Original Article

Solubility Enhancement of Meloxicam by Binary and Ternary Solid Dispersion

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Abstract

The purpose of this study was to improve the solubility and dissolution rate of meloxicam (ME), a water-low soluble analgesic., using binary and ternary solid dispersion by solvent evaporation and kneading methods. Two hydrophilic polymers, polyethylene glycol 4000 (PEG 4000) and polyvinyl pyrrolidine K30(PVPK30), were used in the solid dispersion of (ME), in different drug to polymer ratio. The drug content, percentage yield, and X-ray Diffraction (XRD) and FTIR spectroscopy analyses were used to analyze the pure drug (ME) and its solid dispersion with and without various polymers. The findings of this research revealed a decrease in crystallinity and a change in the drug's crystal habit. The prepared solid dispersions' solubility and dissolution rate were compared to those of the untreated medication. The solubility and dissolution profiles of all prepared formulae improved significantly (p0.05). The best results were obtained using a formula made up of PVP K30 and cross carmelose (CC) in a 1:3 drug-to-polymer ratio with a 5% W/W CC content.

Keywords: Meloxicam, solid dispersion, kneading method solvent evaporation method

INTRODUCTION

Amongst the route of drug administration one can take into consideration the oral route as a broadly wide impressive route because patients can consume medication by themselves, easily production, administration with an easy, correct dose, safely and economical route. Despite the fact that the oral route of drug administration is preferred, it can be a difficult and wasteful means of delivery for many pharmaceuticals for a variety of reasons. Restricted medication absorption, resulting in low bioavailability, is one of the most common issues that might arise when administering an active agent orally. A range of variables can limit drug absorption from the gastrointestinal (GI) tract, with low drug solubility and/or permeability across biological membranes being the most major culprits (1).

A solid dispersion is a type of solid compound that consists of at least two elements, usually a hydrophilic matrix and a hydrophobic medication. A crystal or amorphous matrix can be used. The medications might be disseminated molecularly in amorphous (clusters) or crystalline (particles) form. Solid dispersions are one of the most successful grand designs to enhance the dissolution of drugs with low solubility. According to the physical state of the solid dispersion, formulation of poorly soluble compounds as solid dispersions may result in particle size reduction, enhanced wettability, reduced agglomeration, changes in the physical properties of the drug molecules, and may be a molecular dispersion (2).

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Meloxicam is an enolic acid oxicam derivative and a nonsteroidal anti-inflammatory (NSAID) and analgesic medication. Rheumatoid arthritis, osteoarthritis, and other joint ailments are commonly treated with it (3). Chemically ME (C14H13N3O4S2) is 4-Hydroxy–2–methyl-N-(5–methyl–2–thiazolyl)-2H-1,2–benzothiazine–3–carboxamide–1,1–dioxide). It possesses a pKa (1.1, 4.2) dissociation constant and partition coefficient Log P (octanol/water), 3.43 (4). ME is a relatively permeable drug with low solubility and dissolution rate, both of which are absorption rate limiting factors (5) . The objective of this study is to use solid dispersion to improve ME's solubility and dissolving rate technique.

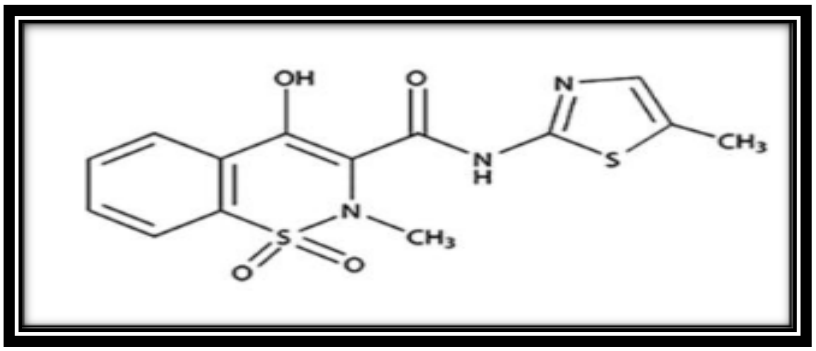

Fig.1: Structural formula of ME

Materials And Method

Materials

Meloxicam (ME), PVPK30 (HA), cross carmelose (cc), were purchased from, Hyperchem / China. All of the other chemicals and reagents utilized were of analytical grade.

Method

Meloxicam solid dispersion preparation:

Solvent evaporation and kneaded mixtures of ME with carriers were made in varied ratios to optimize drug to carrier ratio.

Solvent Evaporation Method

This process entails combining ME and a polymer in a binary system or two polymers in a ternary system in ethanol, then evaporating the entire solvent. The combination is then made in various ratios as illustrated in the diagram (table 1). In a beaker, polymer and drug were added to ethanol, and the solution was vigorously swirled on the magnetic stirrer until the ethanol was completely evaporated then dried overnight and stored in dissector (6).

Kneading method

The carrier is penetrated with water and turned into a paste in this manner. The drug is subsequently added and kneaded for a specific amount of time. After that, the kneaded mixture is dried and, if necessary, sieved (7) .

Table 1: Composition of Solid Dispersion by Solvent Evaporation and Kneading Methods.

Formula Number	*ME Weight ratio*	*PEG4000 Weight ratio*	*PVPK30 Weight ratio*	*CC % w/w*
SD-1	1	1		
SD-2	1	-	1	-
SD-3	1	3	-	-
SD-4	1	-	3	-
SD-5	1	1.5	1.5	-
SD-6	1	3	3	-
SD-7	1	-	3	5

Evaluation of MEL solid dispersion powder

Drug Content

The percentage of drug content of the solid dispersion formed can be determined by crushing and dissolving fixed amount of the powder in sufficient volume of methanol in 100ml volumetric flask and sonicate for 30 minute the solution diluted to the desired level with methanol. The solution was then filter through 0.45Mm Whatman filter paper. and then analyzing by UV spectrophotometer at 362nm (8).

Percentage yield

The product yield of formula of solid dispersion was measured by determining the weight of resulted powder after drying with respect to initial weight of drugs and polymers used in formulation of solid dispersion as in equation (9)

Yeild% = (WSD/Wdp) x 100

WSD practical weight of solid dispersion

Wdp theoretical weight of drug and polymer

solubility study of Meloxicam and solid dispersion

In a closed glass tube, an excess of MEL and prepared formulae were added to 10ml of distilled water. The tubes were submerged in a shaker water bath at 37°C for 72 hours. The tubes were then taken out of the shaker water bath. The concentration of MEL solubilized was evaluated using a UV-spectrophotometer at their 362nm wavelength after samples were filtered using a 0.45 m filter membrane (10).

Dissolution study of solid dispersion

The release profile of ME from formulated solid dispersion was determined by using (paddle) type II USP dissolution test apparatus. A weighed amount of solid dispersion equivalent to 7.5 mg drug was add to (900) ml of phosphate buffer (pH 7.5) media kept at 37± 0.5 ◦C at rotation speed of 75 rpm. sink condition was maintained throughout the study. 5 mL of material was removed at specified intervals and replaced with an equivalent volume of fresh sample kept at the same temperature. The samples were then filtered through 0.45 Mm filter membrane and analyzed spectrophotometrically at 362nm (11)(12)

Fourier Transform Infrared Spectroscopy (FTIR)

Interactions between drugs and polymers were investigated by Fourier Transform infrared spectroscopy (19) (20). The FT-IR spectra of pure ME, PVPK30, CC, solid dispersion of ME (SD7k)and physical mixtures for the selected formula were obtained scanning by preparing the above samples in potassium bromide discs and scanned within scanning range of 4000 cm -1 to 400 cm -1(13).

Powder X-ray Diffraction (PXRD)

A powder X-ray diffraction (PXRD) investigation was carried out to assess changes in the drug's crystalline composition. Using an X-ray diffractometer, PXRD analysis was done on pure drug, solid dispersion of ME(SD7k), and physical mixture of a specified formula. The samples were irradiated with monochromatized CuK α radiation and evaluated between 2° and 50° thetas (14).

Result And Discussion

Drug content

Percent drug content was found to be in the range of 95.44 to 99.8 % that indicated there were negligible loss of drug during process of formulation table (2 and3).

Percentage yield

The % yield for various drug and polymer ratios was computed and displayed in tables (2 and3). When comparing the percentage yield of solid dispersion prepared by kneading to that of solvent evaporation, the results showed that the percentage yield of solid dispersion prepared by kneading was higher.

Solubility study of ML and solid dispersion

All solid dispersions of ME prepared by using PEG 4000 with or without PVP k30 by solvent evaporation and kneading methods showed enhanced drug solubility over the pure meloxicam tables (2 and 3) resulting from wetting effect of hydrophilic polymers. The highest increase in solubility attained by utilizing PVP k30 in the presence of 5% CC, notably at a 1:3 drug-to-polymer weight ratio (SD7k).

Table 2: Drug Content, %Yield and solubility of Pure and Solid Dispersion of Meloxicam by Solvent Evaporation Method (SDs)

Formula Number	*MEL Weight ratio*	*PEG4000 Weight ratio*	*PVPK30 Weight ratio*	*CC % w/w*	*Drug content %*	*Yield %*	*Aqeous solubility mg/ml*
ME	1	-	-	-	100	-	0.007
SD1s	1	1	-	-	95.7	86.7	0.0091
SD2s	1	-	1	-	96.5	90.5	0.012
SD3s	1	3	-	-	95.45	89.8	0.0098
SD4s	1	-	3	-	97.89	85.99	0.0185
SD5s	1	1.5	1.5	-	98.23	96	0.014
SD6s	1	3	3	-	98.33	97	0.0095
SD7s	1	-	3	5	95.9	94	0.0221

Table 3: Drug Content, %Yield and solubility of Pure and Solid Dispersion of Meloxicam by kneading Method (SDk)

Formula Number	*MEL Weight ratio*	*PEG4000 Weight ratio*	*PVPK30 Weight ratio*	*CC% w/w*	*Drug content %*	*Yield %*	*Aqeo. *.,lus solubility mg/ml*
MEL	1	-	-	-	100	-	0.007
SD1k	1	1	-	-	98.9	95.5	0.0129
SD2k	1	-	1	-	99.6	98.5	0.022
SD3k	1	3	-	-	96.15	96.2	0.0189
SD4k	1	-	3	-	95.35	99.4	0.0547
SD5k	1	1.5	1.5	-	96.49	98	0.0205
SD6k	1	3	3	-	100.1	96	0.019
SD7k	1	-	3	5	98.7	98.8	0.205

In-vitro Dissolution study

The results of solubility study show that the kneading method show higher solubility than those prepared by solvent evaporation method so the formulas (SDk 3,4,6,7) select to investigate the influence of polymer type and ratio on medication dissolving rate.

all these four formulas show increase in dissolution rate in comparison of pure drug may be due to the wettability effect of hydrophilic polymer and conversion of crystal form of drug to amorphous form(15).

incorporation of CC 5% in SDk7 show further improvement in rate of drug release in comparison with other formulas due to availability of rich hydrophilic environment in its vicinity because of morphology and high water uptake capability of superdisintegrant (CC)(16) .

SDk6 show increase in time of solubility in comparison with other prepared formulas by kneading method due to increase in thickness of diffusion layer in viscous solution result from higher concentration of polymers. This outcome is consistent with the Noyes–Whitney equation, which describes the dissolution process (17).

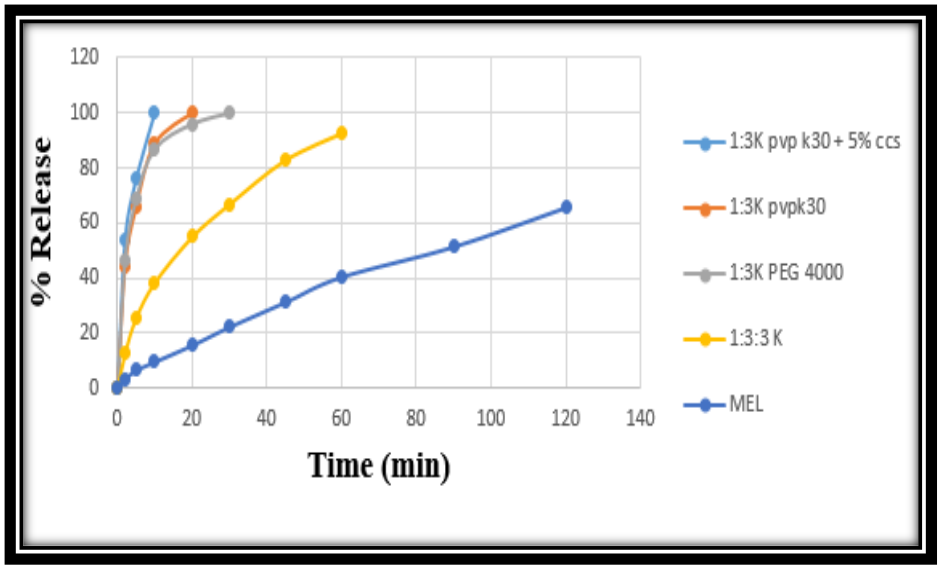

Fig.2: In vitro release study of MEL and prepared formula by kneading method in phosphate buffer pH= 7.5

Ftir Study

Figures (5-8) show the FTIR spectrum of pure ME, PVP K30,CC,PM, and SD7k, respectively.

Pure ME's spectra included three distinct peaks: 3292 cm-1 (N-H stretching vibrations), 1620 cm-1 (C=N stretching vibrations), and 1162 cm-1 (S=O stretching vibrations). The reported results were consistent with earlier research (18) (19).

The stretching vibration of the carbonyl group was the most noticeable peak in the IR spectra of PVP K30, which appeared around 1689.53 cm-1. The FTIR spectrum of PVPK30 revealed a large peak around 3000-3700 cm1 due to O-H stretching vibrations of absorbed water (20)

FTIR spectrum of, SD7K, the physical mixture of drug and polymers for SDK7 show no significant shift reduction in intensity of peaks of ME, and of PVPK30, which indicates there was no interaction between drug and polymer

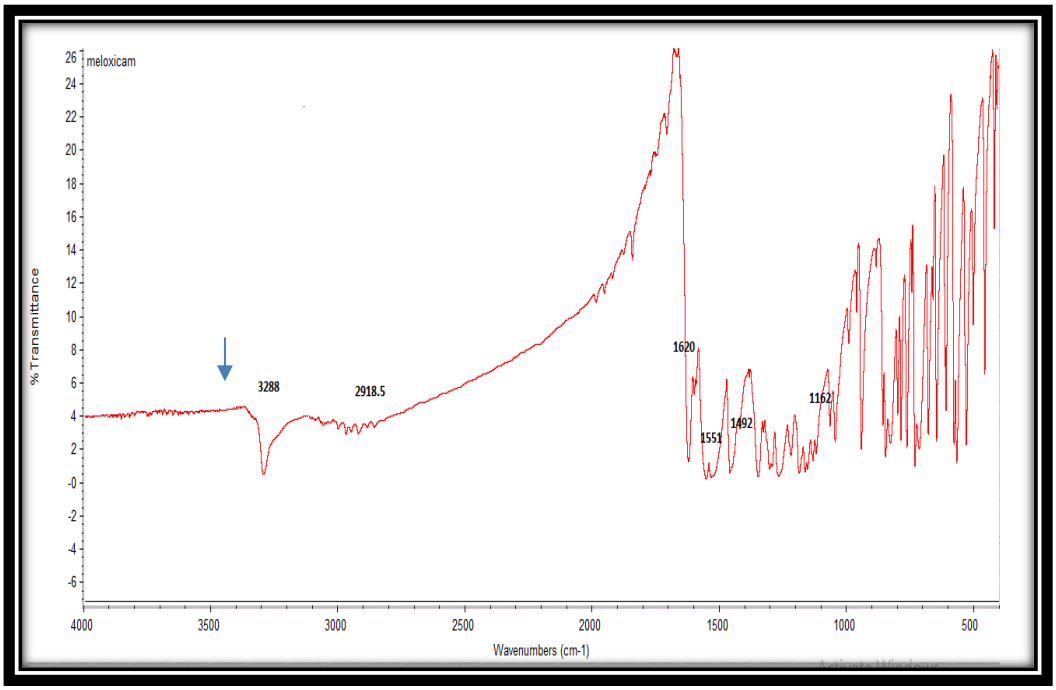

Fig.3: FTIR spectrum of ME

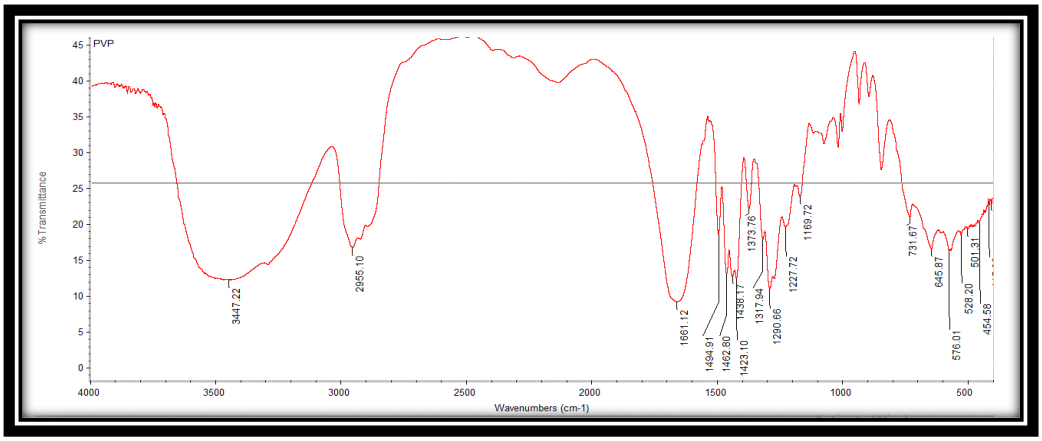

Fig.4: FTIR spectrum of PVP K30

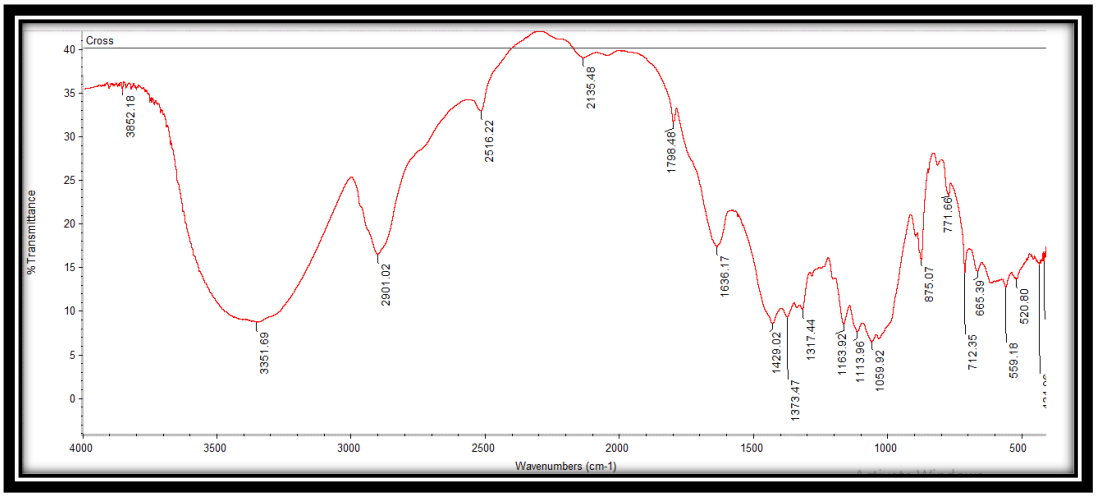

Fig.5: FTIR spectrum of CC

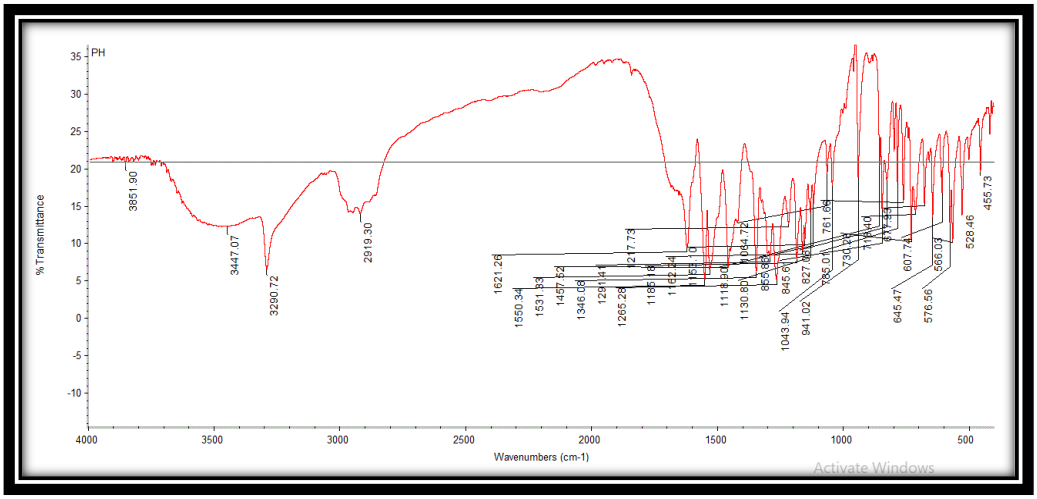

Fig.6: FTIR spectrum of Physical mixture

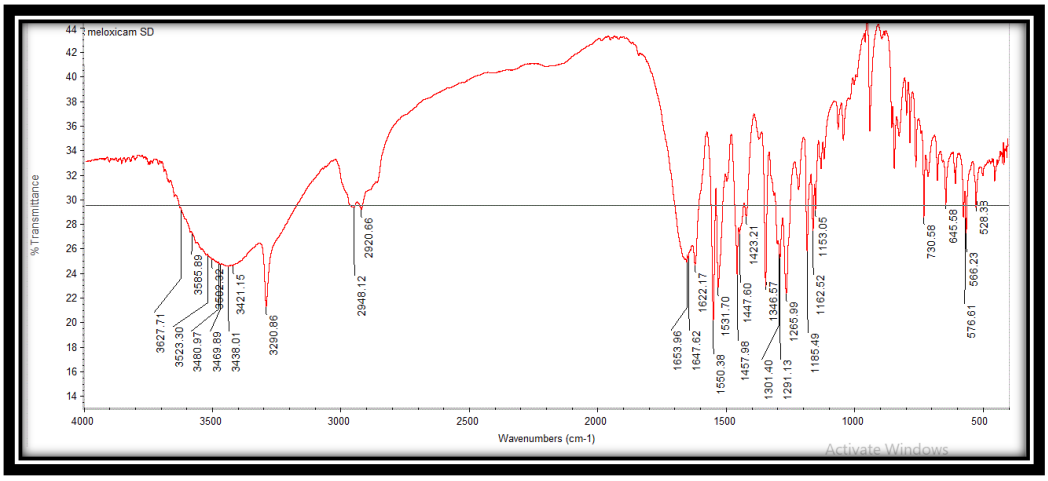

Fig.7: FTIR spectrum of SD7

X.ray diffraction (XRD)

The diffractogram for ME, physical mixture of ME and polymers that utilized in the formulation of the SDK7, and SDK7 are viewed in (figure 9 through 11). The diffractogram of pure drug exposed several diffraction peaks with high intensities at 13.08°, 14.8°, and 18.4° at 2-θ indicating the drug's crystal nature.

Figure 9 shows the XRD patterns of MEL, solid dispersion, and physical mixing. Sharp peaks at diffraction angles (2) of 24°, 8°, and 14° indicate the presence of crystalline drug in ME's x-ray diffractograms, while solid dispersion exhibits sharp peaks at 25.7°, 14.8°, and 13.1°. These findings show that the characteristic drug crystalline peaks were still detectable in the solid dispersion (although at a lower intensity and in fewer numbers). This finding confirms the presence of little amount of crystalline drug in the solid dispersion. The solid dispersion, on the other hand, lacks the distinct drug peaks that correlate to drug. The number of peaks in the XRD of solid dispersion is fewer than the total of the number of peaks in ME in their pure forms. This shows that the solid dispersion reduces the crystallinity of both the medication and the polymer. A decrease in the drug's crystallinity and the polymer's crystallinity may help to improve the drug's solubility (21)

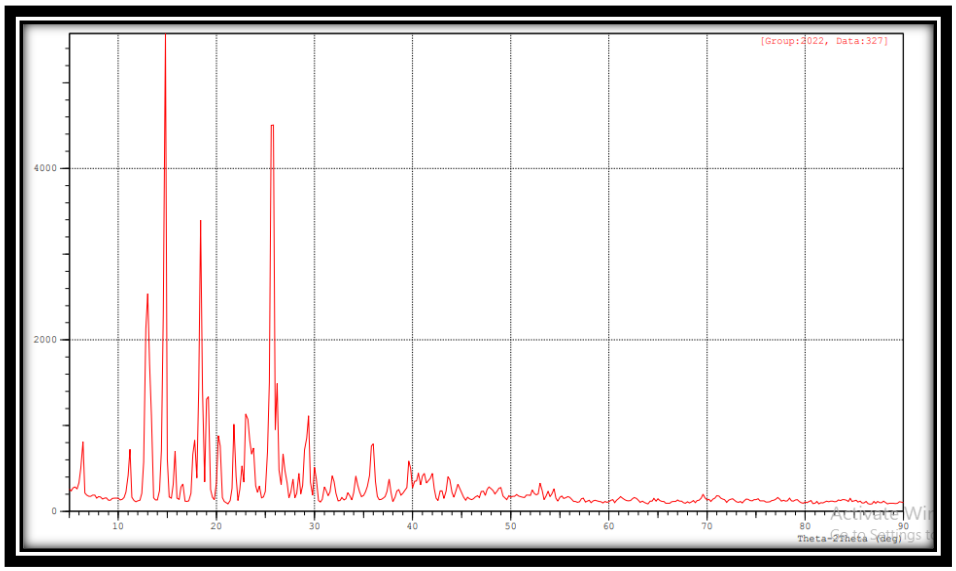

Fig.8: XRD diffractograms of ME

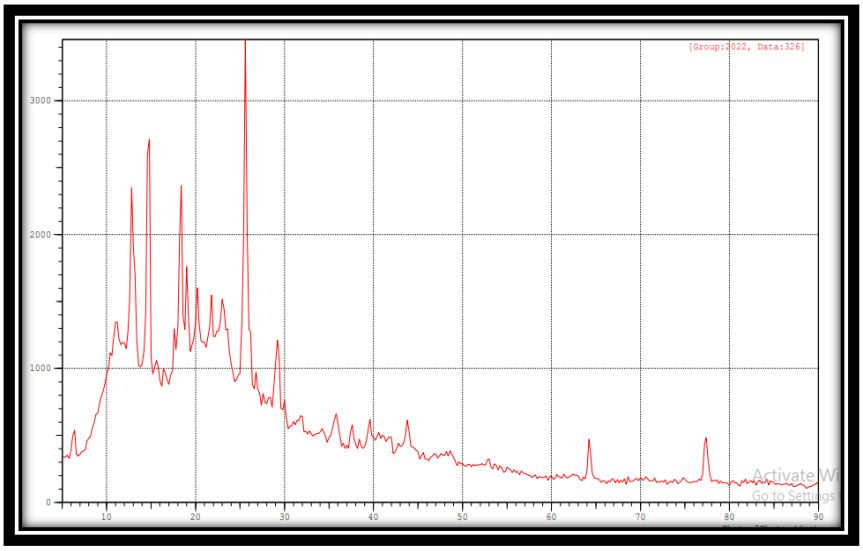

Fig.10: XRD diffractograms of Physical mixture

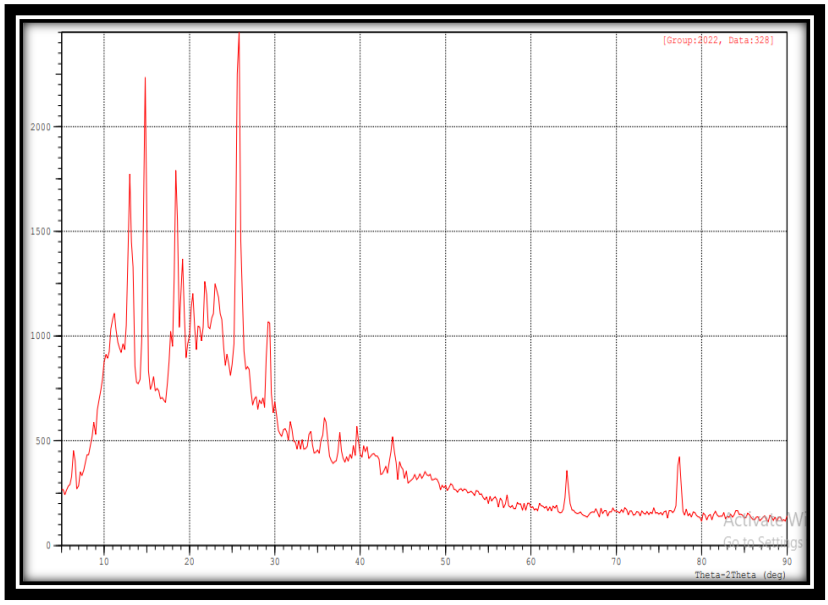

Fig.11: XRD diffractograms of SD7k

Conclusion

(MEL) solid dispersion were prepared successfully by kneading method. .In the present work the combination effect of PVP K30 and cross carmelose improved solubility and dissolution rate of meloxicam . However in vivo bioavailability studies are needed to ensure whether, the results of this work can be extrapolated to the in vivo conditions.

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