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Research Article

# Investigation of physical and physicochemical properties of nimesulide solid dispersion with polyethylene glycol 6000, Kollidon 25, β-cyclodextrin and mechanisms of their interaction

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**ABSTRACT**

Nimesulide is non-steroidal anti-inflammatory drug that is widely used in medical practice and characterized by low solubility. One of solubility modifying method for pharmaceutical substances is preparation of solid dispersions based on macromolecular compounds. The aim is to explore the mechanisms of interaction in the solid dispersions of nimesulide with β-cyclodextrin, polyethylene glycol 6000, Kollidon 25 and physical and physicochemical properties of solid dispersions using the IR absorption spectrophotometry, scanning electron microscopy and X-ray powder diffraction. Characteristic changes detected in solid dispersions by scanning electron microscopy, IR spectroscopy and X-ray powder diffraction indicate at interactions between system components and formation supramolecular complexes.

**Keywords:** nimesulide, β-cyclodextrin, Kollidon 25, polyethylene glycol 6000, solid dispersion and molecular interaction

## INTRODUCTION

Low solubility of the active substance in water, its slow rate of release from the dosage form and the instability in the gastrointestinal tract are the factors which determine the bioavailability and efficacy of many medicines. Nimesulide, *N*-(4-Nitro-2-phenoxyphenyl) methanesulfonamide is a nonsteroidal anti-inflammatory, analgesic and antipyretic drug which is also widely used in medical practice. However, it should be noted that the substance is poorly soluble in water and is class-II drug as per Biopharmaceutical Classification System (low solubility / high penetration)[1]. The topical problem which arouses interest among scientists is the solubility modification of substances for pharmaceutical usage, relating to the class-II. Among the various approaches to improve the solubility of such substances method of solid dispersions (SD) is widely used, with dispersions of one or more active pharmaceutical ingredients in an inert carrier in the solid state being obtained by fusion, dissolution or a combination of these methods[2]. Powder particles of pharmaceutical substance are characterized by a

smaller size, an improved wettability and dispersion in comparison with the pure substance, which consequently increase solubility. In addition, SD can change the state of the pharmaceutical substance from crystalline to amorphous. In many cases, amorphous state of substance is the best compared to crystalline as it increases solubility. Hydrophilic polymers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) with different molecular weights and cyclodextrins (CD) are actively investigated as carriers[3-5].

As of today modern methods of the SD physical properties study are scanning electron microscopy (SEM) and X-ray powder diffraction, which allow to investigate the size, shape, structure and crystalline or amorphous state of substance[6-8]. The main method of studying the mechanisms of compounds interaction, including the formation of SD, is absorption spectrophotometry in the infrared region, which reveals the nature of relations and changes in the fine chemical structure in the formation of new compounds and complexes[9,10].

The aim is to explore the mechanisms of interaction in the SD of nimesulide with β-CD, PEG 6000, Kollidon 25 (K-25) and physical and physicochemical properties of SD using the IR absorption spectrophotometry, scanning electron microscopy and X-ray powder diffraction.

## MATERIALS AND METHODS

The nimesulide substance (Aarti drugs limited, India) that meets the requirements of QCT producer has been used in the studies. PEG 6000 (Sigma, Germany), Kollidon 25 (BASF, Germany), β-cyclodextrin (ISP, Switzerland) meet the requirements of regulatory and technical documents. SD nimesulide with PEG, PVP, β-CD were prepared by co-precipitation in the ratio nimesulide to carrier 1:2. The physical mixture was prepared by mixing nimesulide in the same proportions as the SD.

Scanning electron microscopy was performed using a scanning electron microscope JSM 6060 LA, Jeol, Japan. Samples of the substance carriers (PEG, PVP, β-CD) and solid dispersions fixed on the aluminum tables by using double-sided adhesive tape, covered by a thin layer of gold (20 nm). Research was conducted using parameters voltage 30 kV, working distance (12-14 mm).

IR spectra of the samples were obtained using infrared spectrophotometer Specord-75 (Germany). Samples were prepared as KBr tablets.

Powder X-ray diffraction was performed using diffractometer DRON 3. Sealed X-ray tube with molybdenum anode (current 18 mA, voltage 34 kV) was used. Scanning range $3^0$ – $22^0$, in increments of $0.02^0$ and 1 s counting time.

## RESULTS

*Scanning electron microscopy*. SEM of nimesulide substance is a rounded particle with the size of 1 – 20 µm. Kollidon 25 is a rounded particle with the size of 50 – 90 µm with evenly spaced grooves on their surface. PEG 6000 and β-cyclodextrin are crystalline agglomerates of different shapes, with the size of particles 40 – 80 µm and 20 – 60 µm, respectively (Figure 1).

In the samples of physical mixtures the location of substance nimesulide particles can be observed on the surface of Kollidon 25 and PEG 6000, the latter forms a "substrate", which can be explained by the physical properties of carriers, i. e. PEG high plasticity and stickiness of Kollidon 25 (Fig. 2). SEM of physical mixture with β-CD is a combination of substance and carrier particles. In physical mixtures of nimesulide and carriers retain their structure and do not interact.

SEM of nimesulide solid dispersion with PEG 6000 is presented by agglomerates with a rounded size of 50 - 100 µm, consisting of substance particles and carriers with partial formation of solid solution (Figure 3). SD with Kollidon 25 is a homogeneous particles of different shapes of 20 - 60 µm. In SEM of solid dispersions with β-CD, there are two kinds of particles including particles of recrystallized nimesulide of oblong shape and particles of carrier located in its surface layer of nimesulide particles. SEM of solid dispersion demonstrates the interaction between the pharmaceutical substance and carriers that can increase solubility of nimesulide.

*Powder X-ray diffraction.* Nimesulide substance diffraction pattern is characterized by intense peaks at diffraction angle of $8.8^0$, $10^0$, $10.6^0$ and $10.9^0$, and diffraction pattern of PEG 6000 at $8.6^0$ and $10.5^0$, which are indicators of their crystalline state (Figure 4). In the diffraction pattern of nimesulide physical mixture with PEG 6000 peaks are observed which are characteristic of the substance nimesulide and the carrier. Reduction of major peaks intensity of substance nimesulide and the carrier, as well as the reduction of the substance peak at diffraction angle of $10.6^0$ are characteristics of SD diffraction which indicate transition of pharmaceutical substance into an amorphous state.

β-CD diffraction pattern is characterized by peaks at diffraction angles of $5.7^0$, $9.6^0$, $10.3^0$, $12.2^0$ and $15.8^0$ (Figure 5). In the diffraction pattern of nimesulide-β-CD physical mixture peaks are observed which are characteristic of the substance nimesulide and the carrier. Nimesulide-β-CD solid dispersion diffraction

is characterized by reduction in the substance nimesulide peaks intensity, which indicate at its crystallinity reduction. In the diffraction pattern of the substance diffraction angle peak offset is observed from $8.8^0$ to $9.1^0$ and as well as the β-CD peaks reduction at $9.6^0$, $10.3^0$, $12.2^0$ which indicate the formation of inclusion complexes between the substance and the carrier.

Substance K-25 is in the amorphous state which can be proved by the absence of characteristic peaks in its diffraction pattern (Figure 6). In the diffraction pattern of nimesulide - K-25 physical mixture peaks are observed which are characteristic of the substance nimesulide. These peaks have lower intensity resulting from the presence of a physical mixture of the carrier. Diffraction pattern of nimesulide-K-25 solid dispersion is characterized by a significant reduction in the intensity of substance diffraction peak at the angle of $8.8^0$ and reduction of diffraction peaks at angles of $10^0$, $10.6^0$ and $10.9^0$ which indicates a shift in substance nimesulide amorphous state.

*Absorption spectrophotometry in the IR region*. The possibility to form complexes in SD between nimesulide and PEG 6000, K-25, β-CD was predicted in the research[11] using semi-empirical methods of quantum chemistry. IR spectra of nimesulide is characterized by absorption bands at 1078 $cm^{-1}$ (S=O stretching vibrations), 1152 $cm^{-1}$ (C-O-C bending vibrations), 1320 and 1512 $cm^{-1}$ (N=O stretching vibrations), 3280 $cm^{-1}$ (N-H stretching vibrations). IR spectra of PEG 6000 is characterized by absorption bands at 3448 $cm^{-1}$ (OH stretching vibrations), 2890 $cm^{-1}$ (C-H stretching vibrations), 1100 $cm^{-1}$ (C-O-H stretching vibrations). Interaction between nimesulide and PEG 6000 does not occur in a physical mixture which reflects its IR spectra, while absorption bands intensity reduction can be observed in the IR spectra of SD which correspond to amino and nitro groups of nimesulide and hydroxyl group of PEG 6000, indicating at formation of intermolecular hydrogen bonds between the substance and the carrier (Figure 7).

IR spectra of K-25 is characterized by a strong absorption band at 1672 $cm^{-1}$ (C=O stretching vibrations), 1287 $cm^{-1}$ (C-N stretching vibrations), 2896 $cm^{-1}$ and 1460 $cm^{-1}$ (stretching and bending vibrations of C-H, respectively), 3480 $cm^{-1}$ (OH stretching vibrations). IR spectra of the physical mixture repeat IR spectra of nimesulide and K-25. In the IR spectra of SD intensity reduction can be observed at absorption bands 1320 $cm^{-1}$, 1512 $cm^{-1}$, 3280 $cm^{-1}$, which correspond to nimesulide groups vibrations participating in the formation of hydrogen bonds (Figure 8). In addition there is a significant reduction in the intensity of the absorption band at 2896 $cm^{-1}$, which also indicates the interaction between the substance and the carrier in the SD.

IR spectra of β-CD is characterized by absorption bands at 3388 $cm^{-1}$ (OH stretching vibrations), 2924 $cm^{-1}$ (C-H stretching vibrations), 1028 $cm^{-1}$ (C-O-C bending vibrations). IR spectra of the physical mixture are the same individual spectra of nimesulide and the carrier, which indicates a lack of interaction between the components. In the IR spectra of SD aside from absorption bands intensity reduction of the nimesulide amino and nitro groups, intensity reduction at 2924 $cm^{-1}$ and a significant intensity reduction at 3388 $cm^{-1}$ molecule β-CD also takes place, which is a good reason to speak about the formation of inclusion complexes.

## CONCLUSION

Modern method of modifying the properties of active pharmaceutical ingredients is obtaining a solid dispersions with macromolecular compounds (PEG, PVP) and cyclodextrins.

Scanning electron microscopy revealed formation of agglomerates with partial formation of solid solution in the solid dispersion of nimesulide with PEG 6000. Particles in shape, size and structure different from pure substances and carriers are obtained in solid dispersions with K-25 and β-CD. Characteristic changes detected by SEM indicate at interactions between system components, but particles of different SD differ because of the nature of carrier.

X-ray powder diffraction revealed the rise of amorphous state of nimesulide and inclusion complex formation of nimesulide - β-CD observed in SD of PEG 6000, K-25 and β-CD.

Mechanisms of interaction of nimesulide with PEG 6000, K-25 and β-CD in the SD was studied with the help of absorption spectrophotometry in the IR region. The interactions were established to occur through the formation of hydrogen bonds between amino and nitro groups of substance and hydroxyl groups of carriers.

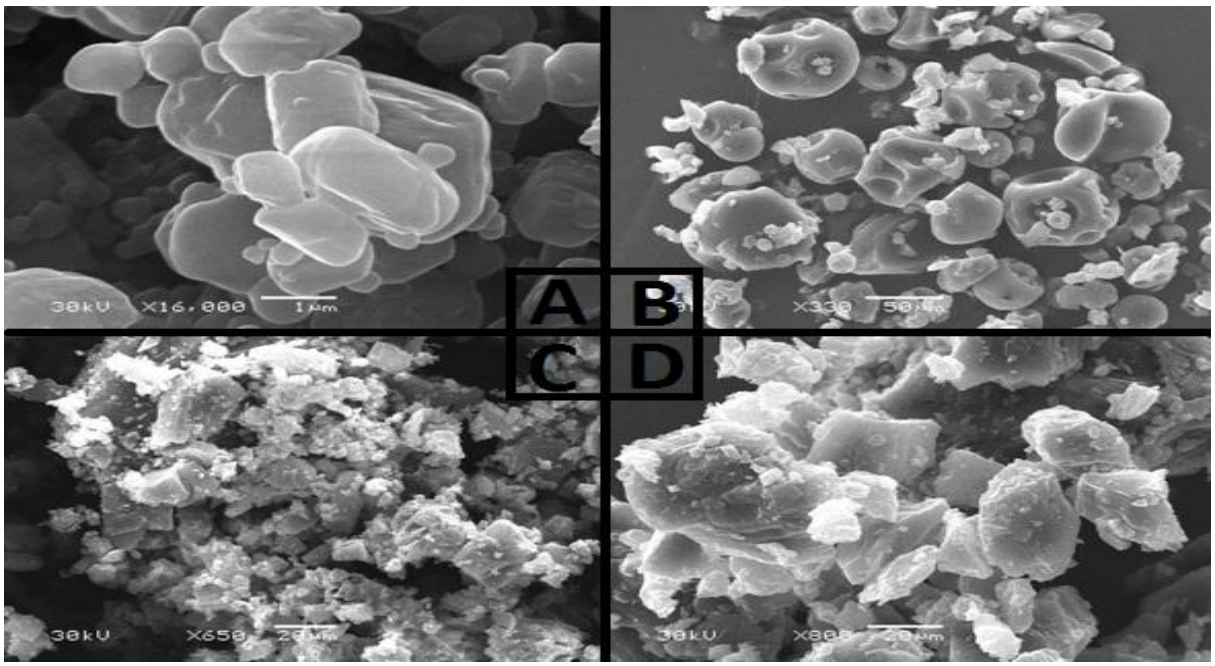


**Fig.1**
**SEM: A – nimesulide (x16000), B – Kollidon 25 (x330), C – β-cyclodextrin (x650), D – PEG 6000 (x800)**

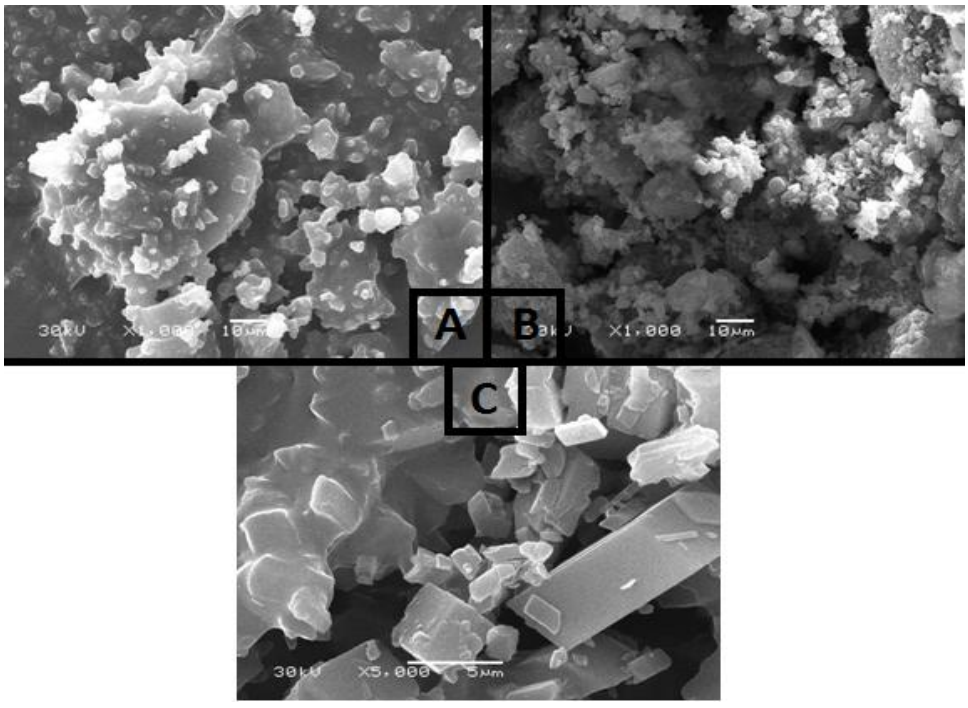


**Fig.2**
**SEM of nimesulide physical mixture with: PEG 6000 - A (x600), Kollidon 25 - B (x1000), β-CD - C (x5000)**

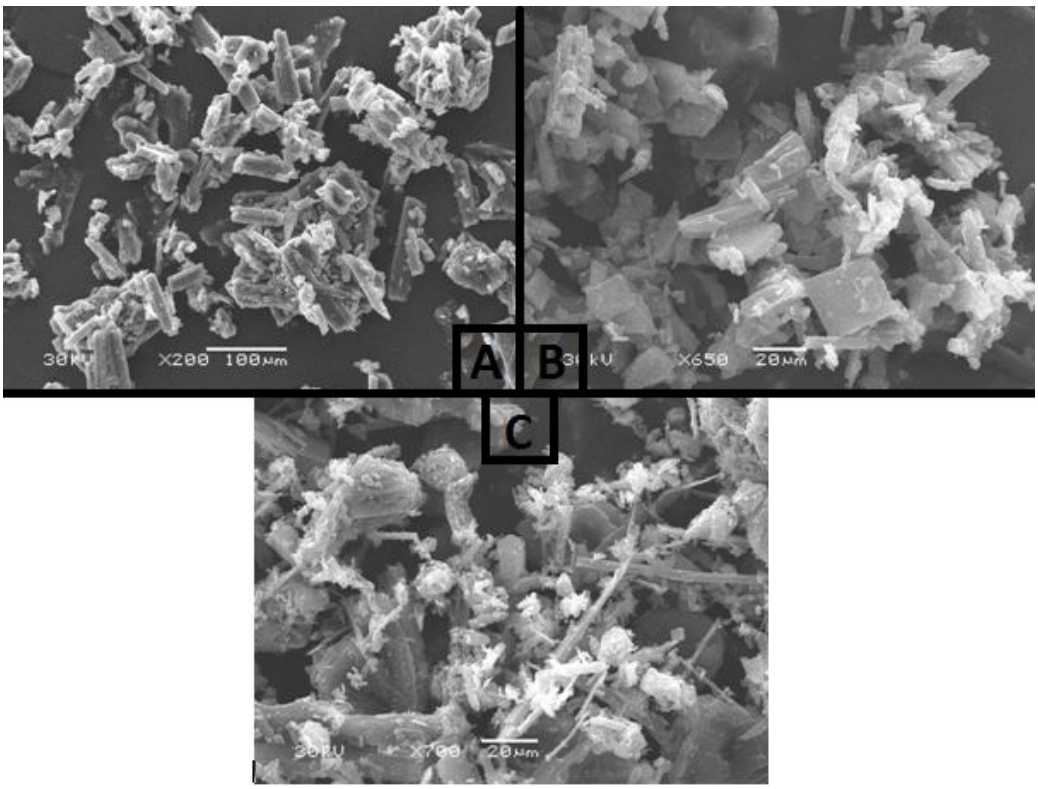


**Figure 3**
**SEM of nimesulide solid dispersions with: PEG 6000 - A (x200) Kollidon 25 - B (x650), β-CD - C (x700)**

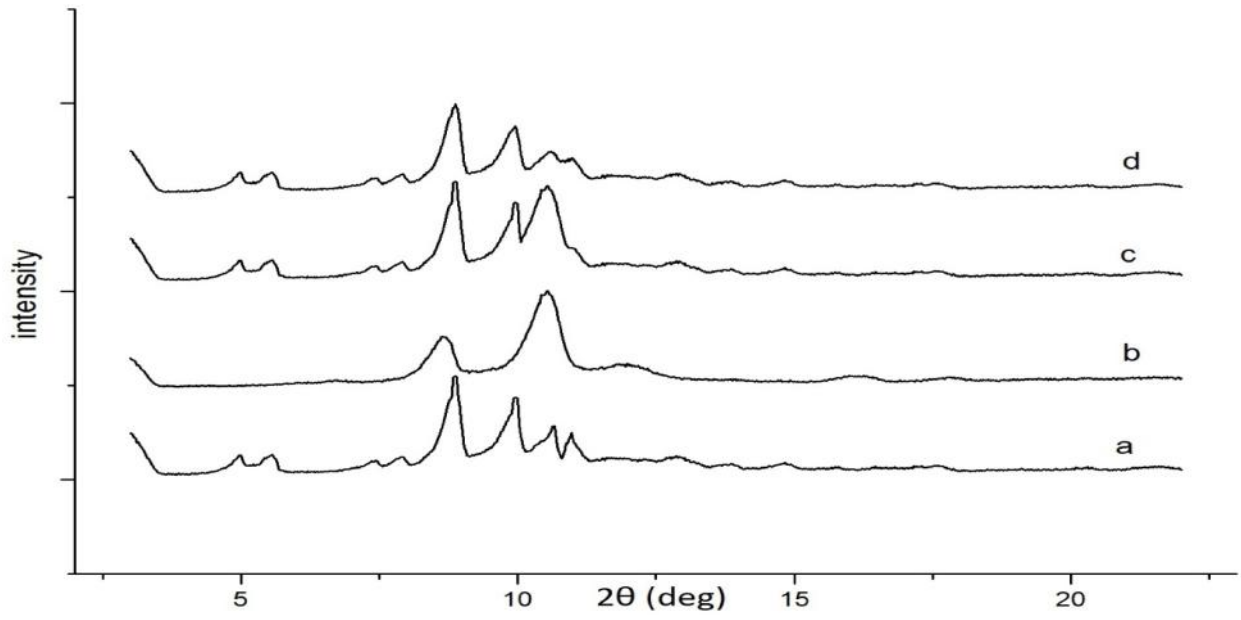


**Figure 4**
**Diffraction pattern: a - Nimesulide, b - PEG 6000, c - a physical mixture nimesulide-PEG 6000, d - SD nimesulide-PEG 6000**

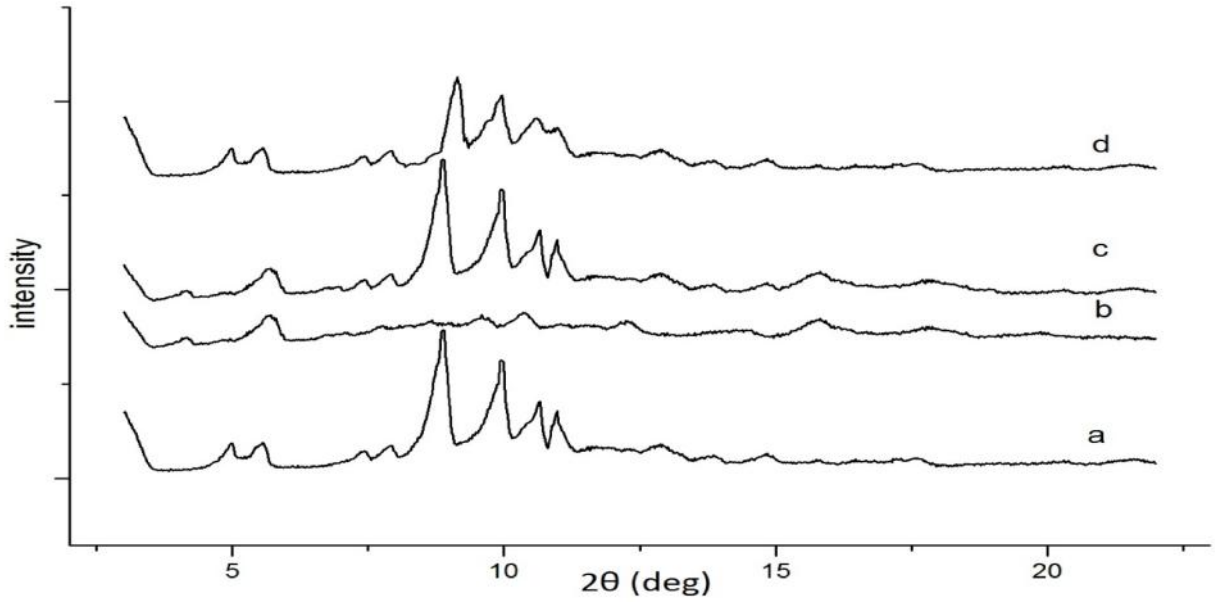


**Figure 5**
**Diffraction pattern: a - Nimesulide, b - β-CD, c - nimesulide-β-CD physical mixture, d - nimesulide-β-CD solid dispersion**

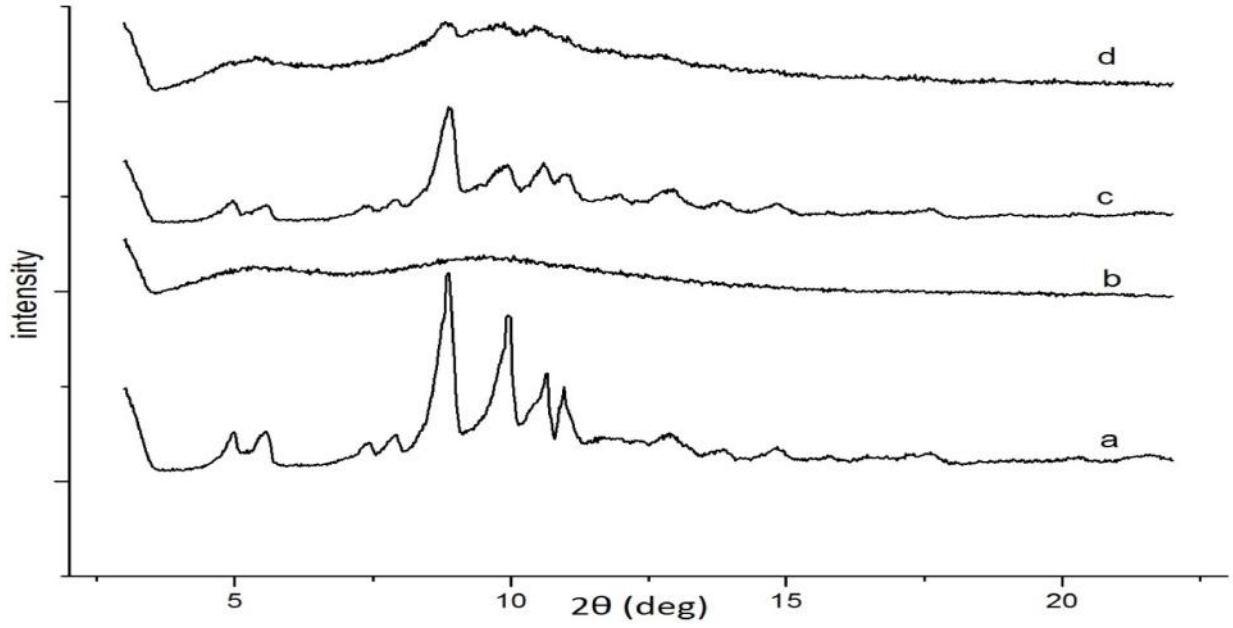


**Figure 6**
**Diffraction pattern: a - Nimesulide, b - Kollidon 25, c - nimesulide-Kollidon 25 physical mixture, d - nimesulide-Kollidon 25 solid dispersion**

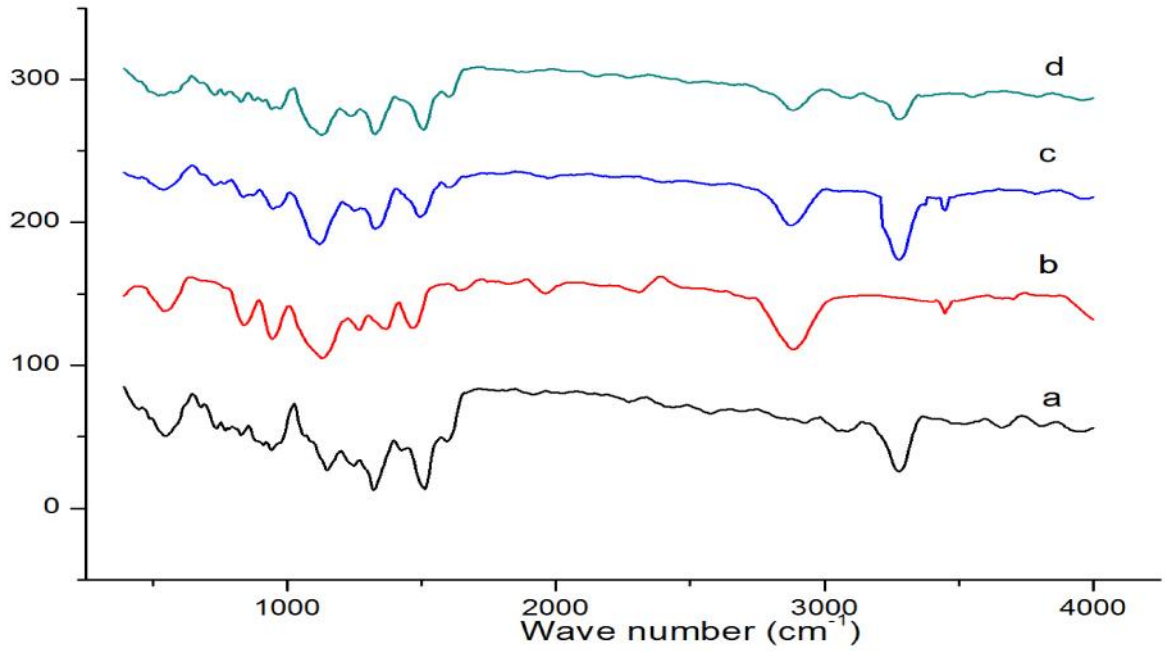


**Figure 7**
**IR spectra: a - Nimesulide, b - PEG 6000, c - nimesulide-PEG 6000 physical mixture, d - nimesulide-PEG 6000 solid dispersion**

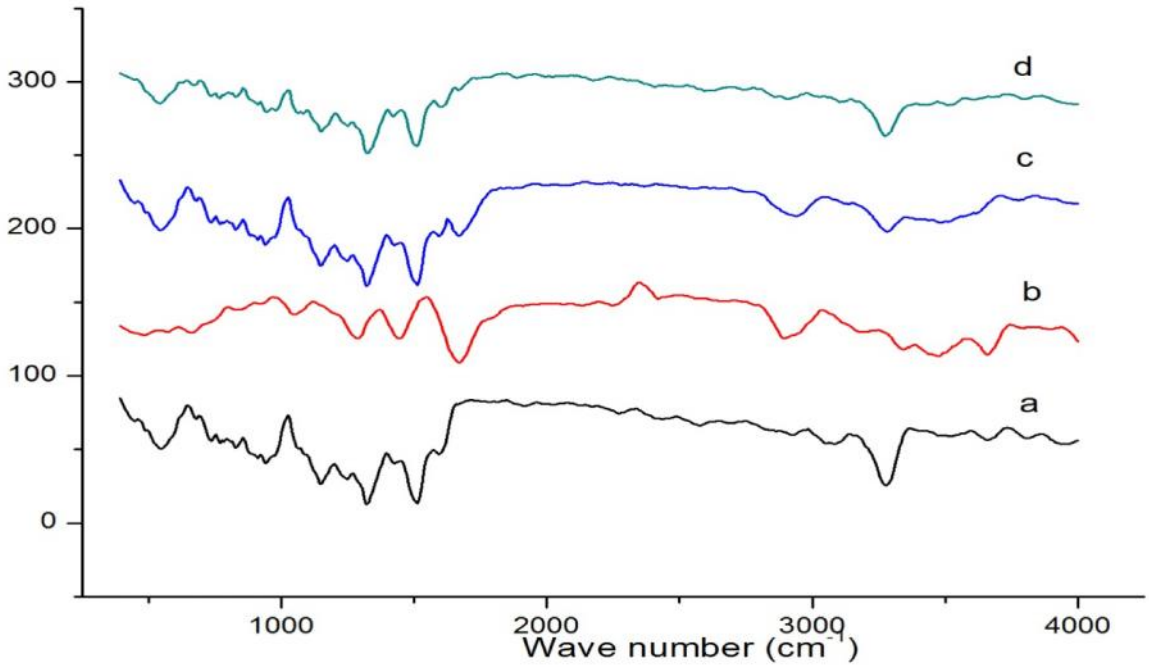


**Figure 8**
**IR spectra: a - Nimesulide, b - 25 K, c - nimesulide -K-25 physical mixture, d - nimesulide -K-25 solid dispersion**

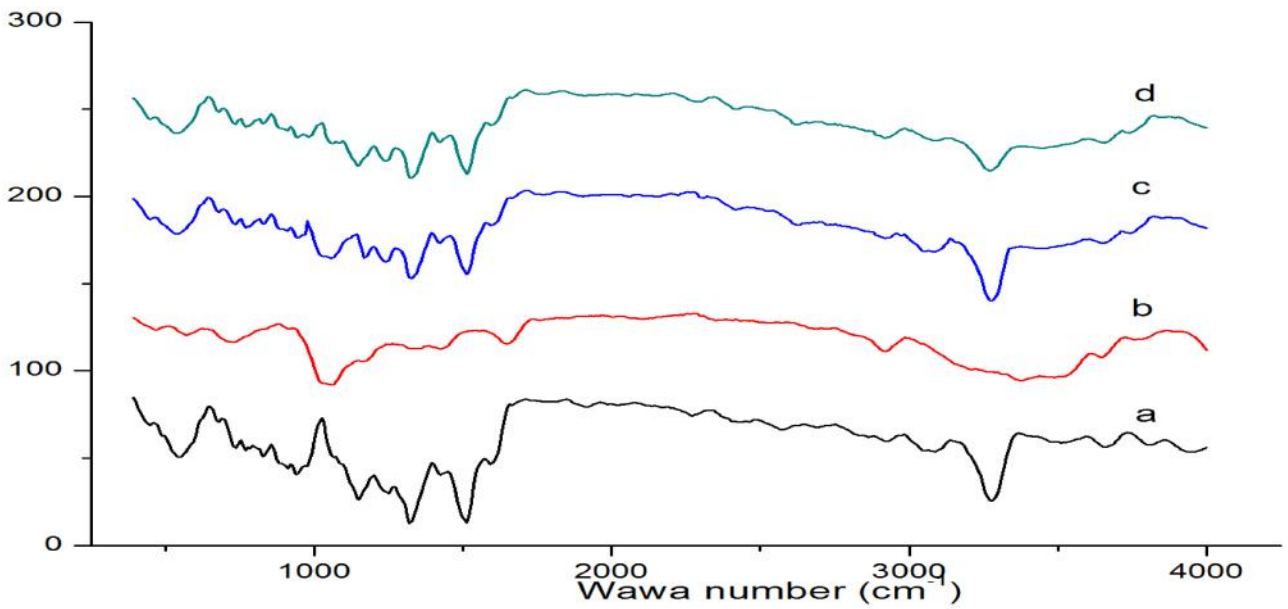


**Fig.9.**
**IR spectra: a - Nimesulide, b - β-CD, c - nimesulide-β-CD physical mixture, d - nimesulide -β-CD solid dispersion**

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