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FORMULATION AND EVALUATION: SOLID DISPERSION OF MELOXICAM BY SOLVENT EVAPORATION METHOD

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ABSTRACT

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. Solid dispersions of a poorly water-soluble drug Meloxicam in Polyvinylpyrrolidone (PVP) were prepared by solvent evaporation method. The physicochemical properties of the Products and drug-polymer interactions were characterized by Fourier Transform Infrared spectroscopy, Determination of drug content, X-Ray Diffraction studies. Meloxicam was found to be amorphously dispersed in solid dispersion systems with the drug to polymer weight ratio of 1:9. The solid dispersion of the Meloxicam (Ratio-1:9) has shown better release of drug and good dissolution rate. 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. PVP processing could provide an effective pharmaceutical formulation technology to improve the bioavailability of poorly water-soluble drug.

Keywords: Solid dispersion, Meloxicam, In-vitro dissolution study, Solvent evaporation method.

INTRODUCTION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles (Aftab Modi *et al*., 2006; Ford JL *et al*., 1986). Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. Prostaglandins are substances that contribute to inflammation of joints. Meloxicam inhibits prostaglandin synthetase (cyclo oxygenase 1 and 2) and leads to a decrease of the synthesis of prostaglandins, therefore, inflammation is reduced.

Anti-inflammatory effects of Meloxicam are believed to be due to inhibition of prostaglandin synthetase (cyclo oxygenase), 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 (Goodman & Gilmans *et al*., 1996).

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MATERIALS AND METHODS

Materials

Meloxicam was obtained as a gift sample from Natco Pharma Ltd, Hyderabad. Polyvinyl Pyrollidone was

purchased from Ponmani chemicals, Coimbatore. All other chemicals used were AR grade.

METHODS

A. Preparation of Physical Mixture

Meloxicam and Polyvinyl Pyrollidone (Ainley Wade *et al*., 194) in all grades and ratios were weighed accurately and mixed thoroughly in mortar with triturating for 10 min. The prepared physical mixtures were then passed through sieve no. 60 and finally stored in airtight container till further use (Aftab Modi *et al*., 2006; Kumar SGV *et al*., 2006; Ke wu, jing li *et al*., 2009).

B. 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 desiccators to congeal. Finally dispersions were passed through a sieve no.60 and stored in an airtight container till further use (Aftab Modi *et al*., 2006; Kumar SGV *et al*., 2006; Ke wu, jing li *et al*., 2009).

EVALUATION PARAMETERS

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 (37^0 c) and agitated continuously for 96 hours. Finally the solutions were filtered by using watmann filter paper. The drug concentration was determined spectrophotometrically at 347.6 nm. Solubility measurements were performed in triplicate (Vippagunta SR *et al*., 2002).

Drug Content Estimation

The percentage drug content in solid dispersions was estimated by dilution method.

Infrared Spectroscopy

Infrared spectra were recorded on a Fourier Transform Infrared Spectrophotometer using KBr pellet method. All samples were recorded in the range of 4000-400 cm^{-1} (Taylor LS *et al*., 1997).

X-Ray Diffraction Studies

X-ray Diffraction studies were performed using Perkin-Elmer instrument for characterization of crystalline structure. The crystallinity of samples chosen for DSC was investigated by XRD (Kumar SGV *et al*., 2006; Ke wu, jing li *et al*., 2009).

In Vitro Dissolution Studies

In vitro dissolution studies of pure drug 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 ± 0.5^0C 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 spectrophotometrically at 347.6 nm. Amount of drug release was calculated. T50 value of Meloxicam in various solid dispersions was calculated from dissolution rate (Van den Mooter .G *Et al*., 1998; Ke wu, jing li *et al*., 2009).

RESULTS AND DISCUSSION

Solubility study

Solubility of Meloxicam was found to be 75.62 µg/ml. 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. The results are shown in table 2 & 3.

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 within the acceptable range. The results are shown in table 4 & 5.

Infrared Spectroscopy

IR spectra of Meloxicam, Carriers, Physical mixtures and solid dispersions of drug: PVP K-15 1:9 ratios are illustrated in Fig. No. 1, 2, 3, & 4. 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 in Fig. No. 5 & 6. Meloxicam has high crystallinity 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 crystallinity 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.

In vitro dissolution studies

Drug release from solid dispersions and physical mixtures was faster than pure drug. Results are shown in table. No 6, 7 and Fig. No 7 & 8. 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 10 & 11). The dispersion of Meloxicam strongly dependent on the relative concentration of drug to PVP ratio. The dissolution rate of 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.

Infrared Spectroscopy

Fig 1. Pure drug (Meloxicam)

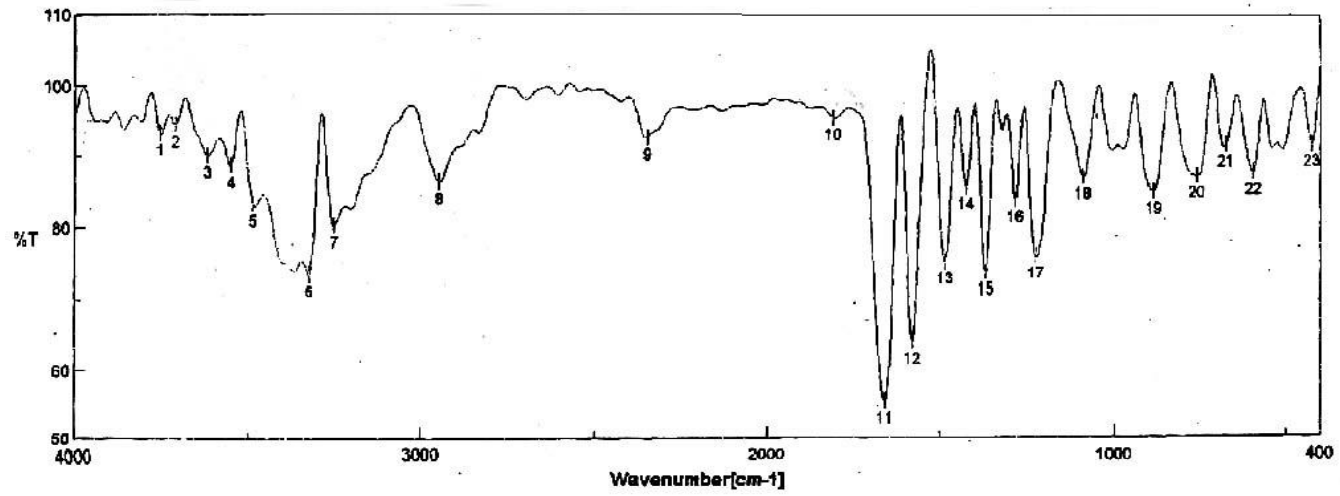


Fig 2. Pure Polymer (PVPK-15)

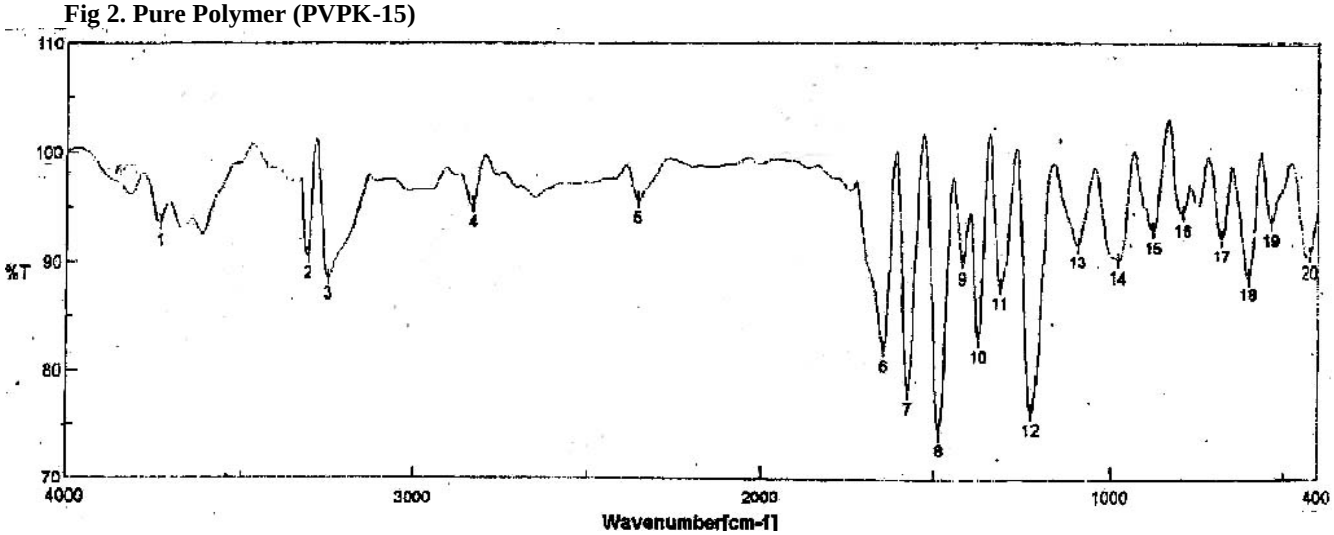


Fig 3. Physical mixtures: PVP K-15(1:9)

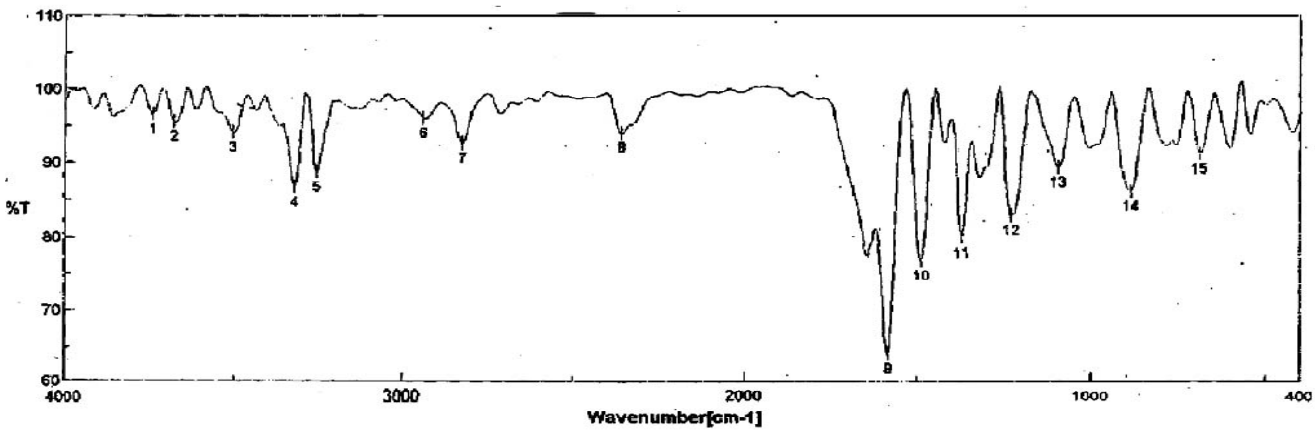
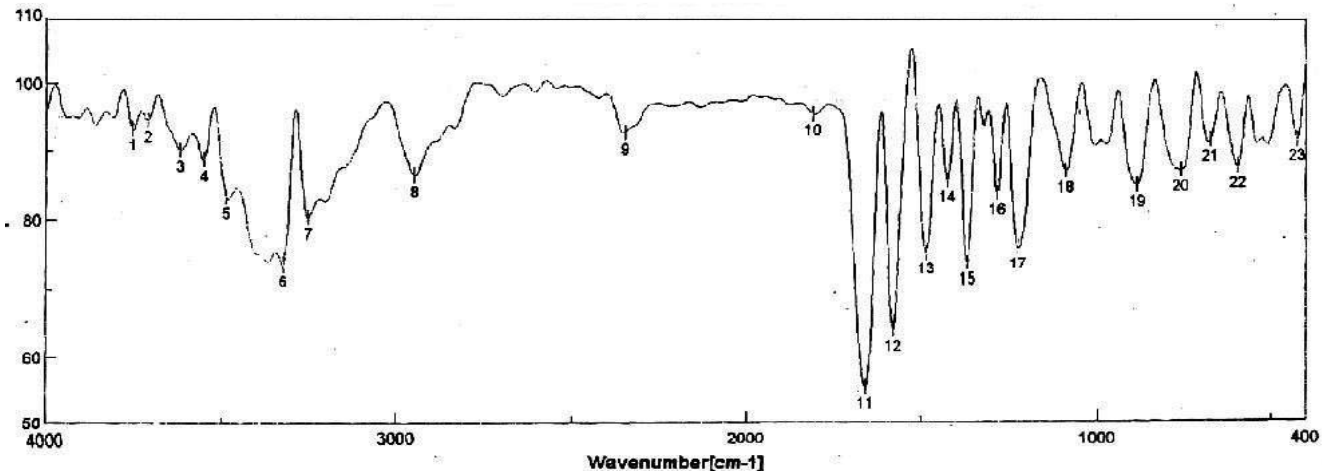


Fig 4. Solid dispersion: PVP K-15(1:9)



X-Ray Diffraction Studies:

Fig 5. Pure drug (Meloxicam):

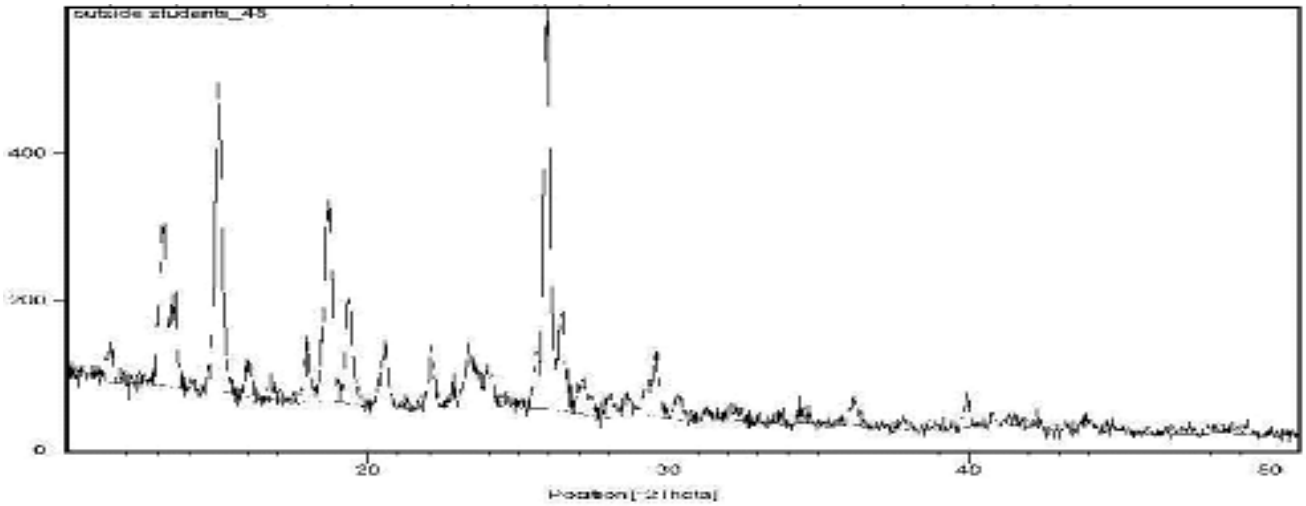


Fig 6. Solid dispersion: PVP K-15(1:9)

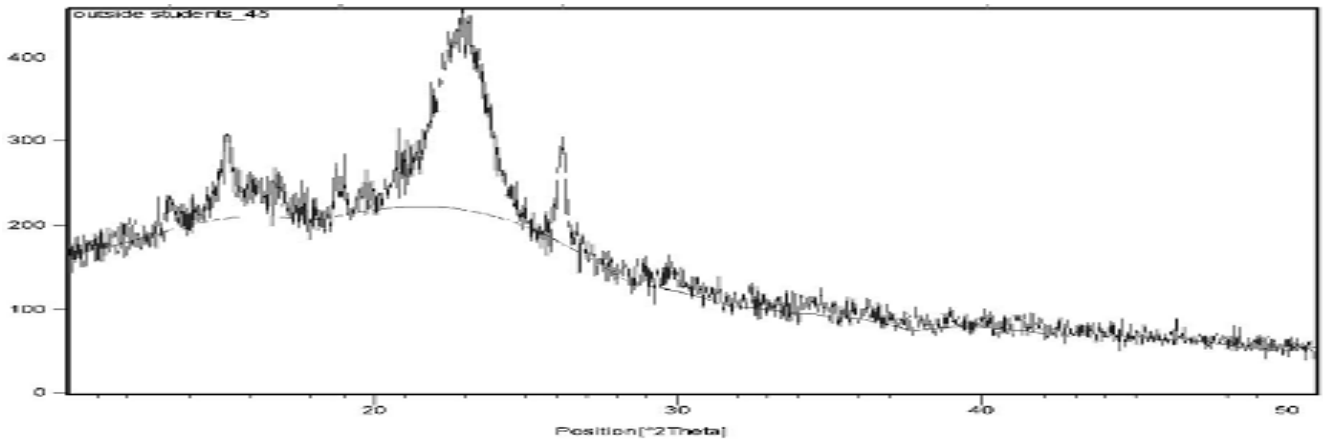


Fig 7. Dissolution Profile of Physical Mixture (Drug: PVP K-15)

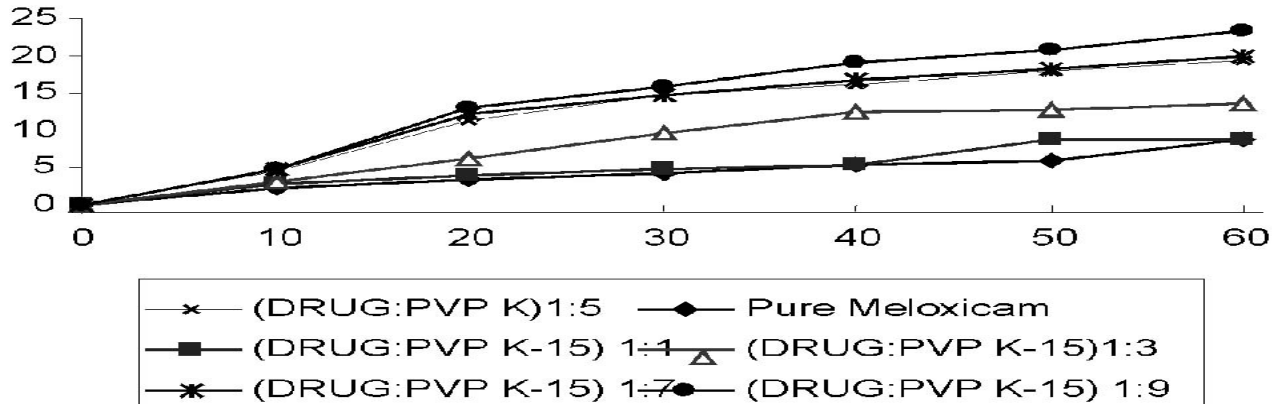


Fig 8. Dissolution profile of solid dispersion (drug: PVP K-15)

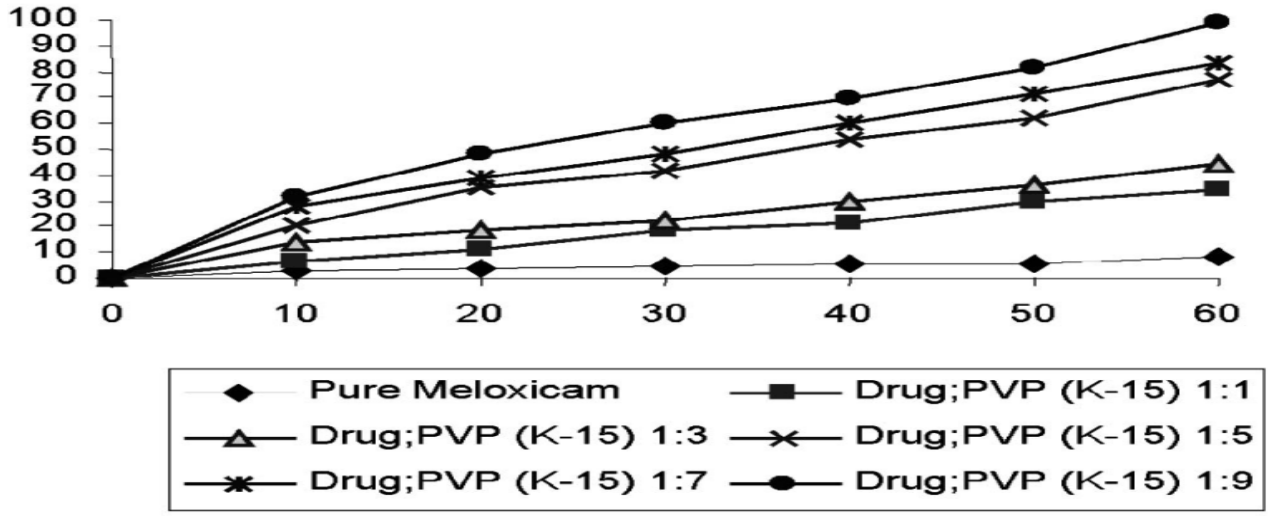


Table 1. Solid dispersion

S. No	Formulation (Drug : Polymer Ratio)		
	Drug PVP K-15	Drug PVP K-30	Drug PVP K-90
1	1:1	1:1	1:1
2	1:3	1:3	1:3
3	1:5	1:5	1:5
4	1:7	1:7	1:7
5	1:9	1:9	1:9

Table 2. Solubility Study for physical mixtures

S.NO	FORMULATION	RATIO	SOLUBULITY(µg/ml)	T50(min)
1	Pure Meloxicam	-	75.62±0.167	>100
2	Drug PVP K15	1:1	78.08±0.916	57.1
3		1:3	83.38±0.155	24.6
4		1:5	89.31±0.131	15.8
5		1:7	95.44±0.160	6.2
6		1:9	98.97±0.143	<6
7	DRUG PVP K30	1:1	89.25±0.159	36.4
8		1:3	92.17±0.141	11.2
9		1:5	94.43±0.133	6.60
10		1:7	96.50±0.151	5.81
11		1:9	98.01±0.163	<5
12	DRUG PVP K 90	1:1	98.39±0.121	60.0
13		1:3	104.08±0.143	25.2
14		1:5	105.84±0.114	16.4
15		1:7	102.26±0.160	10.2
16		1:9	98.39±0.131	7.2

Table 3. Solid dispersion

S.NO	FORMULATION	RATIO	SOLUBULITY (µ g/ml)	T50(min)
1	Pure Meloxicam	-	75.62±0.167	>95
2	DRUG PVP K15	1:1	78.24±0.167	67.1
3		1:3	83.74±0.146	25.7
4		1:5	90.28±0.155	16.9
5		1:7	99.18±0.197	7.2
6		1:9	100.16±0.148	<6
7	DRUG PVP K30	1:1	89.35±0.152	38.2
8		1:3	95.76±0.141	12.3
9		1:5	96.43±0.133	6.80
10		1:7	99.23±0.151	5.75
11		1:9	100.51±0.163	<5
12	DRUG PVP K90	1:1	97.63±0.142	61.1
13		1:3	98.39±0.148	25.7
14		1:5	99.16±0.114	16.8
15		1:7	105.24±0.160	10.21
16		1:9	102±0.131	7.6

Table 4. Drug content estimation for physical mixtures

S.NO	FORMULATION	RATIO	%DRUG CONTENT
1	Pure Meloxicam	-	---
2	Drug PVP K15	1:1	96.35±0.45
3		1:3	96.72±0.33
4		1:5	98.37±0.81
5		1:7	99.62±0.92
6		1:9	98.41±0.62
7	DRUG PVP K30	1:1	99.35±0.61
8		1:3	96.48±0.96
9		1:5	100.21±0.32
10		1:7	99.51±0.53
11		1:9	97.68±0.90
12	DRUG PVP K 90	1:1	100.24±0.43
13		1:3	99.87±34
14		1:5	98.54±0.85
15		1:7	99.62±0.92
16		1:9	99.38±0.91

Table 5. Solid dispersion

S.NO	FORMULATION	RATIO	%DRUG CONTENT
1	Pure Meloxicam	_	---
2	DRUG PVP K15	1:1	96.87±0.43
3		1:3	96.72±0.32
4		1:5	97.73±0.61
5		1:7	98.37±0.73
6		1:9	99.63±0.84
7	DRUG PVP K30	1:1	98.34±0.51
8		1:3	97.81±0.89
9		1:5	100.11±0.21
10		1:7	99.5±0.51
11		1:9	97.68±0.81
12	DRUG PVP K90	1:1	100.19±0.23
13		1:3	99.67±0.34
14		1:5	98.54±0.86
15		1:7	99.68± 0.95
16		1:9	99.36±0.81

In Vitro Dissolution Studies

Table 6. Comparisons of various physical mixtures of drug: PVP K-15 at various ratios: Dissolution Profile of Physical Mixture (Drug: PVP K-15)

S. No	TIME (mins)	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±.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	6.19±0.183	8.69±0.123	12.84±0.102	17.77±0.143	18.25±0.172	19.35±0.172
7	60	8.70±0.164	8.78±0.128	13.77±0.141	19.35±0.132	19.83±0.118	21.43±0.118

Table 7. Comparisons of solid dispersions of drug: PVP K-15 at various ratios: Dissolution profile of solid dispersion (drug: PVP K-15)

S. No	TIME (mins)	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	42.0±0.137	48.15±0.117	60.0±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	6.0±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

CONCLUSION

The research described in this work was focused on solid dispersion of poorly water soluble lipophilic drug in matrices of amorphous sugar. The preparation method is solvent evaporation method, which is suitable for use in combination with low temperature drying like freeze drying. The versatility of this technique is investigated by preparing solid dispersions with various drugs, various matrices and various drug loads. The effects of several process parameters were discussed. A new mechanism was proposed to describe the dissolution of solid dispersions which explores the application of Temperature Modulated Differential Scanning Calorimetry (TMDSC). By all above we can conclude that different techniques are used for the formulation of solid dispersions.

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