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Enhancement of solubility and dissolution rate of meloxicam by solid dispersions in superdisintegrants

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ABSTRACT

The aim of the present work was to improve the solubility and dissolution rate of meloxicam by preparing solid dispersion using different superdisintegrants. Physical mixture and solid dispersion were prepared by using microcrystalline cellulose, crospovidone, croscarmellose sodium at various proportions of (1:1, 1:2, 1:4) ratios by employing solvent evaporation method. The prepared solid dispersion was evaluated for SEM, X-RD, FTIR, DSC, Drug Content, Phase Solubility Study and *In-vitro* drug release. The drug release profile was studied according to USP XXI tyre II apparatus in 0.1N HCl containing 1% SLS and Phase solubility Study was performed in distilled water. The DSC and FTIR studies revealed that there was no interaction between drug and carriers. The absence of meloxicam peaks in the X-ray diffraction pattern of solid dispersion suggested conversion of crystalline meloxicam into amorphous form. All the Physical mixture and solid dispersion formulations showed increase in dissolution rate and solubility. Amongst all the formulations F5 formulation of crosspovidone gave highest release. The increase in dissolution rate may be due to increase in wettability, hydrophilic nature of carrier and the possibility of reduction in crystallinity. The optimized formulation (F5) of meloxicam solid dispersion showed no significant change in drug content, phase solubility study and *In-vitro* drug release after storage at 40°C/75% relative humidity for three months.

Keywords: Meloxicam, Solid dispersion, Solubility, dissolution.

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INTRODUCTION

The solubility behaviour of a drug is key determinant of its oral bioavailability Solubilization may be defined as the preparation of a thermodynamically stable solution of substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphophillic components. Number of poorly soluble drugs has risen sharply and the formulation of poorly soluble compounds for oral delivery presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. The dissolution rate is directly proportional to saturation solubility of drug. Therefore aqueous solubility of a drug can be used as first approximate of its dissolution rate. Drugs with low aqueous solubility have low dissolution rate and hence suffer from oral bioavailability problems, so if the solubility of the drug is less then desirable steps are to be taken to improve its solubility [1, 2].

Various techniques for the improvement of the dissolution rate of poorly water soluble drugs include micronization inclusion complexation, conversion in to amorphous state and solid dispersion. Chiou and Riegelman reported Solid dispersion method to enhance bioavailability of poorly water soluble drugs. Solid dispersion is defined as dispersion of one or more activate ingredients in an inert carrier or matrix at solid state prepared by melting method, solvent method, melting solvent method [3].

Meloxicam, is an oxicam derivative, is a member of the enolic acid group of Nonsteroidal anti-inflammatory drugs (NSAIDs). It is chemically designated as 4hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2*H*-1, 2-benzothiazine-3-carboxamide-1,1dioxide. It is pastel yellow solid, practically insoluble in water, with highest solubility observed in strong acids and bases. It is very slightly soluble in methanol [4].

Anti-inflammatory effects of meloxicam are believed to be due to inhibition of prostaglandin synthesis (cylooxygenase), leading to the inhibition of prostaglandin synthesis. As prostaglandins sensitize pain receptors, inhibition of their synthesis may be associated with the analgesic and antipyretic effects of meloxicam [4].

MATERIALS AND METHODS

Materials

Meloxicam was obtained from Ramdev chemical PVT. Ltd., (Thane, India). Microcrystalline cellulose, Crospovidone, Croscarmellose sodium, Sodium lauryl sulphate were purchased from Pfyzer PVT. Ltd. (Hyderabad, India).

Methods

Preparation of maloxicam solid dispersion

The Solid dispersion of Meloxicam was prepared in 1:1, 1:2, 1:4 ratios shown in table 1.

Physical mixture

Meloxicam and each of surface active carrier microcrystalline cellulose, crospovidone, croscarmellose sodium were weighed accurately and mixed thoroughly in mortar pestle with triturating for about 10 minutes. These mixtures were then passed through sieve number #60 and finally stored in air tight container till further use.

Solvent evaporation method

Meloxicam and each of surface active carriers, micro crystalline cellulose, crospovidone, croscarmellose sodium were weighed accurately in various ratio (1:1, 1:2, 1:4) and transferred to mortar and sufficient quantity of methonol was added to dissolve meloxicam and superdisintegrants at 60^0C. Resulting solid dispersion were stored for 24 hours in desicator to conzeal. The mass obtained was crushed pulverized finally, dispersions were passed through sieve no #60 were stored in air tight container till further use [5-7].

Evaluation of meloxicam solid dispersion

Drug content estimation

10 mg of solid dispersions were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 362 nm by UV spectrophotometer. Each sample was analyzed six times [8, 9].

Phase solubility study

Solubility study was performed to all samples by taking excess quantity of solid dispersions and added to 25ml distilled water taken in a stoppered conical flasks and mixture were shaken for 24 hours in rotary flask shaker. After shaking to achieve equilibrium withdrawn at 1 hour intervals and filtered through whattman filter paper no.41. The filtrate so obtained was analyzed spectrophotometrically at 362 nm. Shaking was continued until three consecutive readings were same [10, 11].

***In-vitro* dissolution studies**

Solid dispersion equivalent to 10 mg of meloxicam and physical mixture equivalent to 10 mg of meloxicam were filled in empty hard gelatin capsules by hand filling method. Dissolution study was carried out by using USP eight stage dissolution test apparatus (veego) employing type II (paddle type) apparatus. Dissolution study was carried out in a 900ml of 0.1N HCl containing 1% w/v of SLS. Aliquates of 5ml sample was taken for 15, 30, 45, 60, 90 minutes and the sample was replaced with standard solution of 0.1N HCL containing 1% w/v of SLS. The sample were taken and analyzed at 343 nm [10, 11].

Scanning electron microscopy (sem)

The Scanning Electron Microscopy analysis was carried out using scanning electron microscope for optimised (F5) formulation using a scanning electron microscope (LEO, 435

VP, and UK). Prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 k [12, 13].

Powder x-ray diffraction analysis (xrd)

Powder X-ray diffraction analysis was performed using Powder X-ray diffractometer for optimised (F5) using a Powder X-ray Diffraction meter under the following conditions/; target Cu; filter Ni; voltage 35kV; current 20mA; receiving slit 0.2 inches. The data were collected in the continuous scan mode using a step size of 0.050º at 20/s. the scanned range was 5-50º [12, 13].

Fourier transform infra red spectra (FTIR)

FTIR spectra of pure drug and optimised (F5) formulation were obtained by a Perkia-Elmer Fourier transform infrared spectrophotometer using KBr pellets. KBr (1:100). The scanning range used was 4000 to 400cm^{-1} [8, 15].

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry was performed for pure drug, physical mixture and solid dispersion of F5 formulation by using Differential Scanning Calorimeter (DSC-60, Shimadzu, Japan). The powered sample (3-5mg) was hermetically sealed in aluminium pans and heated at a constant rate of 10ºC per minute over a temperature range of 25ºC to 300ºC under a stream of nitrogen as purging gas [14,15].

Stability studies

Accelerated stability studies of Meloxicam solid dispersions were carried out as per ICH guidelines. The prepared solid dispersions containing crospovidone (F5) formulation was selected for stability study on the basis of phase solubility study and *In-vitro* drug release. The floating tablets were stored at 40°C / 75% RH in closed high density polyethylene bottles for three months. The samples were withdrawn after period of 30, 60 and 90 days. The samples were analysed for drug content, phase solubility and *In-vitro* drug release [16, 17].

RESULTS AND DISCUSSION

Evaluation of meloxicam solid dispersion

The prepared solid dispersion was evaluated for Drug Content, Phase Salability Study, *In-itro* drug release, SEM, X-RD, FTIR, DSC and Stability Studies. All the studies were performed in replicate and results are expressed in mean ± SD.

Drug content

Drug content of all the formulations was performed. The results were shown in table 2. The drug content of the prepared solid dispersion was in the range of 99.0% to 100.5% indicating the application of present method for the preparation of solid dispersions with high content uniformity.

Phase solubility studies

The Phase solubility was performed for all the formulation. The results were shown in table 3. The solubility was increased in all solid dispersions and physical mixture than the pure drug. Solid dispersions showed more solubility increase than physical mixture. The F5 formulation with crospovidone having (1:2) ratio showed higher solubility. The higher solubility may be due to of hydrophilic carrier present in solid dispersion. As soluble carrier dissolves, the insoluble Drug gets exposed to aqueous environment as very fine particles and solubility got increased.

***In-vitro* dissolution study**

In-vitro dissolution studies of all formulations of solid dispersions were carried out in 0.1 N HCl. The study was performed for 90 min. the results of *In-vitro* dissolution studies of all formulations were shown in table 4 and figure 1. *In-vitro* release studies reveal that there was marked increase in the dissolution rate of pure drug from all the solid dispersions when compared to pure drug alone and physical mixture. The dissolution rate of pure drug in solid dispersion was strongly depended on the concentration of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate was also increased. This may be attributed to the increase in drug wettability, conversion to amorphous from and solubilization of the drug due to hydrophilic carrier. The release was more in formulation 5 with the ratio (1:2). With the increasing carrier in 1:4 ratios there was decrease in dissolution rate due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate.

Scanning electron microscopy analysis (SEM)

Scanning electron microscopy was performed for pure drug, crospovidone, F5 physical mixture and F5 solid dispersion SEM photographs were shown in figure 2. The pure drug crystals seemed to be irregular in shape smaller in size than carriers. The physical mixture of the drug carrier showed the presence of drug in crystalline form. It was easy to recognize the polymer particles from that of drug despite the reduction in size of particles of polymers during mixing and its presence in high amount. In case of solid dispersions, it was difficult to distinguish the presence of pure drug crystals. Pure drug crystals appeared to be incorporated in to the particles of the polymers. The solid dispersion looked like a matrix particles. The result could be attributed to dispersion of the drug in the molten mass of the polymer.

Powder x-ray diffraction analysis(X-RD)

Powder x-ray diffraction analysis was performed for pure drug, F5 physical mixture and F5 solid dispersion. The X-Ray diffraction patterns were shown in figure 3, 4, 5. X-Ray diffraction analysis of pure drug exhibited characteristic diffraction pattern indicating their crystalline nature. In the case of solid dispersions in superdisintegrats many of the sharp diffraction peaks disappeared and reduction in peaks intensity was observed indicated that the drug is partially converted into amorphous from and a reduction in crystallinity these changes in the solid dispersion might have also contributed to the enhanced dissolution rate of drugs from their solid dispersion. Since amorphous forms normally dissolve than the crystalline form. Physical mixture showed diffraction peaks which was observed in the pure drug.

FTIR spectra analysis

Fourier Transform Infra Red Spectra were obtained for pure drug, crospovidone, F5 physical mixture and F5 solid dispersion. The Fourier Transform Infra Red Spectra were shown in figures 6, 7, 8, 9. The major IR peaks observed in solid dispersions and physical mixture were at 3290.56(-N-H-stretching of drug), 1620(-C=O- stretching of drug), 1217.08-1301.95(-CN stretching of drug), 1346.31-1161.15(S=O stretching of drug), 844.82(-C-H-aromatic ring stretching).Thus indicating no evidence of chemical interactions between the drug and carrier.

Differential scanning calorimetry

Differential scanning calorimetry was performed for pure drug, crospovidone, F5 physical mixture and F5 solid dispersion. The thermograms were shown in figures 10, 11, 12, 13. And data 4. The pure drug showed sharp endothermic peaks at 263.17ºc near to its melting point. The peak of crospovidone also shown sharp peak at 63.60ºc indicating crystalline. The thermogram of physical mixture has shown endothermic peaks at 187.07ºc. The thermogram of solid dispersion has shown comparatively broadened peaks at 179.89ºc with less intense peaks of drug indicating decrease in crystallinity due to mixing. The peak due to drug disappeared almost completely due to suppression of melting point there by conforming the no interaction between Drug and carrier in solid dispersion.

Stability studies

Stability study results optioned were shown in table 5, 6, 7, 8, 9. The meloxicam solid dispersions did not show any significant changes in drug content phase solubility studies and *In vitro* drug release studies. Thus it was found that meloxicam solid dispersions were stable at 40ºC / 75% RH for at least three months.

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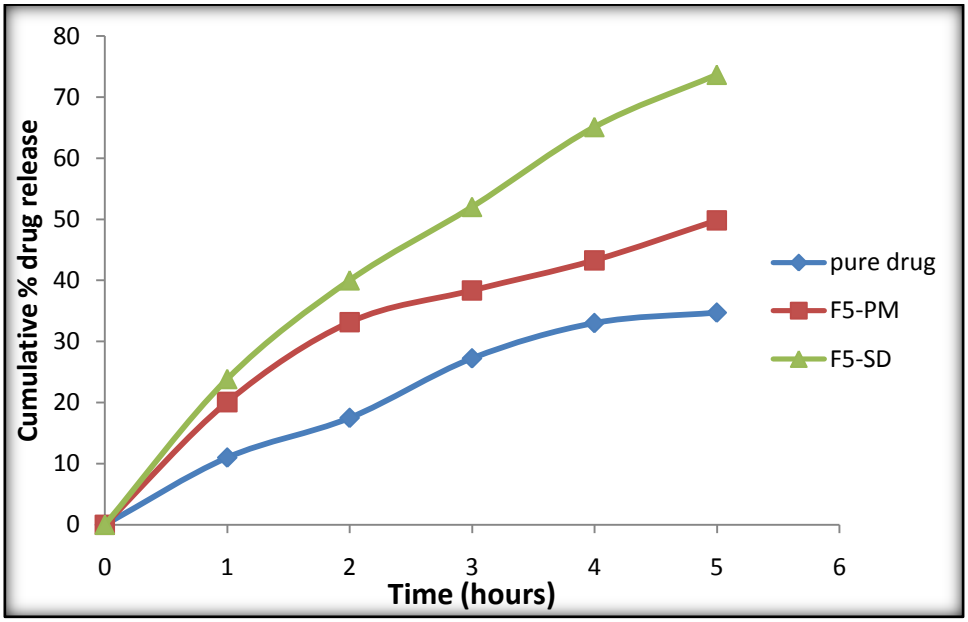
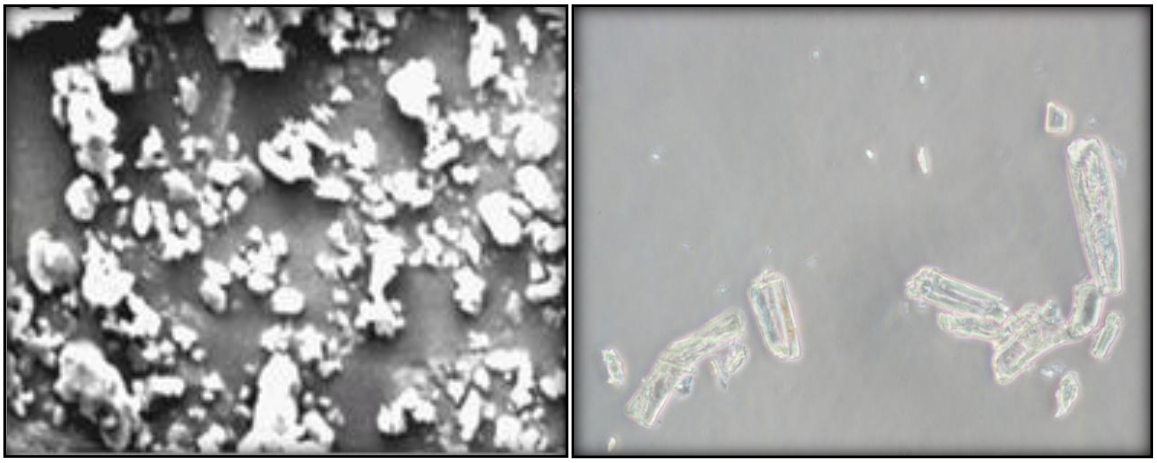
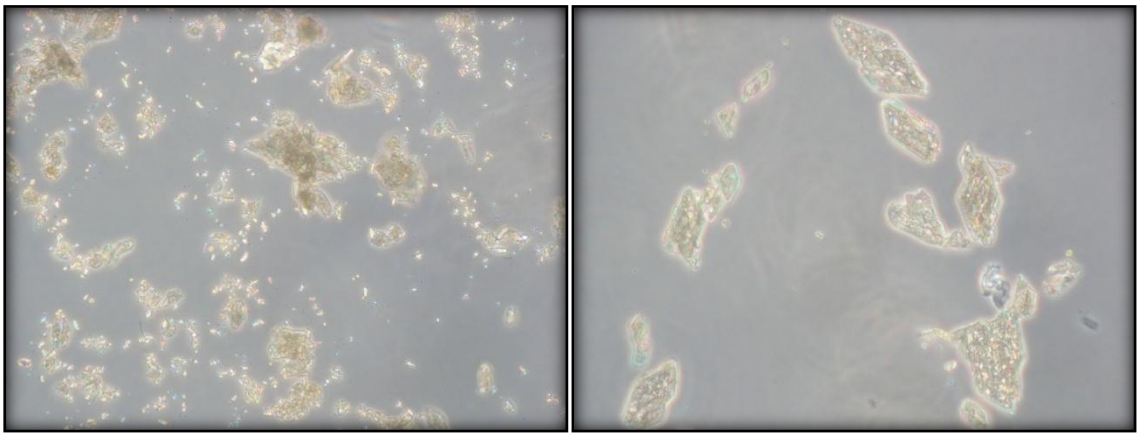


Figure 1 In vitro **Dissolution Profile of Pure drug Physical mixture and Solid Dispersion of F5 formulation.**



A.Pure Drug B. Corspovidone



C. F5 Physical mixture D.F5 Solid dispersion

Figure 2 SEM images of A) Figure 2 Meloxicam B) Corspovidone C) F5 Physical mixture D) F5 Solid dispersion

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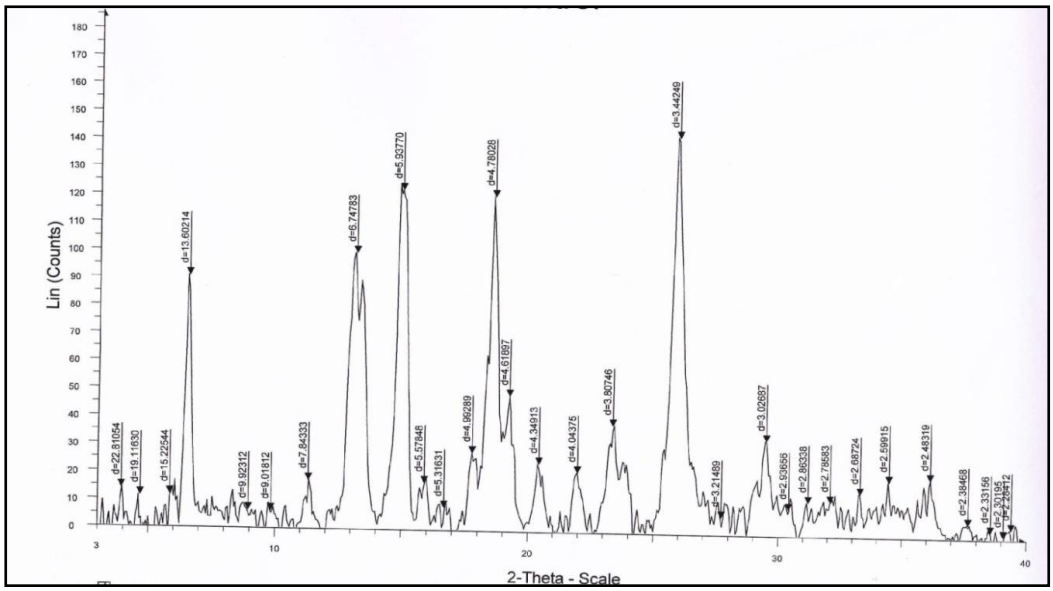

Figure 3:X-Ray diffraction analysis of pure drug

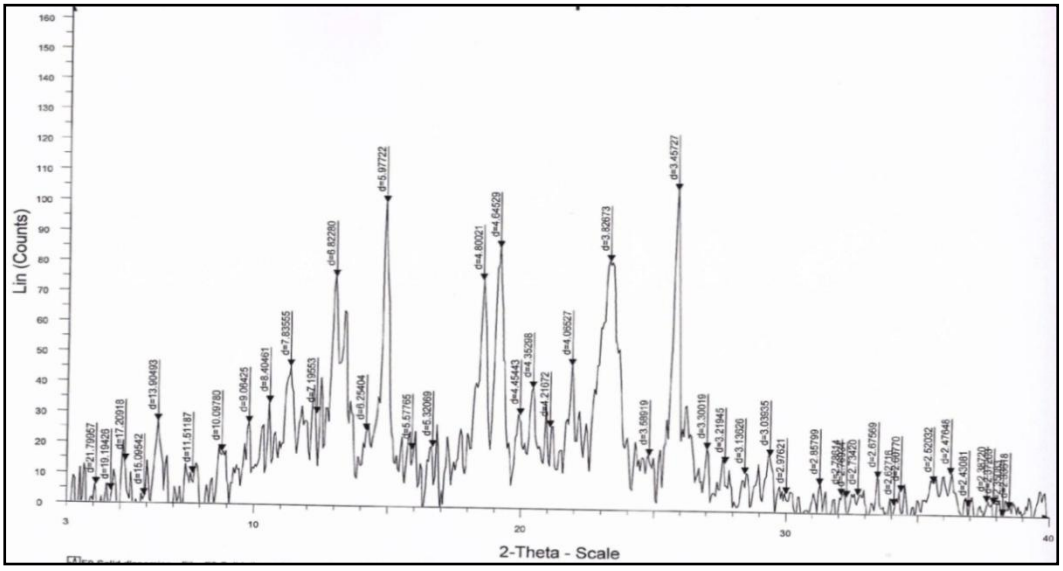

Figure 4: X-Ray diffraction analysis of F5 Physical Mixture

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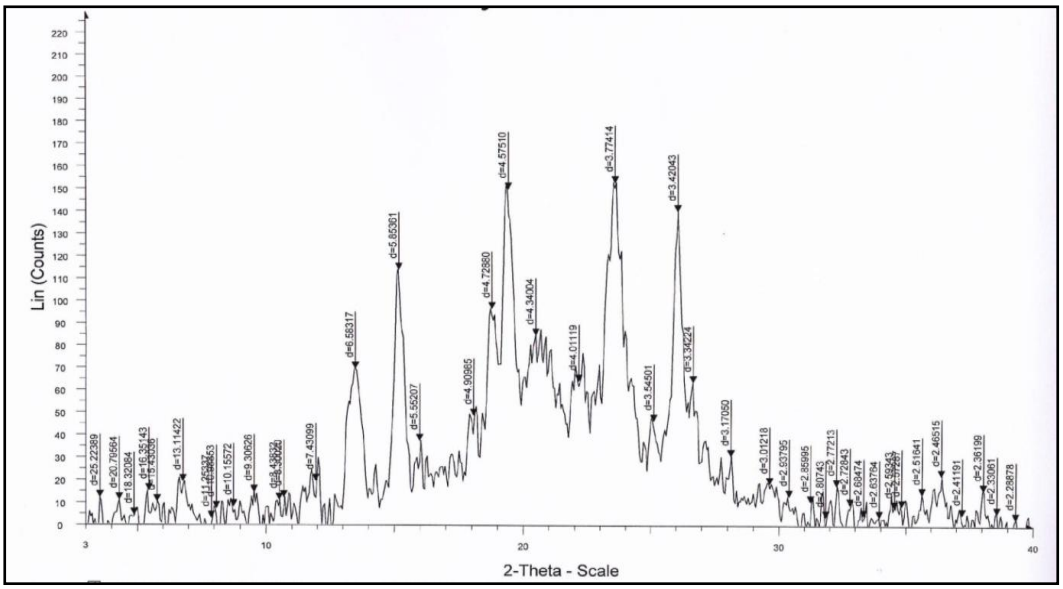
Figure 5: X-Ray diffraction analysis of F5 Solid Dispersion



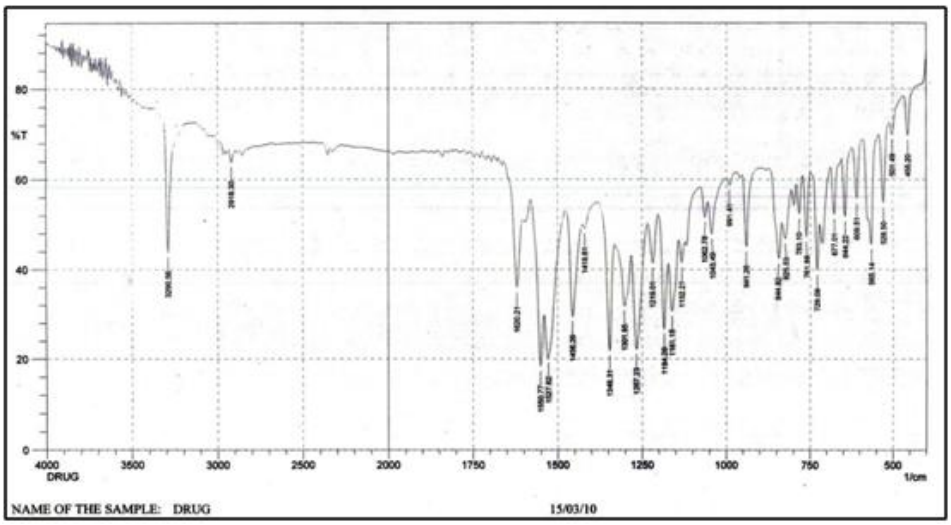


Figure 6: FTIR Spectra of pure drug

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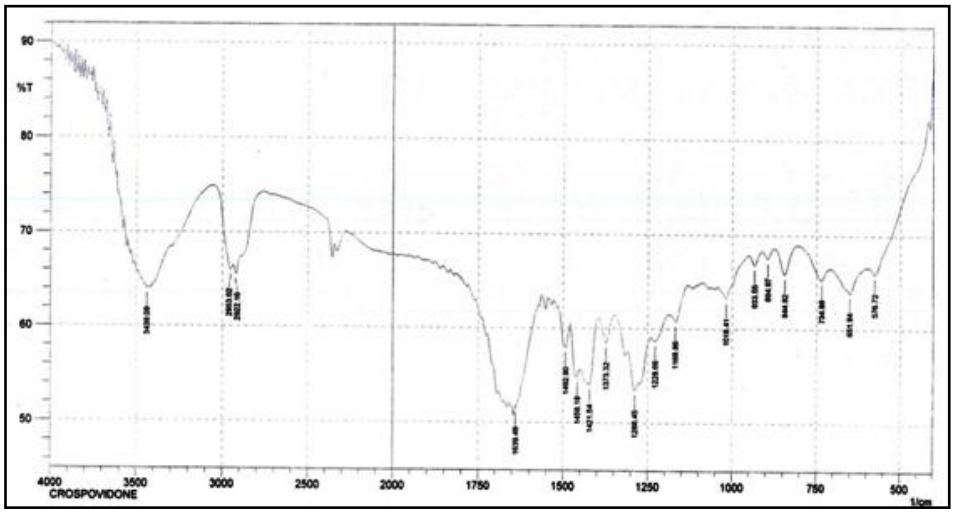

Figure 7: FTIR Spectra of Crospovidone

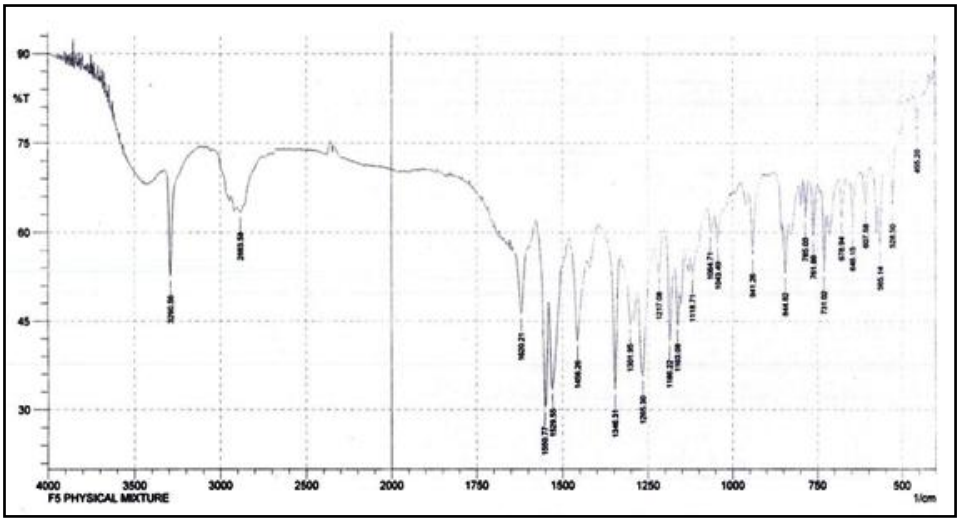

Figure 8: FTIR Spectra F5 Physical Mixture

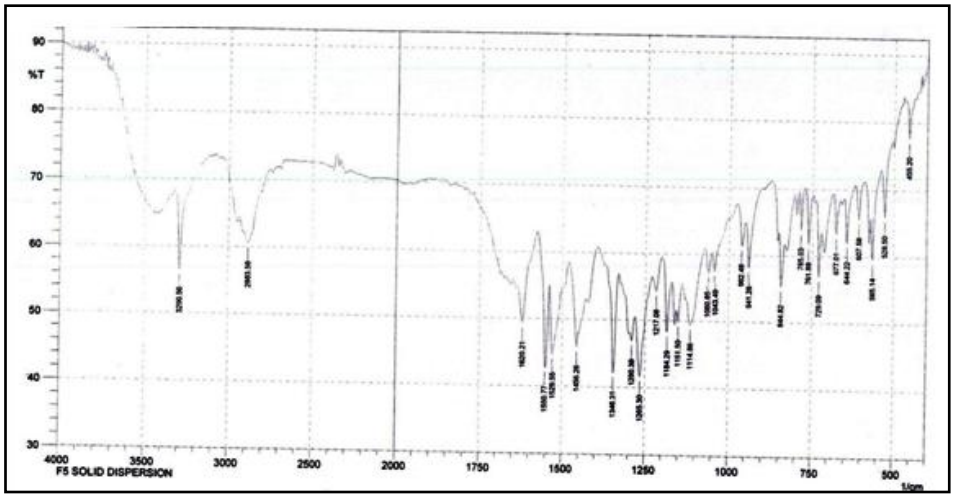

Figure 9: FTIR Spectra F5 Solid Dispersion

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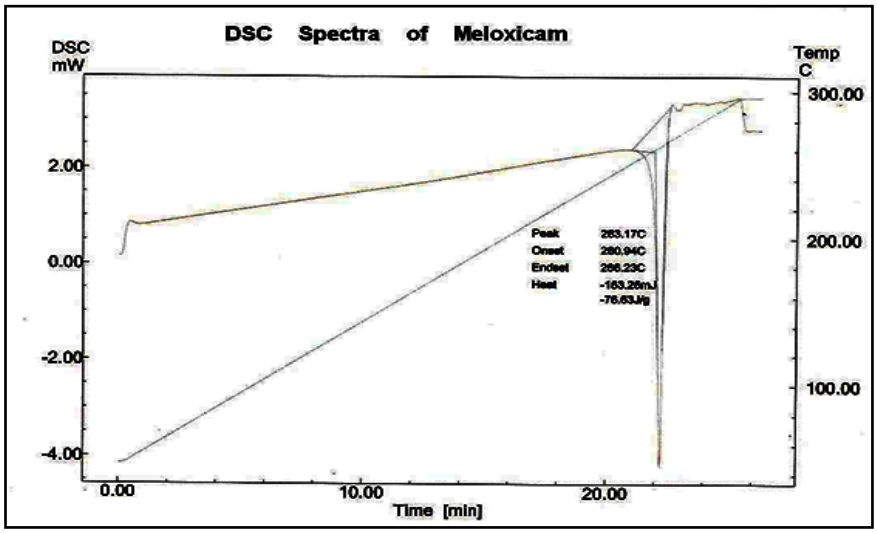

Figure 10: DSC thermogram of Pure drug

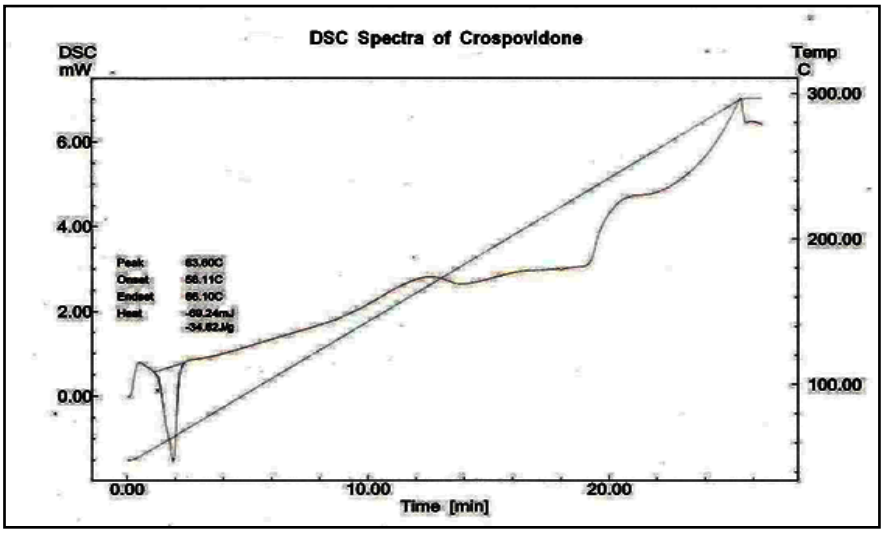

Figure 11: DSC thermogram of Crospovidone

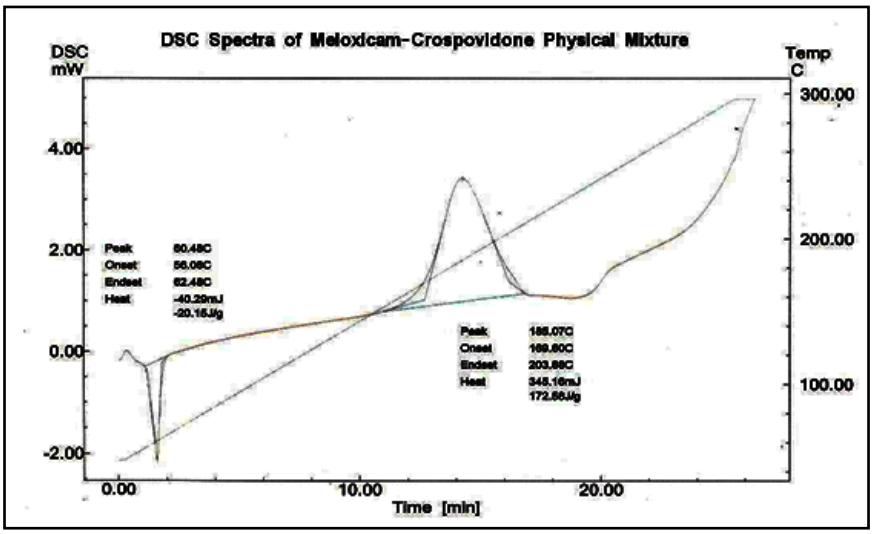

Figure 12: DSC thermogram of F5 Physical Mixture

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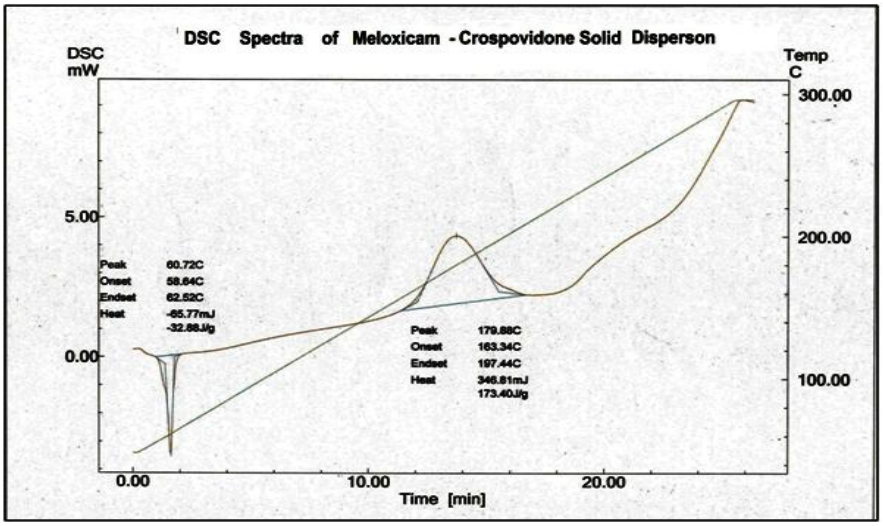

Figure 13: DSC thermogram of F5 Solid Dispersion

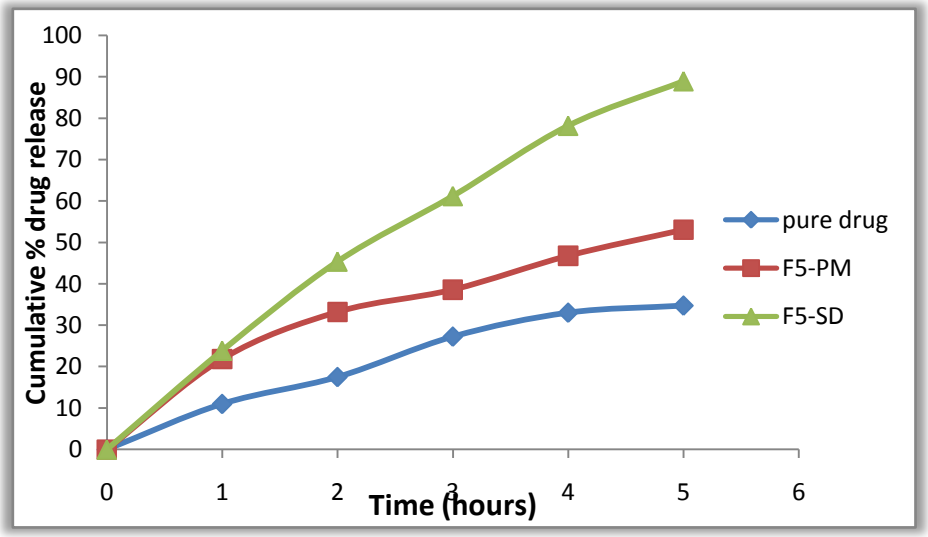

Figure 14: *In-vitro* Drug Release profile After One Month

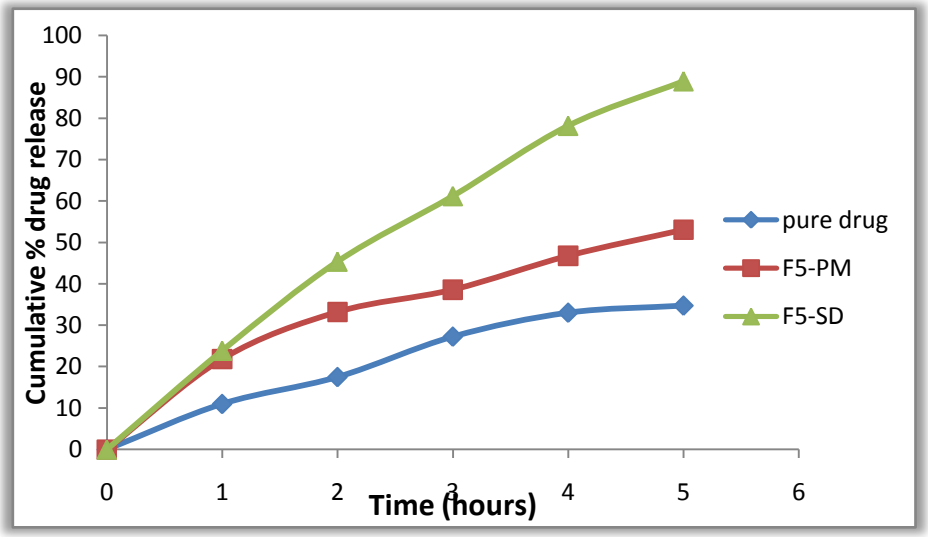

Figure 15: *In-vitro* Drug Release profile after Second Month

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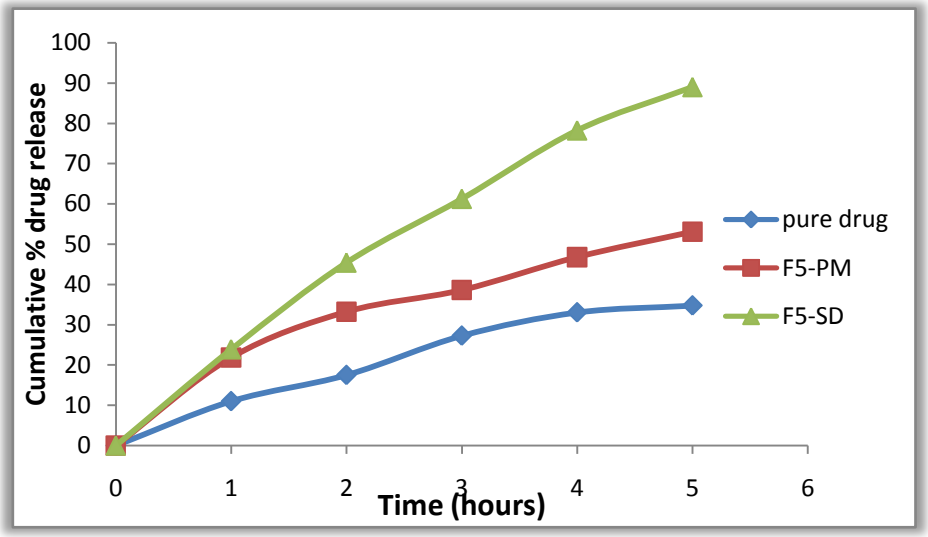

Figure 16: *In-vitro* Drug Release profile after Third Month

Table 1: Formulation of Meloxicam Solid dispersion

Sr. No.	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Meloxicam	100	100	100	100	100	100	100	100	100
2	Avicel ph 102 (mcc)	100	200	400	-	-	-	-	-	-
3	Crospovidone (CCP)	-	-	-	100	200	400	-	-	-
4	Croscarmellose sodium (CCS)	-	-	-	-	-	-	100	200	400

Table 2: Drug content of pure drug solid dispersion and physical mixture

Sr.No.	Formulation	Cumulative % drug content (mean±SD n=6)	
		Physical mixture	Solid dispersion
1	F1	99.01±1.55%w/w	99.07 ± 0.18%w/w
2	F2	99.25±1.58%w/w	99.56 ± 0.54%w/w
3	F3	99.54±1.37%w/w	99.32 ± 0.80%w/w
4	F4	99.23±0.39%w/w	99.01 ± 0.78%w/w
5	F5	99.25±1.58%w/w	99.56 ± 1.05%w/w
6	F6	99.32±1.61%w/w	100.25 ± 0.14%w/w
7	F7	99.23±0.77%w/w	99.23 ± 0.45%w/w
8	F8	99.56±0.52%w/w	99.26 ± 0.90%w/w
9	F9	98.28±1.61%w/w	99.77 ± 1.37w/w

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Table 3: Phase Solubility study for pure drug Solid dispersion, Physical mixture

Sr. No	Formulation	Cumulative % drug content (mean±SD n=6)		
		Pure drug	Physical mixture	Solid dispersion
1	-	0.0344 ± 0.017	-	-
2	F1	-	0.0583 ± 0.005	0.0698 ± 0.010
3	F2	-	0.0115 ±0.001	0.0140 ± 0.001
4	F3	-	0.0418 ±0.003	0.0423 ± 0.004
5	F4	-	0.1097 ±0.003	0.0113 ± 0.043
6	F5	-	0.0497 ±0.001	0.0525 ± 0.001
7	F6	-	0.0555 ±0.001	0.0566 ± 0.000
8	F7	-	0.0769 ±0.009	0.00813 ±0.007
9	F8	-	0.0250 ±0.001	0.0258 ± 0.001
10	F9	-	0.0371 ±0.001	0.038 ± 0.001

Table 4: Data for DSC Thermogram of Pure drug, Crospovidone, Solid Dispersion, Physical Mixture of Formulation F5.

Sr. No	Formulation	Peak Temperature	Onset of Peak	End point of Peak	Delta H (DH)
1	Pure drug	263.17 ºc	260.94 ºc	266.23 ºc	-153.25 -76.63
2	Crospovidone	63.60 ºc	58.11 ºc	66.10 ºc	-69.24 -34.62
3	F5 (SD)	179.88 ºc	163.34 ºc	197.44 ºc	346.81 173.40
4	F5(PM)	185.07 ºc	169.80 ºc	203.88 ºc	345.16 172.58

Table 5: Percentage Drug Content for three months of Stability Study

Formulation	No. of days	Cumulative percentage of drug content (mean± SD n=6)	
		Physical Mixture	Solid Dispersion
F5	30	100. 08±1.08	99.56±1.43
	60	99.97±1.27	99.25±1.58
	90	99.81±1.07	99.01±1.39

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Table 6: Phase Solubility Study for three Month of Stability

Formulation	No. of days	Cumulative solubility in gm/100ml (mean± SD n=3)	
		Physical Mixture	Solid Dispersion
F5	30	0.0554±0.015	0.0565±0.006
	60	0.0552±0.015	0.0561±0.008
	90	0.0547±0.013	0.0559±0.008

Table 7: *In-vitro* Cumulative Percentage Drug Release after One Month of Stability Study

Formulation	Time in min	Cumulative percentage drug release (mean± SD n=3)	
		Physical Mixture	Solid Dispersion
F5	15	21.85±0.70	23.89±0.36
	30	33.20±0.30	45.41±0.50
	45	38.58±0.39	61.24±0.25
	60	46.76±0.48	78.22±0.55
	90	53. 05±0.33	88.98±0.20

Table 8: *In-vitro* Cumulative Percentage Drug Release after Second Month of Stability Study

Formulation	Time in min.	Cumulative percentage drug release (mean± SD n=3)	
		Physical Mixture	Solid Dispersion
F5	15	20.28±0.31	22.42±0.51
	30	32.54±0.29	44.21±0.59
	45	37.50±0.40	60.14±0.58
	60	45.57±0.36	75.93±0.85
	90	51.44±0.37	87.66±0.34

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Table 9: *In-vitro* Cumulative Percentage Drug Release after Third Month of Stability Study

Formulation	Time in min.	Cumulative percentage drug release (mean± SD n=3)	
		Physical Mixture	Solid Dispersion
F5	15	19.31±0.45	21.69±0.57
	30	31.51±0.29	42.80±0.35
	45	36.30±0.19	58.37±0.42
	60	44.54±0.49	74.22±0.59
	90	49.72±0.47	86.30±0.31

CONCLUSION

The aim of the present work is to improve solubility and dissolution rate of meloxicam by preparing solid dispersion which is one of the excellent approaches for improving solubility and dissolution rate of poorly water soluble drugs. Solid dispersion was

prepared by using microcrystalline cellulose, corspovidone, and croscarmellose sodium. All the solid dispersion was evaluated, which showed improvement in solubility and dissolution rate than the pure drug. The F5 formulation show highest release than other formulations. The meloxicam solid dispersion was stable at 40ºC / 75% RH for at least three months.

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