WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

"STUDIES ON THE CRYSTAL FORMS OF MELOXICAM: PREPARATION, CHARACTERIZATION AND DISSOLUTION PROFILE"

[1]Ms.Sangle Sakshi. R., [2]Dr.Joshi Amol. A., [3]Mr.Shinde Mahesh. U., [4]Ms.Quazi Rubiya Saher S., [5] Dr. Aamer I Quazi.

[1]Student, [2] Principal, [3]Assistant Professor, [4]Assistant Professor.[5] Professor.
[1]Department of Pharmaceutics.
Aspm's K.T. Patil College of Pharmacy Dharashiv, Osmanabad, Maharashtra, India.

ABSTRACT :

Meloxicam crystals having different types of habits, were prepared by recrystallization from selected solvents such as ethanol, methanol, THF, acetone, diethylet her under different working conditions and using different additives like HPMC, PEG 4000, gelatin, SCMC, chitosan, sodium alginate. Obtained crystals were characterized by photomicrography,SEM, X-ray powder diffractometry, FT-IR spectrometry, differential scanning calorimetry and Karl Fischer titration. The crystals were evaluated for melting point, LOD, particle size, solubility and dissolution. It was found that the newly developed crystals were different from each other with respect to physical properties, but are chemically identical. The melting point of obtained crystals was slightly varies as compared to pure drug. The crystals obtained from ethanol produced cuboidal crystals and that obtained from methanol thin plate shaped crystals. But the crystals obtained with ethanolic solution of drug in the presence of HPMC, PEG 4000, gelatin, SCMC, sodium alginate, chitosan produced prismatic, thin plate and cuboidal shaped crystals. X-ray diffraction spectra of pure drug and prepared crystals indicate that existence of four distinct crystal modifications i.e., orthorhombic (pure drug), tetragonal (ME1,ME3,MT), triclinic (ME2,ME5,MM) and cubic(ME6,ME7,MA) when modified with different solvents, methods and additives. Hence, both X-ray diffraction spectra and differential scanning calorimetry study of the newly developed crystals, clearly indicate that Meloxicam exists in different crystal modifications. The solubility of newly developed crystals was about 1.28 to 1.62 times higher in distilled water than that of untreated Meloxicam. The dissolution rate of newly developed crystals was also found to be significantly higher ($P<5$) than pure drug Meloxicam with an order: pure drug < recrystallized crystals with additives < recrystallized crystals using different solvents.

Keywords*:* Meloxicam, Recrystallization, Crystal shape, X-ray powder diffractormeter; SEM, S Differential scanning calorimetry; Solubility, Dissolution rate.

I.INTRODUCTION:

Pharmaceutical development faces major challenges such as poor solubility, low bioavailability, and instability of drugs. One effective way to address these issues is by modifying the "solid-state form"of a drug, especially through *crystal engineering. Drugs like :"meloxicam"can exist in different crystal forms (polymorphs, solvates, amorphous forms), which significantly affect their solubility, dissolution rate, and bioavailability.

- **Crystallization**: is the process of forming solid crystals from a solution and is widely used in the pharmaceutical industry to improve purity and performance. Factors such as solvent type, temperature, pH, and the presence of additives influence the shape (habit), size, and purity of the crystals. By modifying these conditions, one can produce crystals with better dissolution and therapeutic performance
- **Polymorphism** :refers to the ability of a compound to exist in more than one crystalline form. Some polymorphs dissolve faster than others and may offer better drug absorption. However, they may convert to more stable forms over time. Therefore, choosing the right crystal form is important for ensuring drug quality, stability, and effectiveness.
- This study focuses on "recrystallizing meloxicam"using different solvents and additives to develop crystal forms with improved solubility and dissolution. Techniques like "XRD, SEM, DSC, and FTIR" are used to characterize these new forms. Understanding and controlling crystal properties is essential for the successful development of effective and stable pharmaceutical products.The development of new pharmaceutical formulations is increasingly challenged by issues like poor solubility, stability, and bioavailability of active pharmaceutical ingredients (APIs). As patents for many drugs expire, pharmaceutical companies face pressure to enhance drug delivery through innovative solid-state engineering, including polymorphic and crystalline form optimization.

- **Solid-state forms**: which include crystalline polymorphs, solvates (e.g., hydrates), and amorphous forms—play a pivotal role in influencing a drug's solubility, dissolution rate, stability, and ultimately its bioavailability. Crystalline forms are highly ordered and vary in shape and internal molecular arrangement. In contrast, amorphous forms lack this order and typically offer higher solubility but lower stability.

OBJECTIVES:

1.Recrystallization meloxicam from different solvents

2. To Modify the crystals of meloxicam using different additives and techniques.

3. To Characterize crystals using: • Photomicrography• XRPD(X-ray powder diffractometry• FTIR• Scanning electron microscopy • Differential scanning calorimetry• Thermogravimetric analysis • Kar Fischer Aquametry

III.REVIEW OF LITERATURE :

1.Luger P et al[38] studied on physiochemical properties of meloxicam which is dependent on pH and solvent used. The meloxicam recrystallized from THF are preferred. The yellow plate like crystals with rhombic cross section were obtained from saturated solution of THF. These crystals have a triclinic lattice and are referred to as the meloxicam enol. For road shaped crystal with an orthorhombic lattice produced using sodium hydroxide/water with subsequent addition acetic acid yielding a solution of pH 7 or below. These crystals referred to as meloxicam zwiter ion. These crystals are characterized by XRD.

2.K.P.R. Chowdary[39] studied physicochemical characterization of meloxicam (ME)–cyclodextrin (CD) binary systems both in solution and solid states and to improve the dissolution properties of meloxicam via complexation with α-, β- and γ- cyclodextrins. Detection of inclusion complexation was done in solution state by means of phase solubility analysis, mass spectrometry and ^{1}H nuclear magnetic resonance (NMR) studies, and in solid state using differential scanning calorimetry (DSC), powder X-ray diffractometry, and in vitro dissolution studies. Phase solubility, mass spectrometry and ^{1}HNMR studies in solution state revealed 1:1M complexation of meloxicam with all CDs. A true inclusion of ME with γ-CD at 1:1 and 1:2M in solid state was confirmed by DSC, powder XRD and scanning electron microscopy (SEM) studies. Dissolution properties of ME–CDs binary systems were superior when compared to pure ME

3.Emirhan Nemutlu, Sedef Kir[40] developed UV spectrophotometric method for the determination of meloxicam in pure and pharmaceutical forms. The analyses were performed in 100nM borate buffer (pH 8.5) and methanol. The measurement of UV absorbance was done at 363 nm. The developed was validated respect to stability, linearity, precision, accuracy, selectivity, robustness and ruggedness and applied to the determination of meloxicam in six pharmaceutical preparations including two dosage forms.

4. Yadav MR et al[41] prepared different crystal forms of pefloxacin using solvents of varying polarity (ethanol, methanol, acetonitrile, isopropanol,dimethylformamide and distilled water) and characterized and evaluated for dissolution profile. They concluded that existence of five polymorphic forms and showed differences in dissolution rate profile in the first 15 min only.

5. Lu J, Wang XJ, Yang X, Ching CB[42] crystallized famotidine in two different polymorphic forms and characterized it in detail. They concluded that the polymorphism of famotidine possesses a monotropic nature, and polymorph A is the thermodynamically favored form, while polymorph B is the kinetically favored form.

6. M. Sheikh zadeh et al[43] studies on polymorphism of buspirone hydrochloride.

The solubility of two polymorphs of buspirone hydrochloride in isopropanol, water and mixture of these two solvents has been investigated. The solubility of buspirone hydrochloride Form 2 in water and isopropanol is higher than buspirone hydrochloride Form 1. Using the solubility data, transformation analysis has been done and the results confirm these two polymorphs are enantiotropies and Form 1 converts to Form 2 at 95 ◦C. The UNIQUAC binary adjustable parameters have been found and based on these parameters, the solubility of these molecules has been predicted and compared with the experimental solubility. The solubility prediction has been performed by using different UNIFAC equations for binary and ternary systems. The UNIQUAC and original UNIFAC showed better prediction capability. Different general solubility equations (GSE) have been used for estimation of solubility which works based on partial charge, hydrogen bond factors and partition coefficients.

IV METHODOLOGY:

Drug profile: Meloxicam -Class: Non-Steroidal Anti-Inflammatory Drug(NSAID) Structure: Enolic acid derivative, known for its selective COX-2 inhibition.

Mechanism: Slective COX-2 Inhibitor.Inhibits prostaglandin synthesis, reducing inflammation and pain.

Uses: Treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

Physiochemical Properties:

Appearance: crystalline powder

Solubility: Poor in water; better in organic solvents (ethanol, methanol, THF)

Analytical Techniques Used:XRPD, SEM, FTIR, DSC, TGA, Photomicrography, Karl Fischer Aquametry

EXCIPIENT PROFILE- Purpose: Enhance crystal habit, solubility, dissolution, and bioavailability of meloxicam.

Ex Excipient	Fu Function	Ef Effect	Code
HPMC	Polymer	In Inhibits crystal growth	M ME1
Gelatin	Binder	Alters lattice packing	M ME2
PEG 4000	W Wetting agent	I Improves solubility	M ME3
So Sodium alginate	Ge Gelling agent	Modifies crystal surface	M ME4
SCMC	Stabilizer	Controls nucleation	M ME5
Chitosan	Bioadhesive polymer	Enhances dissolution	M ME6

.1 Materials: Meloxicam was selected as the model drug and obtained as a gift sample. All solvents used were of analytical grade. Additives such as HPMC, PEG 4000, PVP, chitosan, gelatin, and sodium alginate were used to examine their effect on crystallization.
Equipment Used -1.UV-Visible Spectrophotometer (Shimadzu-1700)
2 Dissolution Test Apparatus (USP XXIII)
3 Scanning Electron Microscope (JEOL 6360A)
4 Powder X-Ray Diffractometer (Philips PW 3710)
5 Differential Scanning Calorimeter (SDT 2960)
6 Karl-Fischer Titrimeter (Aqua Cal)
7 Stereozoom Microscope (Leica S8APO)

Selection of Solvent:The solubility of meloxicam was evaluated in various polar and non-polar solvents such as ethanol, methanol, acetone, diethyl ether, and THF. Solvents were selected based on:
Moderate solubility at room temperature
High solubility at boiling point
Polarity, boiling point, volatility, and compatibility
Solvent Selection Process

Start
↓
Assess solubility in solvents
↓
Select solvents with suitable profile
↓
Confirm crystal yield
↓
Final solvents:
ethanol, methanol, THF, etc.
↓
End

Crystallization Techniques
Method I: Rapid Cooling
Hot saturated solutions were rapidly cooled using an ice bath.
Method II: Cooling to Room Temperature → Fridge
Solution was cooled at room temperature (\~25°C), then stored in a refrigerator at 6–8°C for 48 hours
Method III: Slow Evaporation at Room Temperature
Crystals were obtained by allowing solvent to evaporate slowly at ambient temperature.
Method IV: Watering-Out Technique
Hot organic solution (\~55–60°C) was added to cold water (10°C) with stirring. This induced crystallization by reducing solvent power.

Crystal Preparation Workflow

Prepare Saturated Solution
↓
Choose Crystallization Method
↓ ↓ ↓ ↓
Rapid Slow Cooling Watering
Cooling Evaporation + Fridge Out
↓ ↓ ↓ ↓
Collect Crystals via Filtration
↓
Dry, Store in Desiccator

Crystal Preparation with Additives

To study habit-modification, "Method IV" was modified using 0.25% w/v aqueous solutions of:

HPMC
PEG 4000
Chitosan
Sodium alginate
Gelatin
PVP
These additives acted as crystal growth inhibitors and altered morphology significantly.
Storage of Samples :All prepared crystals were stored in desiccators containing calcium chloride to prevent atmospheric moisture absorption and degradation.

Characterization Techniques

A. Photomicrography
Crystals were viewed under a stereozoom microscope using polarized light to determine shape and surface morphology.
B. Scanning Electron Microscopy (SEM)
Provided high-resolution images to assess surface texture and shape. Crystals were mounted on stubs with conductive adhesive.
C. Powder X-Ray Diffractometry (PXRD)
Used for determining crystalline form and polymorphic structure. Crystals were packed in an aluminum holder and analyzed at room temperature.
D. Differential Scanning Calorimetry (DSC)
DSC was used to evaluate thermal behavior such as melting points and transitions. The heating rate was 5°C/min under nitrogen.
E. Karl-Fischer Titration
Assessed moisture content in crystals to detect hydrates or solvates.
F. FT-IR Spectroscopy
Confirmed chemical identity and helped distinguish polymorphic forms through vibrational fingerprinting.

Data Collection and Evaluation

Melting Point: Using standard capillary method.
Solubility Tests: Conducted in distilled water and organic solvents.
Dissolution Studies: Carried out in pH 7.4 phosphate buffer using UV-spectroscopy.
Statistical Analysis: Mean, standard deviation, and regression (for calibration curves) were calculated for reproducibility assessment.

Full Experimental Workflow

MATERIAL SELECTION
↓
Solubility Screening
↓
Solvent and Additive Selection
↓
→ Crystal Preparation Methods ←
↓
Crystal Collection & Drying
↓
Characterization (PXRD, SEM,

DSC, KF, IR, Photomicrography)
↓
Data Analysis and Comparison

V .RESULTS-

Meloxicam crystals were successfully recrystallized using various solvents (ethanol, methanol, THF, acetone, diethyl ether) and with different additives (HPMC, PEG 4000, gelatin, SCMC, chitosan, sodium alginate), leading to formation of distinct crystal forms.
Photomicrography and SEM analysis :revealed noticeable differences in crystal habits. Pure meloxicam appeared as irregular particles, whereas modified forms exhibited cuboidal, thin plate, or prismatic shapes depending on crystallization method and excipient used.

X-ray powder diffraction (XRPD): confirmed the existence of multiple polymorphic forms: orthorhombic (pure drug), tetragonal (ME1, ME3, MT), triclinic (ME2, ME5, MM), and cubic (ME6, ME7, MA). This was further supported by DSC thermograms, which showed variations in melting points and thermal behavior among forms.

Solubility studies: indicated a 1.28–1.62-fold increase in water solubility for recrystallized forms compared to pure drug. Dissolution studies showed significantly enhanced drug release, with prepared crystals displaying faster dissolution profiles than the untreated meloxicam. Formulations with excipients (e.g., ME1–ME6) exhibited the most notable improvements.

Thus, crystal engineering effectively modified meloxicam's physical characteristics, resulting in improved solubility and dissolution rate, crucial for enhancing bioavailability.

VI.DISCUSSION:

The present study focused on altering the crystal forms of Meloxicam to enhance its solubility and dissolution behavior. Recrystallization using various solvents (ethanol, methanol, THF, acetone, and diethyl ether) and additives (HPMC, PEG 4000, gelatin, SCMC, chitosan, sodium alginate) resulted in crystals with diverse morphological and physicochemical properties.
Photomicrography and SEM analysis revealed significant changes in crystal habit—ranging from cuboidal to plate-like and prismatic structures—indicating the influence of crystallization conditions. XRD data confirmed the presence of multiple polymorphic forms, with orthorhombic structure for the pure drug and tetragonal, triclinic, and cubic systems for modified forms. This polymorphism was further supported by DSC thermograms showing variations in melting behavior.
Solubility studies demonstrated that all recrystallized forms exhibited improved aqueous solubility (1.28 to 1.62 times) over the untreated Meloxicam. Dissolution profiling showed a clear enhancement in release rates, especially for crystals formed in the presence of hydrophilic additives like HPMC and PEG 4000. This enhancement is attributed to modified surface characteristics and reduced particle size, increasing wettability and surface area.
The study reinforces that crystal habit and polymorphism significantly impact the dissolution and bioavailability of poorly water-soluble drugs. The use of crystal engineering and habit-modifying agents is a promising approach for improving the pharmaceutical performance of APIs like Meloxicam.

VII.CONCLUSION:

The study successfully demonstrated that crystal modification of Meloxicam through recrystallization using various solvents and additives significantly influences its physicochemical properties. The modified crystals exhibited distinct morphological changes, confirmed polymorphic variations, and enhanced solubility and dissolution rates compared to the pure drug. This indicates that crystal engineering is an effective strategy to improve the biopharmaceutical performance of poorly soluble drugs like Meloxicam.

VIII: SUMMARY:

This study aimed to improve the solubility and dissolution profile of Meloxicam by altering its crystal forms through recrystallization using various solvents and additives. Crystals were prepared using solvents such as ethanol, methanol, acetone, THF, and diethyl ether, as well as additives like HPMC, PEG 4000, gelatin, SCMC, sodium alginate, and chitosan. The resulting crystals were characterized using techniques including PXRD, FT-IR, DSC, SEM, and Karl Fischer titration. Significant variations in crystal habit and structure were observed, including orthorhombic, tetragonal, triclinic, and cubic forms. These changes led to enhanced solubility (1.28–1.62 times) and improved dissolution rates compared to the pure drug. The study concludes that crystal engineering is an effective strategy for enhancing the biopharmaceutical properties of poorly water-soluble drugs like Meloxicam

IX.REFERENCES:

Huang LF, Tong WQ. Impact of solid-state properties on developability assessment of drug candidates. Advanced Drug Delivery Reviews 2004; 56: 321-324.
Stephen PF, Miller, Andre SR and Lawrence XY. Scientific Considerations of Pharmaceutical Solid Polymorphism in Regulatory Application Polymorphism: in the Pharmaceutical Industry. Edited by Rolf Hilfiker WILEY- VCH Verlag GmbH & Co. KGaA, Weinheim pg.no. 385-389.

S. Subramanian, M.J. Zaworotko, Manifestations of noncovalent bonding in the solid-state. 6. H-4(cyclam) (4+) (cyclam=1,4,8,11-tetraazacyclotetra-decane) as a template for crystal engineering of network hydrogenbonded solids, Can. J. Chem. 73 (1995) 414–424.

J.M. Lehn, Supramolecular chemistry — scope and perspectives molecules, supermolecules, and molecular devices, Angew. Chem., Int. Ed. Engl. 27 (1988) 89–112.

A.R. von Hippel,Molecular designing of materials, Science 138 (1962) 91.

G.M.J. Schmidt, Topochemistry. Part III. The crystal chemistry of some trans-cinnamic acids, J. Chem. Soc. (1964) 2014.

J.W. Steed, J.L. Atwood, Supramolecular Chemistry, JohnWiley & Sons, Ltd., 2000.

Paradkar AR. Crystallization is a complex unit operation. Introduction to Pharmaceutical Engineering. 3rd Edn., Nirali Prakashan.2001; pp 199-222.

Sudha R.Vippagunta, Harry G.Britain, David J.W. Grant. Crystalline solids

Advanced Drug Delivery Reviews.2001; 48:3-26 Matthew L, Peterson, Magali B, Hickey, Michael J. Zaworotko, Orn Almarsson Expanding the Scope of Crystal Form Evaluation in Pharmaceutical Science J Pharm Pharmaceut Sci 2006; 9(3): 317-326.

11.Subranmanyam CVS, Setty J Thimma, Suresh Sarasija, Kusum Devi V, Introduction of Crystallization. Principles and Practices of Pharmaceutical Engineering, 1st Edn., Vallabh Prakashan, 2001; 361- 381.

12.Lachman L, Lieberman HA, Kanig JL. Preformulation. The Theory and Practice of Industrial Pharmacy, 3rd Edn,Varghese Publishing House, Bombay,1987; 176- 177.

13.S.R. Byrn Jr., R.R. Pfeiffer, J.G. Stowell, Solid-State Chemistry of Drugs, 2nd ed., SSCI, West Lafayette, IN, 1999.

14.J.K. Haleblian, Characterization of habits and crystalline modification of solids and their pharmaceutical applications, J. Pharm. Sci. 64 (1975) 1269–1288.

15.Andre S. Raw,1, M. Scott Furness1, Devinder S. Gill1, Richard C. Adams1, Frank O. Holcombe Jr.1, Lawrence X. Yu1 Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAs) Advanced Drug Delivery Reviews 56 (2004) 397– 414

16.Dr. Jasmina Khanam editor, Pharmaceutical Engineering. 2007; 3-8

17. Alleso M et al. Solvent Diversity in Polymorph Screening. Journal of Pharmaceutical Sciences 2008; 97(6): 2145-2159.

18.www.google.com/solvents.htm.

19.Rolf Hilfiker, Susan M. De Paul, and Martin Szelagiewicz Polymorphism: in the Pharmaceutical Industry. Edited by Rolf Hilfiker WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim pg no 289-290.

20.N. Blagden, M. de Matas, P.T. Gavan, P. York Crystal engineering of active pharmaceutical i n g r e d i e n t s t o i m p r o v e s o l u b i l i t y a n d d i s s o l u t i o n rates< Advanced Drug Delivery Reviews 59 (2007) 617–630

21.D. Hörter, J.B. Dressman, Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract, Adv. Drug Deliv. Rev. 46 (2001) 75–87.

22.G. Buckton, A. Choularton, A.E. Beezer, S.M. Chatham, The effect of comminution technique on the surface energy of a powder, Int. J. Pharm. 47 (1– 3) (1988) 121–128.

23.G.H. Ward, R.K. Schultz, Process induced crystallinity changes in albuterol sulfate and its effect on powder physical stability, Pharm. Res. 12 (5) (1995) 773– 779.

24.J.Y.Y. Heng, F. Thielmann, D.R. Williams, The effects of milling on the surface properties of form I paracetamol crystals, Pharm. Res. 23 (8) (2006) 1918–1927

25.A.H.L. Chow, C.K. Hsia, J.D. Gordon, J.W.M. Young, E.I. Vargha- Butler, Assessment of wettability and its relationship to the intrinsic dissolution rate of doped phenytoin crystals, Int. J. Pharm. 126 (1,2) (1995) 21–28.

26.Y. Kato, Y. Okamoto, S. Nagasawa, I. Ishihara, Relationship between polymorphism and bioavailability of drug. IV. New polymorphic forms of phenobarbital, Chem. Pharm. Bull. 32 (10) (1984) 4170–4174.

27.www.google.com/ethanol,methanol,acetone,THF,diethylether- Wilkepedia, the free encyclopedia.htm

28.Yi Lu a, Xingwang Zhang a, Jie Lai b, Zongning Yin b,, WeiWua, Physical characterization of meloxicam-β-cyclodextrin inclusion complex pellets prepared by a fluid-bed coating method. Particuology 2009; 7: 1–8.

29.Mutalik S, Anju P, Manoj K, Usha AN. Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan-based solvent change approach. International Journal of Pharmaceutics 2008; 350: 279-290.

30.Operating instructions for Automatic Karl Fischer titrator. Model: V e n g o / Matic I, Veego instruments corporation, Mumbai: 1-7.

31.British Pharmacopoeia. The Department of Health, Social Services & Public Safety, London, 2001:12-14.

32.Kulkarni PK, Bose SC. Spherical Agglomeration of Nabumetone. Indian Journal of Pharmaceutical Education & Research.2007; 41 (1) : 18-23.

33.Bhaskaran S. Preparation and evaluation of alginate-chitosan beads. Indian J Pharm Sci. 2002; 389-391.

34.Wittaya-areekul S, Kruenate J, Prahsarn C. Preparation and *in vitro* evaluation of mucoadhesive properties of alginate/ chitosan microparticles containing prednisolone. Int J Pharm. 2006; 312: 113-118.