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Influence of polymeric precipitation inhibitors on dissolution behaviour of Meloxicam

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ABSTRACT

The scope of this study was to analyse the effect of polymeric precipitation inhibitor on *in-vitro* dissolution of Meloxicam which is a weak acid, water-insoluble and a crystalline compound. Meloxicam is used to treat pain or inflammation caused by rheumatoid arthritis. HPMC was used as polymeric precipitation inhibitor. Solvent evaporation method was employed to formulate solid dispersions with and without polymeric precipitation inhibitor. IR spectra suggested that there were no interactions between drug and polymers used in the study. DSC thermograms indicated that the drug was completely miscible with the molten carrier. Amorphization of the drug in the solid dispersion was established by a reduction in the enthalpy of drug melting in solid dispersion versus pure drug. The drug crystallinity in the solid dispersion was found to be reduced from X-ray Diffraction analysis. SEM analysis showed that Meloxicam exhibited irregular crystals, but the surface morphology of solid dispersions was smooth. Formulated solid dispersions showed increased solubility than the pure drug. Meloxicam solid dispersions with HPMC exhibited less precipitation rate compared to the Meloxicam solid dispersions without HPMC. Increase in the dissolution was attributed to the decrease in crystallinity of the drug and inhibition of drug precipitation. Thus, dissolution of Meloxicam can be enhanced by formulating solid dispersion using polymeric precipitation inhibitors.

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INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory multi-system disorder with characteristic features like a pain in the joints, stiffness, swelling and involvement of multiple systems. The aetiology of rheumatoid arthritis described by a combination of three factors: A moderate deficiency of cortisol, deficiency of dehydro-epi-androsterone (DHEA) and infection caused by micro-organisms like mycoplasma, leading to inflammation and destruction of tissue in periarticular and articular areas of immune-compromised hosts (Morissette SL *et al.,* 2004). The following strategies can be employed to treat arthritis; Early aggressive treatment; Tight control of RA. Non-steroidal anti-inflammatory drugs (NSAIDs), offered as non-prescription (OTC)or by prescription can be used to help ease arthritis pain and inflammation. Corticosteroids, anti-rheumatic drugs, Biologics, JAK inhibitors etc., are the drugs that slow disease activity (Trask AV 2007).

In recent times, supersaturation based drug delivery has to receive attraction as it improves the solubility of lipophilic molecules. Supersaturation is a

state where the concentration of solute is greater when compared with equilibrium solubility of the solution (Brouwers J *et al.,* 2009). Though there are various supersaturated systems, solid dispersion is the most widely studied system. To develop any supersaturated drug delivery the main obstacle is to maintain the solution at high energy supersaturated state, for a certain period preventing precipitation (VandecruysR *et al.,* 2007). Supersaturation can be maintained by inhibiting either nucleation or crystal growth, in order to maintain the supersaturation precipitation inhibitors were generally included which are polymers that avoid precipitation in solution and crystallization in solids (Raghavan SL *et al.,* 2001). Both in solid or solution state mobility of molecules, drug's tendency to recrystallize and polymer-drug reactions plays a prominent role in inhibition of precipitation in a supersaturated system (Chauhan H *et al.,* 2014). PVP and HPMC have shown great potential in inhibiting the precipitation and increasing the solubility of the drug. Introducing these polymers within solid dispersions or lipid-based formulations can help in sustaining supersaturation of the drug in the vehicle after dispersion, improving its variability in exposure and bioavailability (Good DJ *et al.,* 2010).

Meloxicam is an oxicam derivative and an enolic acid type of non-steroidal anti-inflammatory drug, approved by the US Food and Drug Administration for use in rheumatoid arthritis and osteoarthritis. Meloxicam has a selective COX-2 inhibitory effect, which is expected to have lesser GI toxicity as in contrast to non-selective NSAIDs. From the clinical trials, it was found that 7.5-15 mg/day of meloxicam was not only similar in efficacy when compared to current standard anti-inflammatory and analgesic drugs like Diclofenac, Piroxicam and Naproxen but also was associated with few GI adverse effects. Additionally, Meloxicam was reported to show side effects such as digestive tract upset, liver toxicity and Breathing problems (Aoki T *et al.,* 2006)

MATERIALS AND METHODS

Materials

Meloxicam was purchased from Mysore Drug House and General Store, Bengaluru. Hydroxypropylmethylcellulose(HPMC) was purchased from LOBA Pharmaceuticals, Mumbai. Sorbitol was purchased from Merck specialities private limited, Mumbai. Chloroform was purchased from Merck specialities private limited, Mumbai.

Methods

Formulation of Meloxicam Loaded Solid Dispersions

Formulation of Meloxicam loaded solid dispersions with and without polymeric precipitation inhibitors was done by solvent evaporation method. Accurately 80mg of Meloxicam was weighed and dissolved in 20ml of chloroform and then varying quantities of HPMC (polymeric precipitation inhibitor) was added to the drug solution. The solution was dissolved and allowed to evaporate at room temperature, the resultant residue was further dried, and solid dispersions were stored in a desiccator until use. Different compositions of Meloxicam solid dispersion done by solvent evaporation are depicted in Table 1.

Characterization of Meloxicam in Solid Dispersion

Fourier Transform Infrared Spectroscopy (FTIR)

About 2mg of pure drug and prepared solid dispersion were acquired for FTIR analysis. Pure drug and formulated solid dispersions were dispersed in KBr powder and pellets were prepared by applying 4 tons of pressure and FT-IR spectra were recorded (Patel DD *et al.,* 2011).

Differential Scanning Calorimetry

1mg of meloxicam was crimped in aluminium pans using crimper and heated under nitrogen flow (20ml/min) at a scanning rate of 10˚C min^{-1}, from 100˚ - 300˚C. An empty aluminium pan was used as a reference to obtain the peaks (Patel DD *et al.,* 2011).

Degree of Crystallinity

The heat diffusion of the drug in the formulated solid dispersion was done by measuring the peak area of the obtained endotherm. In order to calculate the % crystallinity of the loaded drug in solid dispersion ratio between fusion, energies were considered and calculated using the following equation (Ghosh I *et al.,* 2011)

Scanning Electron Microscopy

The SEM analysis was carried out using Hitachi Noran System 7 manufactured by Thermo Fischer Scientific. The photographs were acquired to iden- tify and validate the nature and morphological characteristics of solid dispersions (Patel DD *et al.,*2011).

Evaluation of Solid Dispersion

Drug Content

10mg of meloxicam was accurately weighed and dissolved in 50ml of 0.1N HCl and stirred well. Absorbance was measured at 228 nm for the diluted and filtered solutions to estimate the drug content by following equation (Takatsuka T *et al.,* 2009).

%Drug content = Concentration (µg/ml) × Dil. Factor × 100 / 50

Solubility Studies

The solubility of Meloxicam was carried out in distilled water. Excess of Meloxicam was added to 10ml distilled water in the volumetric flask. Samples were shaken well and the saturated solutions after 24hrs were filtered through Whatman filter paper no.1. Filtrates were suitably diluted and used to determine Meloxicam concentration spectrophotometrically at 228nm(Takatsuka T *et al.,* 2009).

Turbidity Measurement and in-vitro precipitation studies

Nephelometer is an instrument which calculates the amount of light scattered when a sample was introduced in turn indicating number of particles present in a sample. 3ml of the supersaturated solution was mixed with 30ml of FaSSGF and was introduced into nephelometer (Systronics 131) and signals were recorded periodically(Takatsuka T *et al.,* 2009).

In - vitro dissolution studies

In-vitro dissolution studies for formulated solid dispersions was done using USP-XXIV Type – II paddle dissolution test apparatus. The solid dispersions equivalent to 80mg of Meloxicam were placed in dissolution container holding 900ml of 0.1N HCl as dissolution medium (pH 1.2 at 37˚C±0.5˚C and stirred at 100 rpm. A sample of 5 ml was withdrawn intermittently and an equal amount of fresh dissolution medium was replaced to maintain sink conditions. After filtration through Whatman filter paper, Meloxicam was estimated spectrophotometrically at 228nm with suitable dilutions (Masanori Ochi *et al.,* 2014).

RESULTS AND DISCUSSION

Characterization of Meloxicam in Solid Dispersion

Fourier transform Infrared spectroscopy (FTIR)

The FT-IR spectra of Meloxicam and formulated solid dispersions were studied for the compatibility and possibility of non-covalent interactions. As shown in Figure 1 there was no significant shift observed in the positions of featured peaks of Meloxicam as well as carriers. Hence, it can be inferred that the drug and carriers are chemically compatible and can be incorporated together in the formulation.

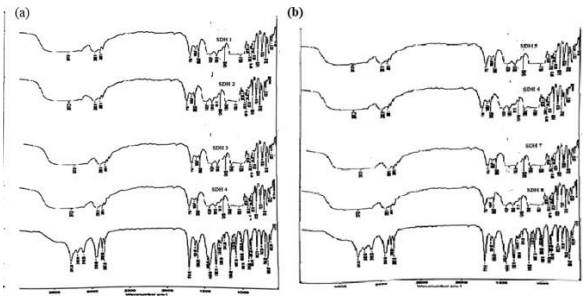

Figure 1: FT-IR spectra of Meloxicam and its solid dispersions of SDH 1, SDH 2, SDH 3, SDH 4; SDH 5, SDH 6, SDH 7, SDH 8

Differential Scanning Calorimetry (DSC)

From Figure 2, it was evident that both Meloxicam and Meloxicam loaded solid dispersion had shown an endothermic peak at 171.83˚C. Thermogram of Pure Meloxicam showed a sharp endothermic peak at 171.83˚C corresponding to its melting point, indicating the crystalline nature of the drug. Thermogram of Meloxicam loaded solid dispersion had shown a reduction in intensities suggesting, amorphization of crystalline drug in drug-carrier systems.

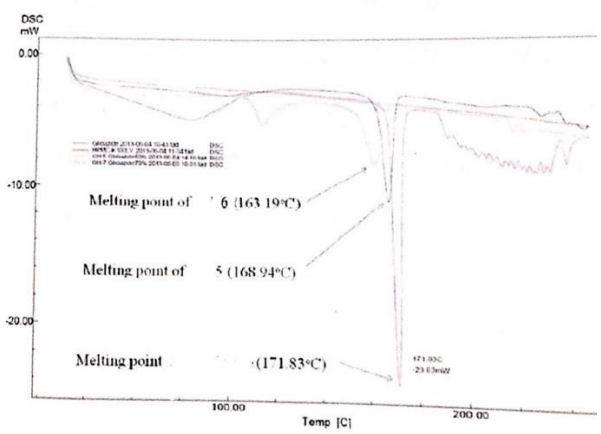

Figure 2: Endothermic peaks of Meloxicam and Meloxicam in solid dispersion

The degree of Crystallinity -X-Ray Diffraction analysis (XRD)

Pure Meloxicam showed sharp and intense peaks of crystallinity at a diffraction angle of 2^{o} at 10.67, 15.05, 16.805, 17.1, 18.195, 20.97 and 22.21 indicating the crystalline nature of the drug. The XRD patterns of the formulations exhibited a reduction in intensity of peaks (SDS-204 to 620 and SDH-151 to 538) compared to Meloxicam alone. SDH formulations found more significantly useful in the reduction of crystalline characteristics of the drug (RDC ranging from 0.0832 to 0.296) than SDS (RDC ranging from 0.112 to 0.341). The Relative Degree of Crystallinity by XRD study was shown in Table 2. The XRD spectra of Meloxicam and its solid dispersions (SD1, SD 2, SD 3, SD 4, SD 5 and SD 6) was depicted in Figure3.

Table 1: Formulation of meloxicam solid dispersion by solvent evaporation method

Formulation code	Meloxicam (mg)	Hydroxypropyl methylcellulose Ratio	Hydroxypropyl methylcellulose (mg)	Chloroform (ml)
SDH1	80	1:0.5	40	20
SDH2	80	1:0.75	60	20
SDH3	80	1:1	80	20
SDH4	80	1:1.25	100	20
SDH5	80	1:1.5	120	20
SDH6	80	1:1.75	140	20
SDH7	80	1:2	160	20
SDH8	80	1:2.25	180	20

Table 2: Relative Degree of Crystallinity by XRD study

Sample	Angle 2^{θ}	Peak intensity (count)	RDC
Meloxicam	10.775	1229	1.0000
SDS 1	10.90	634	0.3515
SDS 2	10.630	343	0.1866
SDS 3	10.620	320	0.1738
SDS 4	10.570	299	0.1619
SDS 5	10.670	268	0.1399
SDS 6	10.580	203	0.1024

Table 3: Drug content with and without polymeric precipitation inhibitor

Formulation code	Drug content (%w/w) with polymeric precipitation inhibitor.	Formulation code	Drug content (%w/w) without polymeric precipitation inhibitor.
SDH 1	98.12	SDS 1	98.23
SDH 2	99.18	SDS 2	98.91
SDH 3	99.43	SDS 3	98.44
SDH 4	99.58	SDS 4	99.19
SDH 5	97.0	SDS 5	98.91
SDH 6	99.94	SDS 6	100.11
SDH 7	98.45	SDS 7	98.39
SDH 8	96.39	SDS 8	99.18

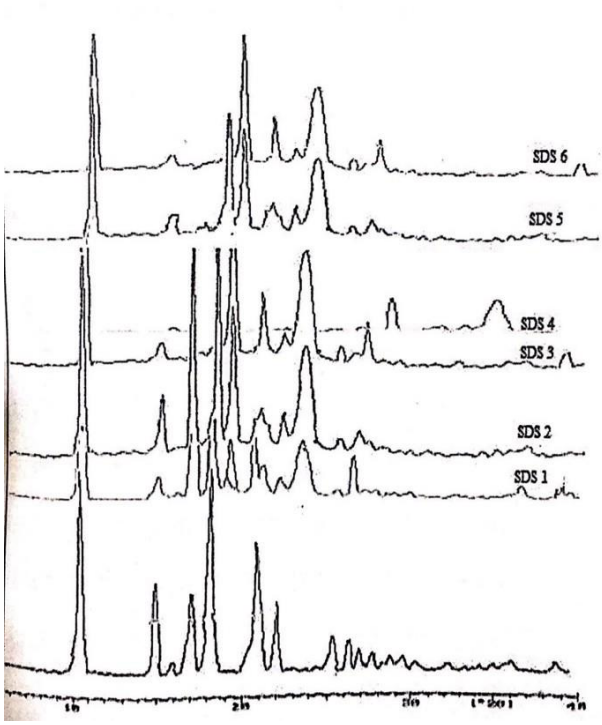

Figure 3: XRD spectra of meloxicam and its solid dispersions (SD 1, SD 2, SD 3, SD 4, SD 5 and SD 6

SEM of Meloxicam loaded solid dispersion

To identify the morphology of the pure drug and the solid dispersions prepared with and without polymeric precipitation inhibitor by solvent evaporation method the Scanning Electron Microscopy (SEM) was done. As depicted in Figure 4a & 4b prepared solid dispersion was smooth and the pure drug appeared as irregular crystals.

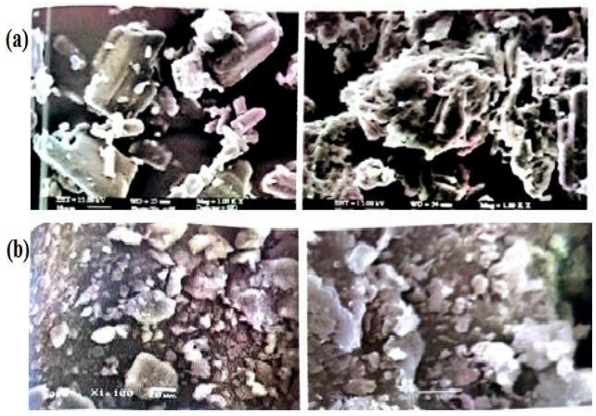

Figure 4: a) SEM image of Pure Meloxicam; (b) SEM image of meloxicam with HPMC

Evaluation of Solid Dispersions

Drug Content

The drug content in prepared solid dispersions was ranging from 97.03 to 100.3 % (w/w), complying with IP limits. Meloxicam content in the prepared solid dispersions were shown in Table 3. The highest drug content with polymeric precipitation inhibitor(99.94%) was found in solid dispersion SDH 6 and lowest drug content(96.39%) was found in solid dispersion SDH 8. The highest drug content without polymeric precipitation inhibitor(100.11%) was found in solid dispersion SDS 6 and lowest drug content(98.23%) was found in solid dispersion SDS 1

Solubility Studies

Solubility studies were performed for the pure drug and the prepared solid dispersions. Solid dispersions with HPMC exhibited maximum solubility as compared to other solid dispersions as shown in Figure 5(a) and Figure 5(b). SDH 8 exhibited less solubility compared to the SDS 8 due to an increase in the concentration of precipitation inhibitor HPMC.

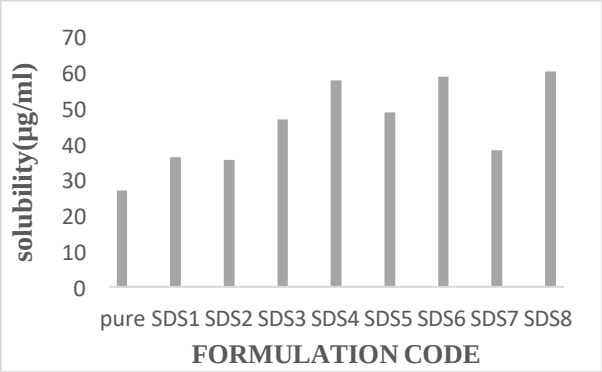

Figure 5a: Aqueous solubility of Meloxicam and its solid dispersions without HPMC

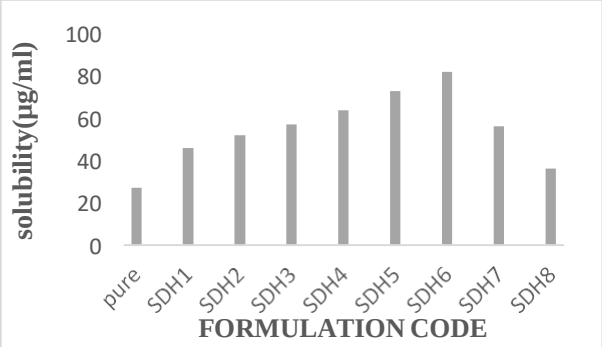

Figure 5b: Aqueous solubility of Meloxicam and its solid dispersion with HPMC

Turbidity Measurement and in-vitro precipitation studies

The drug precipitation in the medium was monitored by measuring the turbidity using a nephelometer. Turbidity measurement determines the amount of light scattered by particles in a sample. By using the nephelometer, signal versus time data was acquired and the signal provides a measure of the amount of the precipitate present in the solution. The comparison of the degree of drug precipitation with and without polymeric precipitation inhibitors in the prepared Meloxicam solid dispersions are shown in Figure6a and 6b. From the results, it can be inferred that as the concentration of HPMC increases there was a reduction in precipitation of the loaded Meloxicam.

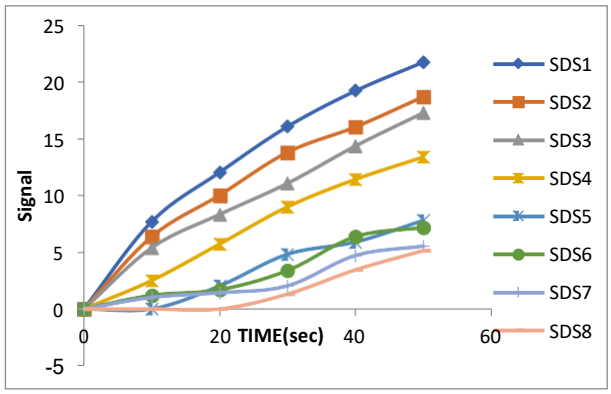

Figure 6a: Precipitation rate of meloxicam solid dispersions without polymeric precipitation inhibitor

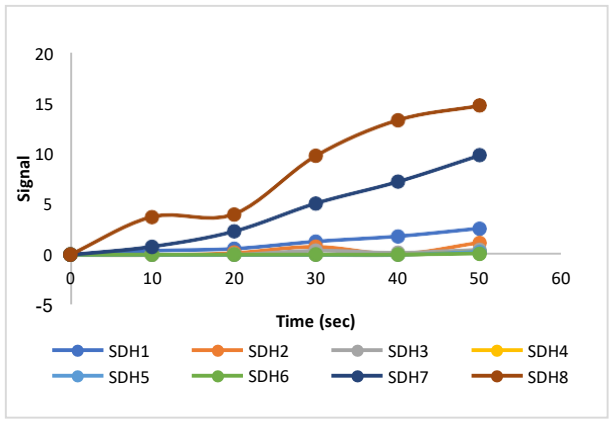

Figure 6b: Precipitation rate of meloxicam solid dispersions with polymeric precipitation inhibitor

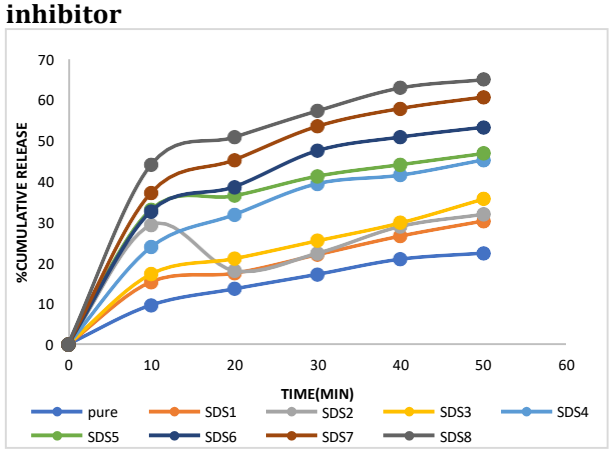

Figure 7a: Dissolution behaviour of Meloxicam and its solid dispersions without polymeric precipitation inhibitor

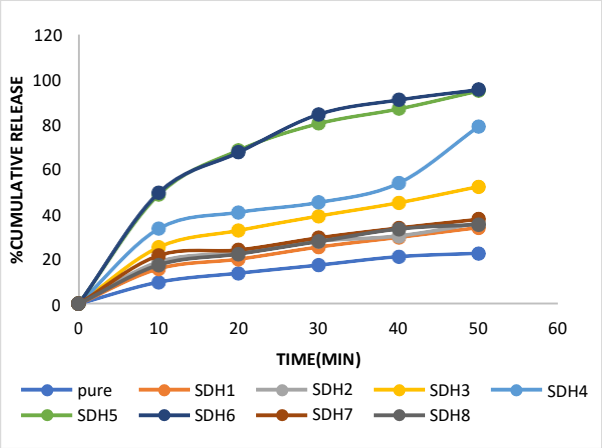

Figure 7b: Dissolution behaviour of Meloxicam and its solid dispersions with polymeric precipitation inhibitor (HPMC)

In – vitro Dissolution studies

Results obtained from dissolution studies suggested that Solid dispersions with HPMC exhibited faster as well as improved dissolution when compared with solid dispersions without HPMC as depicted in Figure 7a &7b. It can be inferred that the polymeric precipitation inhibitor (HPMC) used in the solid dispersion system keeps the drug molecules away from each other and prevents the crystal growth. Thus, the crystalline drug is converted to amorphous form hence increasing the dissolution profile of the loaded Meloxicam.

CONCLUSION

Solid dispersions loaded with Meloxicam were successfully formulated using solvent evaporation method, validated using FT-IR, DSC, XRD and SEM, evaluated for drug content, solubility, *in - vitro* drug precipitation rate and *in - vitro* dissolution behaviour. The FT-IR spectra of Meloxicam Solid dispersions exhibited no shift in the peaks. The melting peaks in the DSC thermograms demonstrated a reduction in intensities, suggesting conversion of the drug from a crystalline state to amorphous state. The SEM images showed that the surface morphology of pure Meloxicam was irregular and agglomerated, but the prepared solid dispersions were fine and smooth. Meloxicam solid dispersions with polymeric precipitation inhibitor showed better solubility when compared to solid dispersions without polymeric precipitation inhibitors. Meloxicam solid dispersions with HPMC exhibited less precipitation rate and improved dissolution profile compared to the Meloxicam solid dispersions without HPMC. Thus, polymeric precipitation inhibitor successfully inhibited drug precipitation in bio-relevant media and shown a marked improvement in solubility and dissolution profile of Meloxicam.

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Conflict of Interest

The author confirms that this article content has no conflict of interest.

REFERENCES

Aoki T, Yamaguchi H, Naito H, Shiraki K, Izawa K, Ota Y, Sakamoto H, Kaneko A. Premedication with cyclooxygenase-2 inhibitor meloxicam reduced postoperative pain in patients after oral surgery. Int J Oral Maxillofac Surg. 35(7), 2006, 613-7.

Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: The answer to solubility-limited oral bioavailability. J. Pharm. Sci. 98(8), 2009, 2549-72.

Chauhan H, Kuldipkumar A, Barber T, Medek A, Gu CH, Atef E. Correlation of inhibitory effects of polymers on precipitation in solution and amorphous solid crystallization based on molecular interaction. Pharm. Res. 31(2), 2014, 500-15.

Ghosh I, Bose S, Vippagunta R, Harmon F. Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. Int. J. Pharm. 409(1), 2011, 260-268.

Good DJ, Rodríguez-Hornedo N. Cocrystal eutectic constants and prediction of solubility behaviour. Cryst. Growth Des. 10(3), 2010, 1028-32.

Masanori Ochi, TakakiKawachi, EriToita, Kayo Yuminoki. Development of nanocrystal formulation of Meloxicam with improved dissolution and pharmacokinetic behaviours. Int. J. Pharm. 474(1), 2014, 151-156

Morissette SL, Almarsson Ö, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv Drug Delivery Rev. 56(3), 2004, 275-300.

Patel DD, Joguparthi V, Wang Z, Anderson BD. Maintainance of supersaturation I-Indomethacin crystal growth kinetic modelling using an online second derivative Ultraviolet spectroscopic method. J. Pharm. Sci. 100(7), 2011, 2623-41.

Raghavan SL, Trividic A, Davis AF, Hadgraft J. Crystallization of hydrocortisone acetate: Influence of polymers. Int. J. Pharm. 212(2), 2001, 213-21.

Takatsuka T, Endo T, Jianguo Y, Yuminoki K, Hashimoto N. Nanosizing of poorly water-soluble

compounds using rotation/revolution mixer. Chem. Pharm. Bull. 57(10), 2009, 1061-7.

Trask AV. An overview of pharmaceutical co-crystals as intellectual property. Mol. Pharm. 4(3), 2007, 301-9.

Vandecruys R, Peeters J, Verreck G, Brewster ME. Use of a screening method to determine excipients which optimize the extent and stability of supersaturated drug solutions and application of this system to solid formulation design. Int. J. Pharm. 342(2), 2007, 168-75.