PREPARATION AND ENHANCEMENT OF DISSOLUITON CHARACTERSTICS OF MELOXICAM BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Meloxicam is a poorly water soluble Non steroidal anti-inflammatory drug, COX—2 inhibitor. Due to its poor solubility, its bioavailability rate is limited by drug dissolution. In the present study, an attempt has been made to increase the solubility of Meloxicam using solvent evaporation technique with macromolecules such as Polyvinyl Pyrrolidone in different grades such as PVP K-15, PVP K-30 and PVP K-90 in 1:1, 1:3, 1:5, 1:7 and 1:9 ratios to improve the dissolution of drug. Effects of several variables such as type of carrier used, drug: carrier ratios were studied. The evaluation of physical mixture, solid dispersion was done by XRD study, IR Spectroscopy, solubility study and dissolution study. Improvement in dissolution of drug was observed in all the physical mixtures and solid dispersions was observed as compared to pure Meloxicam.The dissolution rate of Meloxicam was directly proportional to increment in the proportion of water soluble carrier. The maximum drug release was obtained from the solid dispersions prepared by Meloxicam with PVP K-15 in the ratio of 1:9.The XRD studies revealed that the pure drug of Meloxicam existed in amorphous form. IR spectra conclude that there is no interaction between the drug and the polymer.

KEY WORDS: Meloxicam, Solid dispersion, Bioavailability, Polyvinyl Pyrrolidone, Solvent evaporation method.

1.INTRODUCTION

Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The dissolution rate is directly proportional to solubility of drug. Drug with low aqueous solubility have low dissolution rate and hence suffer from oral bioavailability problem. Solid dispersion technique is widely used to increase the intrinsic solubility and dissolution and in turns oral bioavailability of poorly water soluble compounds(Serajuddin,1999;Leuner,2000). Solid dispersion(Chiow,1971) is defined as the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by melting (fusion), solvent or melting solvent method. The release mechanisms of drugs from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods.

Meloxicam, a non steroidal anti-inflammatory drug (NSAID), exhibit potent anti- inflammatory and analgesic action by inhibiting prostaglandin synthesis especially COX-2 enzyme. It is practically insoluble in water and its dissolution is considered to be a rate determining step in its absorption from gastro intestinal tract. So the solid dispersion system provides the possibility of reducing the particle of drugs to nearly a molecular level, to transform the drug from the crystalline to the partial amorphous state or to locally increase the saturation solubility. Many hydrophilic excipients like PEG 6000, PEG 4000, Mannitol and Polyvinyl Pyrrolidone can be used to enhance the dissolution of drugs. In the present investigation an attempt was made to improve the solubility and dissolution rate of drug by solid dispersion technique using hydrophilic carriers such as PVP K-15, PVP K-30 and PVP K-90 by solvent evaporation method.

2.MATERIALS AND METHODS

Meloxicam was obtained as a gift sample from Natco labs Ltd, Hyderabad (Andhra Pradesh), Polyvinyl Pyrrolidone was purchased from Ponmani chemicals, Coimbotore. All the chemicals were AR grade.

Preparation of Physical Mixture

Meloxicam and Polyvinyl Pyrrolidone in all grades and ratios were weighed accurately and mixed thoroughly in mortar with trituration for 10 min.The prepared physical mixtures were then passed through

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sieve no. 60 and finally stored in airtight container till further use(Gowthamrajan,2002).

Preparation of Solid Dispersion

Meloxicam and each of the water soluble carrier PVP K-15, PVP K-30 and PVP K-90 were weighed accurately in various ratios (1:1, 1:3, 1:5, 1:7 and 1:9) and transferred to a beaker containing sufficient quantity of N,N-Dimethyl Formamide to dissolve. N,N-Dimethyl Formamide was evaporated on rotary vacuum evaporator. The resulting solid dispersions were stored for 24 hours in a dessicator to congeal. Finally dispersions were passed through a sieve no.60 and stored in a airtight container till further use(Soniwala,2005).

Solubility Study

Solubility study was performed using shaker method. An excess of compound was placed in solvent in a screw capped glass tube connected to a rotating sample then immersed in a water bath while being maintained at the required temperature (37^{o}c) and agitated continuously for 96 hours. Finally the solutions were filtered by using filter Whatmann paper. The drug concentration was determined spectrophotmetrically at 347.6 nm. Solubility measurements were performed in triplicate(Palmode,1999).

Drug Content Estimation

The percentage drug content in physical mixtures and solid dispersions was estimated by dissolvent.

Infrared Spectrosocpy

Infrared spectra were recorded on a Fourier transform infrared (Jasco FT-IR 410) Spectrophotometer using KBr pellet method. All samples were recorded in the range of 4000-400 cm^{-1}(Palmode,1999).

X-Ray Diffraction Studies

X-ray Diffraction studies were performed using Perkin-Elmer instrument for characterization of crystalline structure(Gopal Rao,2005).

In Vitro Dissolution Studies

Invitro dissolution studies of pure drug, physical mixtures and solid dispersions were carried out for 60 minutes using USP dissolution apparatus type II at 50 rpm. Phosphate buffer P^{H} 7.4 (900ml) maintained at 37±0.5^{0}c was used as a dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals and was replaced with fresh dissolution medium. The drug content was measured spectrophotmetrically at 347.6 nm. Amount of drug release was calculated. T50 value of Meloxicam in various physical mixtures and solid dispersions were calculated from dissolution rate(Swathi Rawat,2003).

3.RESULTS AND DISCUSSION

Solubility study

Solubility of Meloxicam was found to be 75.62 µg/ml. While improvement in the solubility was observed with all physical mixtures and solid dispersions. Increase in the weight fraction of hydrophilic carrier results in the increase in solubility of all solid dispersions. Maximum solubility enhancement was found in 1:9 ratio of drug: PVP K-15 (Table 2).

Drug content Estimation

The content uniformities of Meloxicam were found to be in the range of 96.35±0.45 to 100.24±0.43. These values are with in the acceptable range (Table - 2).

Infrared Spectroscopy

IR spectra of Meloxicam, Carriers, Physical mixtures and solid dispersions of drug: PVP K-15 1:9 ratios are illustrated in (Fig - 1). The peaks observed for imines C=NC, NH secondary amines, NH bonding vibrations were shifted to the final product. Characteristic peaks of Meloxicam 3291.89 cm^{-1}, 2356.59 cm^{-1}, 1625.7 cm^{-1}, 1536.99 cm^{-1}, 1452.14 cm^{-1} and 1263.15 cm^{-1} were observed .These characteristic peaks were shifted to the physical mixtures and solid dispersion confirms that there is no chemical interaction between drug and carrier when formed as solid dispersion.

X-Ray Diffraction studies

The XRD pattern of Meloxicam and PVP K-15, PVP K-30, PVP K-90, physical mixtures and solid dispersions were analyzed. (Fig - 2) Meloxicam has high crystallanity because of presence of numerous peaks. PVP K-15, PVP K-30, PVP K-90 were found to be amorphous powders having no crystalline structure. XRD peaks in all the physical mixtures were similar to Meloxicam indicating that the crystallanity of Meloxicam did not change in physical mixtures.

In the case of solid dispersions the number of peaks and peak height was reduced as the polymer concentration increased. These findings suggest that meloxicam crystals gets converted to amorphous form in the polymer matrix in solid dispersion and indicates that enhanced rate of dissolution of dispersion with increase in polymer concentration.

INVITRO DISSOLUTION STUDIES

Drug release from solid dispersions and physical mixtures was faster than pure drug (Fig – 3&4). Drug release was found to increase with increasing concentration of polymers. The dissolution of drug from solid dispersion was found to be faster than from physical mixtures. This may be due to molecular and colloidal dispersion of drug

in hydrophilic carrier matrix of PVP. Among the solid dispersions prepared PVP K-15 1:9 showed greater solubility than PVP K-30 and PVP K-90.

The drug release in the solid dispersions Drug: PVP K-15 (1:9), Drug: PVP K-30 (1:9) and Drug: PVP K-90 (1:9) are 98.85%, 97.14% and 84% respectively. The physical mixtures of Meloxicam: PVP K-15 (1:9), Meloxicam: PVP K-30 (1:9) and Meloxicam: PVP K-90 (1:9) showed the release of 23.28%, 23.26% and 20.82% respectively as indicated in (Table – 3&4). The dispersion of Meloxicam strongly dependent on the relative concentration of drug to PVP ratio. The dissolution rate Meloxicam from PVP was increased with increment in PVP concentration up to the ratios 1:9. As the amount of carriers increase in the formulation T50 (time for 50% dissolution of drug) values decreased. T50 values indicated that there was enhancement in dissolution rate of Meloxicam.

Table No. 1:
ABSORBANCES OF MELOXICAM AT DIFFERENT CONCENTRATIONS

S.NO.	Concentration (µg /ml)	Absorbance
1	0	0
2	4	0.152
3	8	0.324
4	12	0.472
5	16	0.636
6	20	0.818

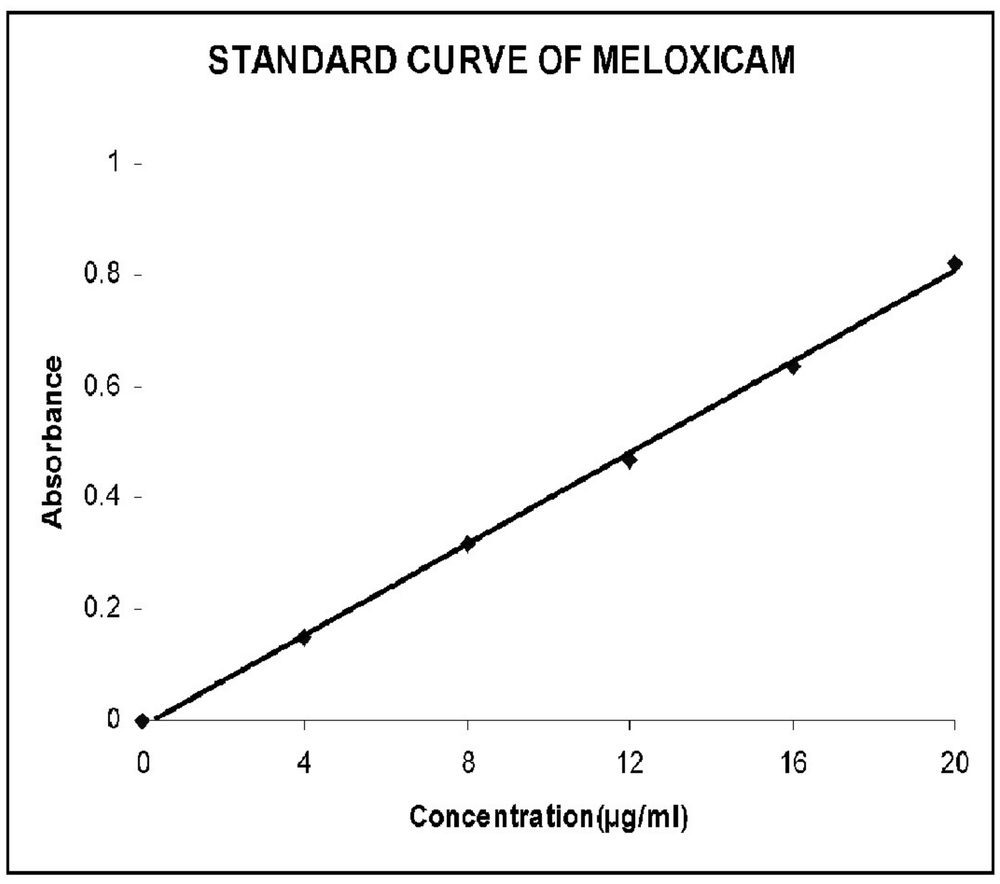


Table No. 2(a)
FOR PHYSICAL MIXTURE

S.No	FORMULATION	RATIO	%Drug content	Solubility (µg/ml)	T50 (min)
1	Pure meloxicam		-----	75.62±0.167	>100
2	Drug:PVP K-15	1:1	96.35±0.45	78.08±0.196	57.1
3		1:3	96.72±0.33	83.38±0.155	24.6
4		1:5	98.37±0.81	89.31±0.131	15.8
5		1:7	99.62±0.92	99.44±0.160	6.2
6		1:9	98.41±0.62	116.97±0.143	<6
7	Drug:PVP K-30	1:1	99.35±0.61	89.25±0.159	36.4
8		1:3	96.48±0.96	94.17±0.141	11.2
9		1:5	100.21±0.32	99.43±0.133	6.60
10		1:7	99.51±0.53	106.50±0.151	5.81
11		1:9	97.68±0.90	105.01±0.163	<5
12	Drug:PVP K-90	1:1	100.24±0.43	98.39±0.121	60.0
13		1:3	99.87±.34	104.08±0.143	25.2
14		1:5	98.54±0.85	105.84±0.114	16.4
15		1:7	99.62±0.92	102.26±0.160	10.2
16		1:9	99.38±0.91	98.39±0.131	7.2

Table No.2(b)
FOR SOLID DISPERSION

S.No	FORMULATION	RATIO	%Drug content	Solubility (µg/ml)	T50 (min)
1	Pure meloxicam		-----	75.62±0.167	>95
2	Drug:PVP K-15	1:1	96.87±0.43	78.24±0.167	67.1
3		1:3	96.72±0.32	83.74±0.146	25.7
4		1:5	97.73±0.61	90.28±0.155	16.9
5		1:7	98.37±0.73	99.18±0.197	7.2
6		1:9	99.63±0.84	100.16±0.148	<6
7	Drug:PVP K-30	1:1	98.34±0.51	89.35±0.152	38.2
8		1:3	97.81±0.89	95.76±0.141	12.3
9		1:5	100.11±0.21	96.43±0.133	6.80
10		1:7	99.5±0.51	99.23±0.151	5.75
11		1:9	97.68±0.81	100.50±0.163	<5
12	Drug:PVP K-90	1:1	100.19±0.23	97.63±0.142	61.1
13		1:3	99.67±0.34	98.39±0.148	25.7
14		1:5	98.54±0.86	99.16±0.114	16.8
15		1:7	99.68±0.95	105.24±0.160	10.21
16		1:9	99.36±0.81	102.28±0.131	7.6

Table No.3
DISSOLUTION PROFILE OF PHYSICAL MIXTURE (DRUG: PVP K-15)

S.NO	TIME (mts)	PERCENTAGE DRUG RELEASE					
		PURE DRUG	1:1	1:3	1:5	1:7	1:9
1	0	0	0	0	0	0	0
2	10	2.40±0.118	2.71±0.134	3.12±0.180	4.57=0.173	4.91±0.126	4.88±0.115
3	20	3.40±0.138	3.88±0.101	6.24±0.126	11.47±0.167	12.32±0.135	13.02=0.156
4	30	4.35±0.163	4.71±0.159	9.71±0.115	14.67±0.162	14.71±0.129	16.00=0.175
5	40	5.40±0.152	5.50±0.196	12.52=0.146	16.13±0.180	16.88±0.151	18.93=0.152
6	50	6.00±0.183	8.69±0.123	12.84±0.102	17.77±0.143	18.25±0.172	20.81±0.134
7	60	8.70±0.164	8.78±0.128	13.77±0.141	19.35±0.132	19.83±0.118	23.28±0.111

Table No.4

DISSOLUTION PROFILE OF SOLID ISPERSION (DRUG: PVP K-15)

S.NO	TIME (Mts)	PERCENTAGE DRUG RELEASE					
		PURE DRUG	1:1	1:3	1:5	1:7	1:9
1	0	0	0	0	0	0	0
2	10	2.40±0.118	6.14±0.130	14.25±0.116	20.25±0.129	28.05±0.163	31.35±0.168
3	20	3.40±0.138	11.10±0.186	18.60±0.157	35.55±0.167	39.30±0.107	48.15±0.117
4	30	4.35±0.163	18.75±0.141	22.05±0.132	42.00±0.137	48.15±0.117	60.00±0.142
5	40	5.40±0.152	21.45±0.040	29.70±0.115	53.25±0.126	60.15±0.123	69.60±0.142
6	50	6.00±0.183	29.25±0.024	36.15±0.164	62.10±0.175	71.40±0.151	81.15±0.115
7	60	8.70±0.164	34.05±0.032	44.25±0.155	76.50±0.142	83.55±0.136	98.85±0.110

FIGURE: 3

COMPARISION OF PHYSICAL MIXTURES OF DRUG: PVP K-15 AT VARIOUS RATIOS

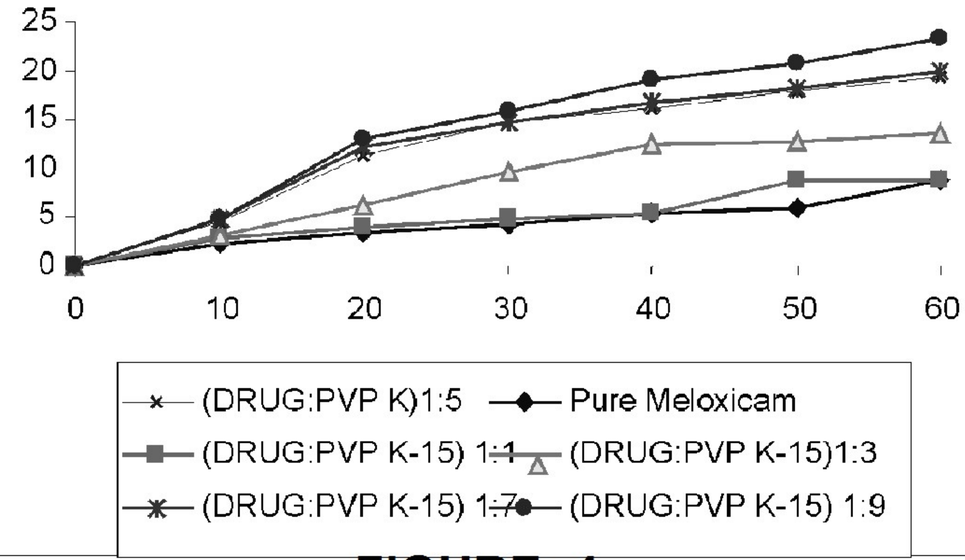


FIGURE: 4

COMPARISION OF SOLID DISPERISONS OF DRUG: PVP K-15 AT VARIOUS RATIOS

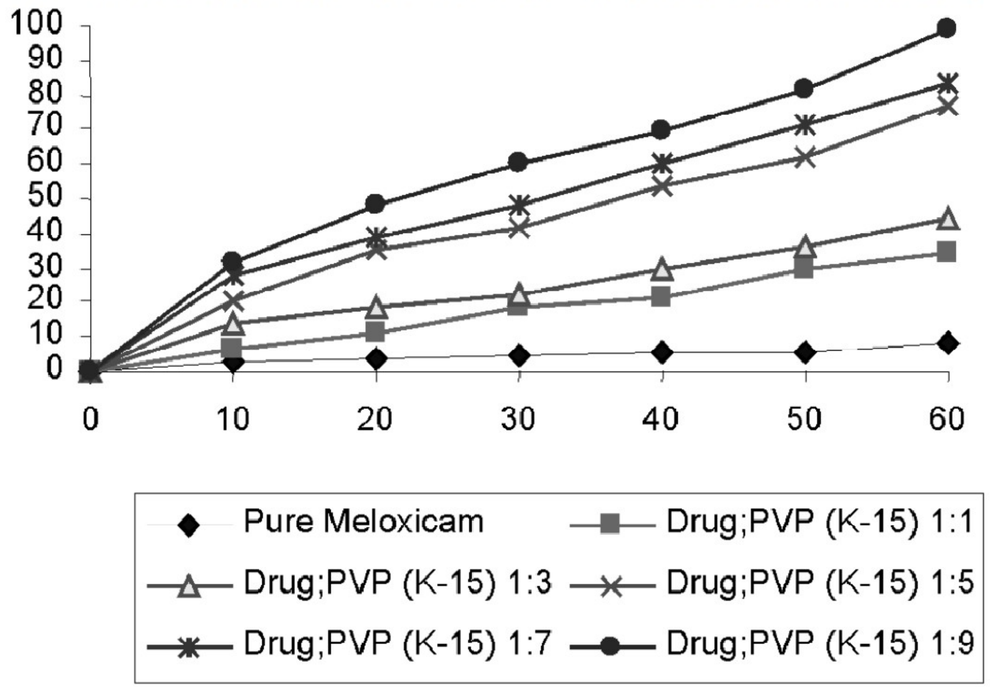
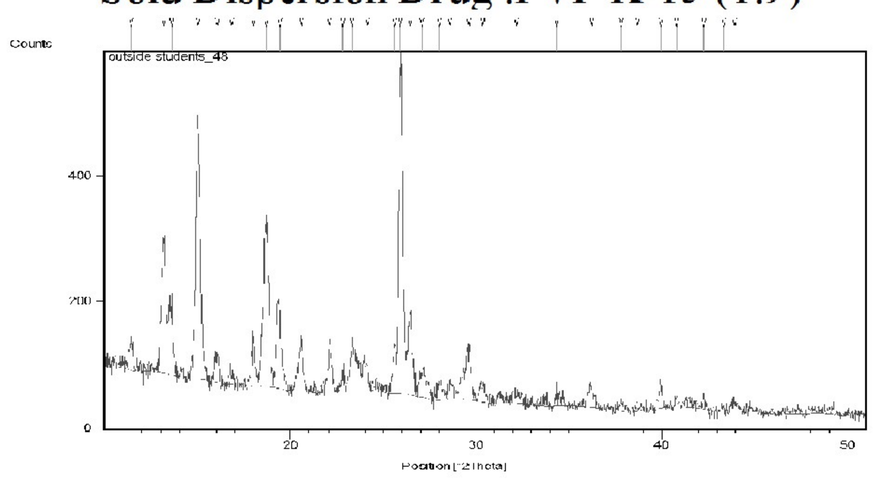
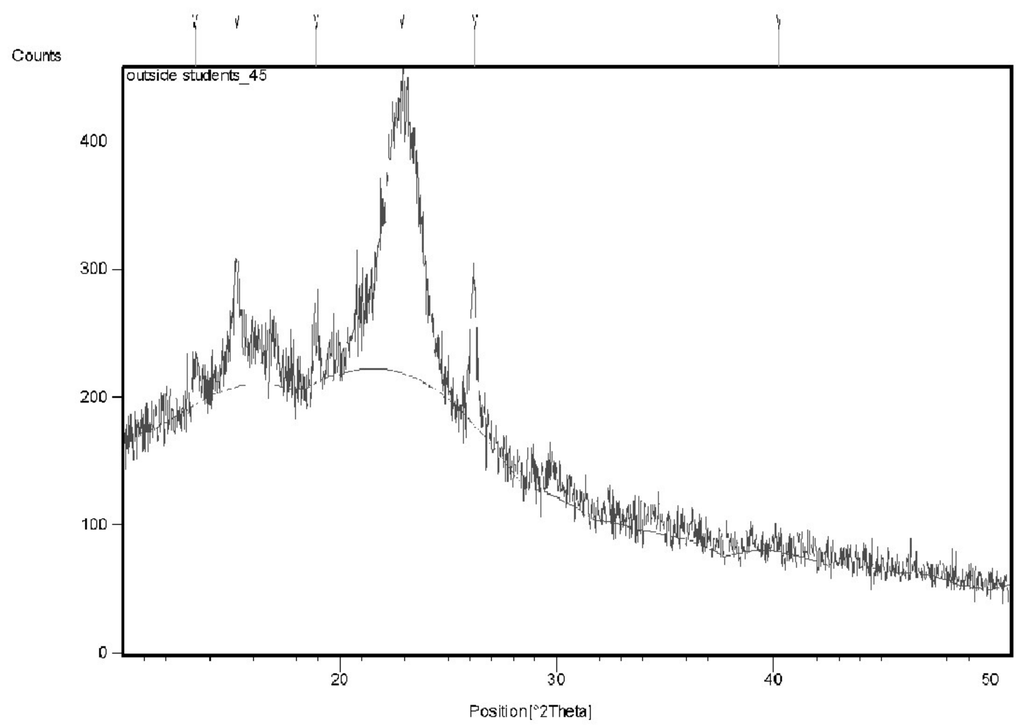


FIGURE 2: XRD Studies of Pure Meloxicam and Sold Dispersion Drug :PVP K-15 (1:9)



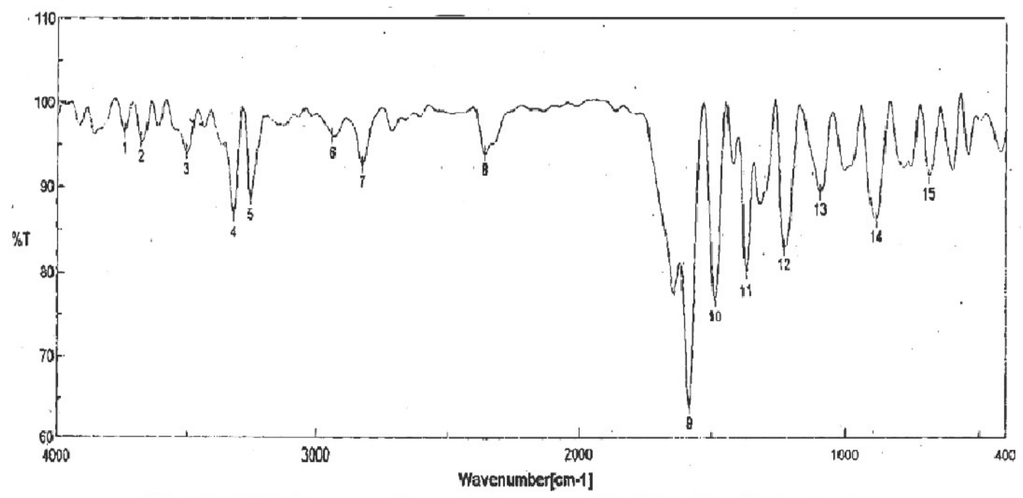
PURE MELOXICAM



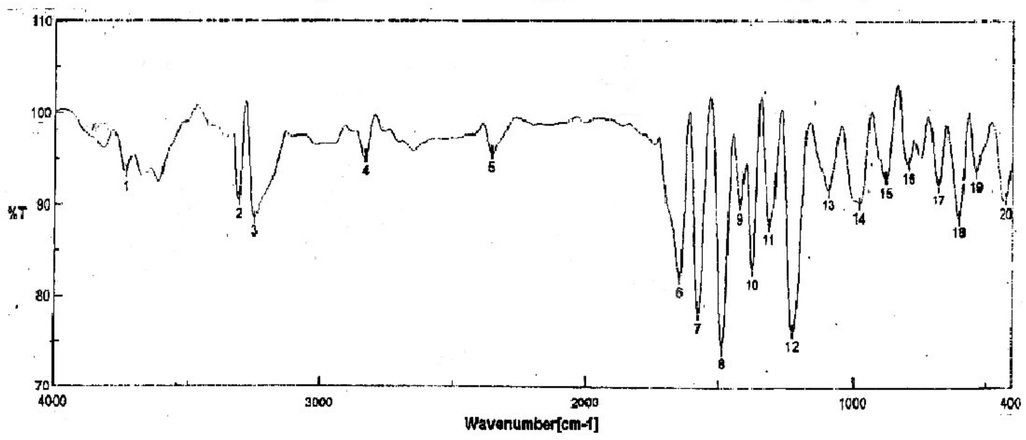
SD DRUG: PVP K-15

FIGURE 1

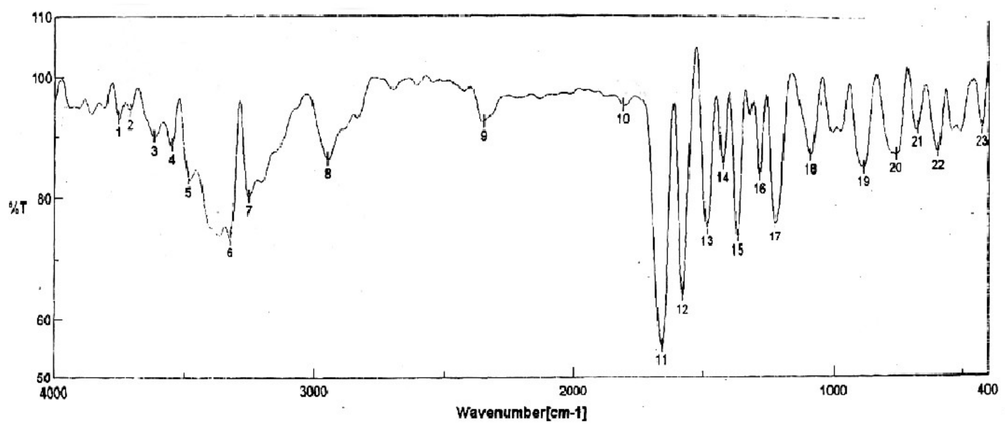
IR Spectrum of Solid Dispersion Drug: PVP K-15 (1:9), Physical Mixture Drug: PVP K-15 (1:9), PURE PVPK-15 and Pure Meloxicam



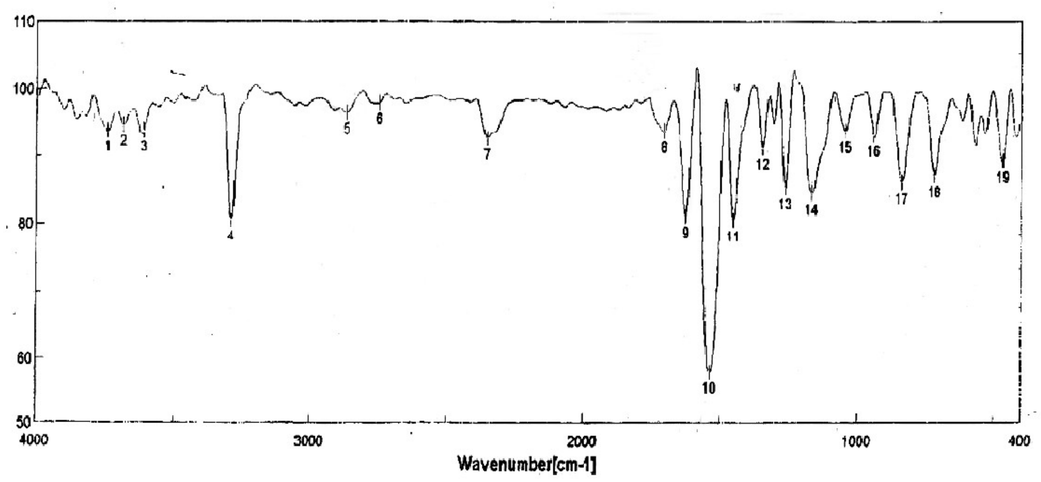
Solid Dispersion Drug: PVP K-15 (1:9)



Physical Mixture Drug: PVP K-15 (1:9)



PURE PVPK-15



Pure Meloxicam

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