dispersions may prevent the agglomeration of ketoprofen molecules and increase the wettability of drug molecules, thus intensifying the drug solubility.

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

DSC thermograms are presented in ***Figure 2***. The ketoprofen heating curve contains a sharp, single endothermic peak of melting at 93 ºC, Peak height was (ΔH = 133.3 J/g). In solid dispersions, a sharp peak of pure ketoprofen was observed at 91.3 ºC. The peak height was reduced to 9.0 J/g. Sharp peaks indicated that ketoprofen remained in the crystalline state in solid dispersion. The polymer heating curves revealed broad, endothermic heat effects accompanying melting of the drug. Chitosan S heated to 180 ºC did not undergo dissolution.

On the heating curve of chitosan S in the temperature range 25 - 130 ºC, a wide endothermic thermal answering effect was observed; probably, dehydration of a sample of solid dispersion of ketoprofen with chitosan is characterised by thermal stability in the investigated range of temperatures.

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

Thermograms for solid dispersions of drug with chitosan S demonstrated a distinct shift in the peak corresponding to the ketoprofen melting point towards lower temperatures in comparison to the pure drug. The degree of lowering of temperature and increased heat effects is correlated with the increased solubility of the drug in all of the formulations tested. All of the solid dispersions of ketoprofen with chitosan A and chitosan B are characterised by thermal stability in the investigated range of temperatures, regardless of the drug-polymer ratios applied. Thermograms of chitosan A and chitosan B were identical; their spectra were not low, shallow and readable enough (little).

### 3.3. Analysis of infrared spectroscopy

The state of drug molecule with 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 solid dispersion were compared with the standard spectrum of ketoprofen. ***Figure 3*** shows the IR spectra of ketoprofen solid dispersion SD formulation of ketoprofen-chitosan weight ratios 1:9, 3:7 and 5:5.

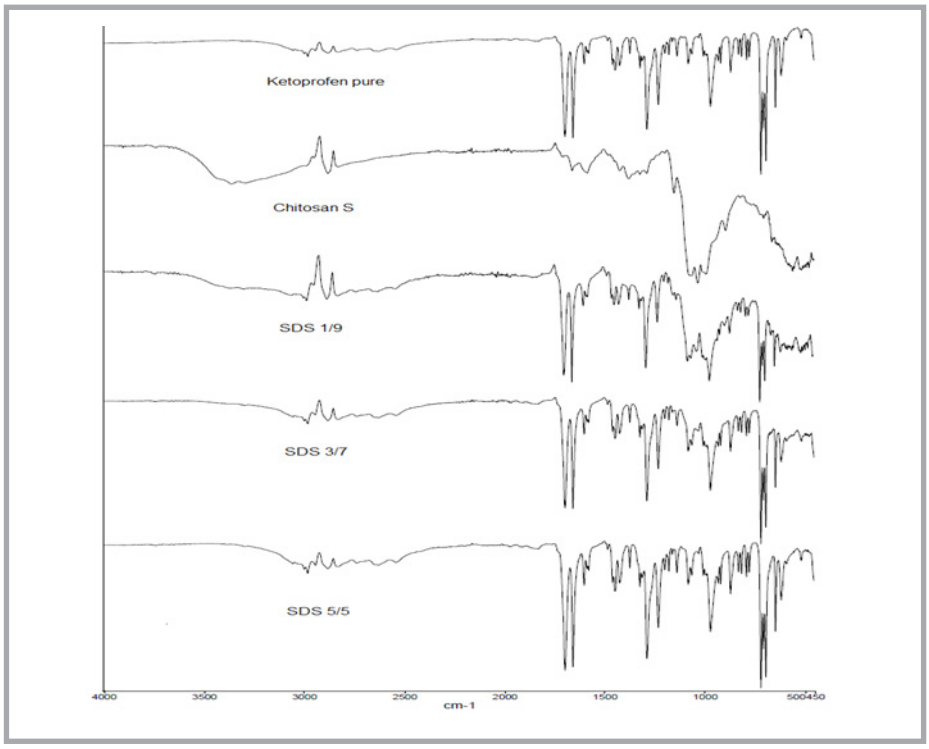


***Figure 3.*** *Infrared spectra of ketoprofen, chitosan S, and solid dispersion (SDS) drug/polymer ratios of 1:9, 3:7 and 5:5.*

The IR-spectra of drug and ketoprofen-chitosan formulations are exactly the same. There is no change in the chemical structure of the drug after incorporation onto the polymer.

The characteristic peaks of pure ketoprofen are observed at 2983 $cm^{-1}$ to 2930 $cm^{-1}$, indicating the presence of aromatic C-H stretch and carboxylic acid O-H stretch, at 1695 to 1649 $cm^{-1}$, indicating the presence of the carbonyl group, the 1595 $cm^{-1}$ aromatic C=C bond, and the 1437 $cm^{-1}$ CH-CH 3 deformation and 2891 $cm^{-1}$ C-H stretch plus OH deformation. IR spectra in the range of 860 - 640 $cm^{-1}$ indicate the presence of aromatic rings. Specific peaks for ketoprofen are observed in the prepared solid dispersions formulation.

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

## 4. Conclusions

1. Solid dispersions prepared using the evaporation of solvent technique with chitosan increased the dissolution of ketoprofen. The effect depended on the drug/polymer weight ratio and on the molecular weight of chitosan.
2. The highest dissolution of ketoprofen was achieved at the drug/polymer ratio of 1:9 in the presence of medium-molecular-weight chitosan B.
3. The results of IR spectroscopy reveal that there was no chemical interaction between the drug and the polymer. DSC studies showed that there was no change in the crystal structure of the drug during the solid dispersion technique.
4. Chitosan has been proposed as a useful excipient for enhancing the bioavailability of poorly water-soluble compounds.

## 5. References

1. Shohin I.E., Kulinich JI, Ramenskaya GV. Abrahamsson B, Kopp S, Langguth P, Polli J E, Shah V P, Groot DW, Barends DM, Dressman JB; (2012) Monographs for immediate-release solid oral dosage forms: Ketoprofen, J. Pharm. Sci., 101, 3593-3603, DOI: 10.1002/jps.23233.
2. Nashwan YK, Alaa AA, Moafaq M2, Saad AH; (2011) Solubility and dissolution improvement of ketoprofen by solid dispersion in polymer and surfactant using solvent evaporation method. Int J Pharm Pharm Sci, 3, 431-435.
3. Saffoon N, Uddin R., Huda NH., Sutradhar K.B; (2011) Enhancement of oral bioavailability and solid dispersion: a review; J. Applied Pharm. Sci. 1, 13-20.
4. CKS Pillai, Willi P. Chandra P. Sharma; (2009) Chitin and chitosan polymers: Chemistry, solubility and fibre formation. Prog. in Polym. Sci. 34, 641-678. DOI: 10.1016/j.progpolymsci.2009.04.001.
5. B1 Tiţa, A Fuliaş, G Bandur, E Marian,D Tiţa;(2011) Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms. J. Pharm. Biomed. Anal. 56, 221-227, DOI: 10.1016/j.jpba.2011.05.017.
6. Czechowska-Biskup R., Jarosińska D, Rokita B, Ulański P, Rosiak JM; (2012) Determination of degree of deacetylation of chitosan -comparision of methods. Progress on Chemistry and Application of Chitin and Its Derivatives, 17, 5-20.
7. Polish Pharmacopoeia (2011) vol. 9, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Warsaw, Poland.