Research article Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

Physical Properties and Dissolution Behaviour of Meloxicam/Poloxamer Solid Dispersions Prepared By Hot Melt Method and Microwave Assisted Method

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ABSTRACT

The aim of this study was to enhance the solubility of meloxicam by various solid dispersion techniques using poloxamer 188 and to investigate the effect of different techniques of preparation of solid dispersion on *in vitro* dissolution of meloxicam. Solid dispersions were prepared by two methods namely, hot melt method and microwave assisted method. The Drug and polymer were used in 1:1, 1:3 and 1:5 ratios. Different batches SD 1, SD 2, SD 3 (hot melt) and MSD 4, MSD 5, MSD 6 (microwave assisted) were evaluated by drug content determination, solubility study, *in vitro* drug release study, DSC, FTIR and XRD. All the batches showed higher solubility and dissolution rate as compared to pure drug. Maximum solubility and *in vitro* release (in phosphate buffer pH 7.4) was exhibited by batch MSD 6, which was prepared by microwave assisted method and consisted of drug and polymer in 1:5 ratio. The best – fit model indicating the mechanism of dissolution from the formulation showing the highest release for was found to be Higuchi matrix release. It revealed that release mechanism could be diffusion from a matrix system. The Change in the nature of drug from crystalline to amorphous form was confirmed by DSC and XRD analysis. Stability study was carried out by storing the solid dispersions in a stability chamber at 40°C & 75% RH. The microwave assisted method was found to be better then melting method for preparing solid dispersions.

KEYWORDS: Solid dispersion, Meloxicam, Microwave, Dissolution

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INTRODUCTION

According to Biopharmaceutical classification system (BCS), drugs have been classified on the basis of their solubility and permeability characteristics. Drugs with poor water solubility (Class II & IV) present a big challenge for the formulation scientists.[1]

Meloxicam belongs to Class II and was selected as a model drug for this study. Meloxicam is 4-hydroxy-2-methyl-*N*-[(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide. It is a COX-2 inhibitor used to treat joint diseases such as osteoarthritis, rheumatoid arthritis and other musculoskeletal disorders. It is practically insoluble in water.[2] The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development although salt formation, solubilization and particle size reduction have commonly been used to increase the dissolution rate and thereby oral absorption and bioavailability of such drugs. Preparation of solid dispersions using water soluble carriers is yet another popular approach used to improve the oral bioavailability of poorly water soluble drugs.[3]

The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug [4, 5]. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubilities and dissolution rates as compared with crystalline material. The mechanisms for the enhancement of the dissolution rate of solid dispersions have been proposed by several investigators. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates [6]. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process [7], and drug solubility and wettability may be increased by surrounding hydrophilic carriers [6]. The most common methods used to prepare solid dispersions include the melting method and the solvent method [8], the melting method and the solvent method have some limitations. In the case of the melting method, incomplete miscibility between drug and carrier may occur due to the high viscosity of a polymeric carrier in the molten state and thermally unstable drugs can be degraded due to the requirement of relatively high preparation temperatures. In the case of the solvent method, since both drug and carrier must be dissolved completely in organic solvent, subtle alterations in the conditions used for solvent evaporation may lead to large changes in product performance [5, 9]. The solvent method also introduces residual solvent, which may bring up the environmental issues.

Recently a novel approach based on the use of microwave irradiation has been proposed for the preparation of solid dispersions. Microwaves irradiation (MW) is a well-known method for heating and drying materials[10]. Microwaves, with their ability to penetrate any substance, allow the production of heat in any point of the sample at the same time. The efficient heating of materials by

microwaves depends on the capacity of a specific material to absorb microwave energy. Microwaves irradiation offers several advantages such as: rapid volumetric heating, no overheating at the surface, addressable heating, energy-saving and low operating cost[11]. In addition the main advantage of not using organic solvents is the absence of any risk originating from residual solvents[12]. Microwave energy can influence the crystalline status of the drug and the time of exposure plays an important role in achieving the amorphous state of the drug, improving consequently its dissolution rate[13]

The aim of the present work was to compare the efficiency of several methods such as physical mixing, melting method and microwave assisted method in improving dissolution of meloxicam.

MATERIALS AND METHODS

MATERIALS

Meloxicam was supplied as a gift sample by jubilant orgenosys. Poloxamer 188 was purchased from Spectrochem pvt. Ltd. Bombay. Hydrochloric acid and sodium chloride were purchased from Sisco Research Laboratories, Mumbai. Potassium dihydrogen PO_4 was purchased from S.D.Fine Chemical Ltd. Mumbai.

PREPARATION OF SOLID DISPERSIONS

Hot melt method

Poloxamer 188 was melted to their melting temperature and then accurately weighed quantity of drug was slowly incorporated into molten polymer with continuous stirring. Then product was cooled down to room temperature, pulverized, sieved and stored in desicator.

Microwave assisted method

A mixture of drug and polymer (poloxamer 188) was taken in a separate glass beaker for each batch. Initially drug and polymer were gently mixed for 3 minutes. Then these beakers were subjected to microwave heating for one minute at the power of 1000 W. only one beaker at a time was placed inside the microwave oven (Bajaj 2300 ETB) at a precise place. After one minute beaker was removed from oven and the product was cooled at room temperature. Product was pulverized, sieved and stored in a desiccator.

The ratio of drug and polymer used for both method (Hot melt method and Microwave assisted method) are shown in **table 1** and **table 2** respectively.

Table 1: Ratio of Drug: Poloxamer 188 used for solid dispersions by melting method

S.No.	Batch Code	Drug: Poloxamer 188
1	SD 1	1:1
2	SD 2	1:3
3	SD 3	1:5

Table 2: Ratio of Drug: Poloxamer 188 used for solid dispersions by microwave method

S.No.	Batch Code	Drug: Poloxamer 188
1	MSD 4	1:1
2	MSD 5	1:3
3	MSD 6	1:5

EVALUATION OF SOLID DISPERSIONS

Drug content determination

Solid dispersions equal to 20 mg of active meloxicam were accurately weighed and dissolved in small volume of methanol then further diluted with phosphate buffer pH 7.4 to 20 ml. The content of meloxicam was determined spectrophotometerically at 362 nm using UV-visible spectrophotometer (Cary 5000, Varian, Australia).

Solubility Studies

Saturation solubility of pure drug and different batches of solid dispersions was determined by shaking flask method. In this method excess amount of drug (20 mg) or solid dispersion equivalent to 20 mg of meloxicam were taken in 20 ml medium (Phosphate buffer pH 7.4) in conical flask. These samples were then placed in water shaker bath for 24 hours at 28°C. After 24 hours samples were removed, filtered and after appropriate dilutions analyzed by UV-visible spectrophometer at 362 nm.

In vitro release study

Release of meloxicam from the solid dispersions was studied in phosphate buffer of pH 7.4 using a United States Pharmacopeia (USP) XXIII 8-station (Electrolab TDT-08L) dissolution rate test apparatus with a rotating paddle stirrer at 75 rpm and 37° ± 0.5°C. A sample of solid dispersion equivalent to 15 mg of meloxicam was used in each test. Samples of dissolution fluid were withdrawn through a filter (0.45 m, Millipore Millex-HN) at different time intervals and were analyzed at 362 nm for meloxicam content using a double-beam UV-visible spectrophotometer (Cary,5000, Varian, Australia). The drug release experiments were conducted in triplicate (n = 3).

Characterization of solid dispersions by DSC

Thermogram of meloxicam, PEG 6000 and Poloxamer 188, physical mixture of drug and polymer and different batches of solid dispersions were obtained using DSC (Model No. Q10, TA Instruments Pvt. Ltd., USA). The samples were sealed in the aluminum crimp cell and heated at the speed of 10°C/min from 40°C to 300°C for meloxicam and for solid dispersion and from 40°C to 100°C for polymers in nitrogen atmosphere.

X-Ray diffraction Analysis of solid dispersions

To study the change in the structure of meloxicam from crystalline to amorphous, the samples were analyzed by powder X-ray diffractometer (X'Pert Pro PANalytical, Netherlands). The experimental conditions were as follows: tube voltage 45 kV, tube current 40 mA and scanning angle $2\theta = 5–50^{\circ}$.

Stability study

To observe the effect of storage conditions on the formulations for 3 month, stability study of optimized formulation was carried out by storing the solid dispersion in stability chamber at a condition of 40°C/75% RH. Evaluations of the stability formulations were done by: -

1. Assay of drug content in the samples followed by with the initial drug content.
2. Dissolution studies were performed after storage of one month, two month and three month. Percentage drug release from the formulations was compared with the initial formulation.

RESULTS AND DISCUSSION

Drug content

Drug content of different batches of solid dispersions was found to be between 75% - 90%

Solubility studies

The solubility of drug was found to increase with increase in the polymer (Poloxamer 188) concentration. Solid dispersions prepared by microwave assisted method showed greater solubility then the solid dispersions prepared by melting method. Solubility of pure drug and different batches of solid dispersions are shown in **figure 1.**

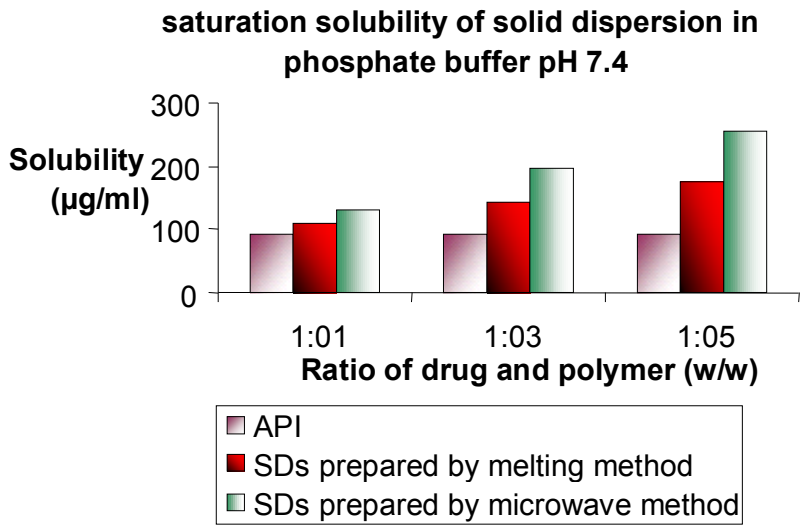

Figure 1: Saturation solubility of drug and different batches of solid dispersions

In vitro drug release study

In vitro release profile of drug and different batches of solid dispersion are shown in **figure 2.** Drug exhibited slow dissolution whereas solid dispersion showed marked enhancement in dissolution rate. Thus drug release up to about 92 % was observed from solid dispersions. Furthermore, the dissolution profile of drug from solid dispersions was found to be dependent on drug – carrier ratio. As the proportion of the carrier in solid dispersion increased, dissolution rate also increased. For all the batches maximum dissolution rate was observed for drug to carrier ratio 1:5 (SD 3 and MSD 6). Among these MSD 6 prepared by microwave assisted method exhibited maximum release as compared to SD 3.

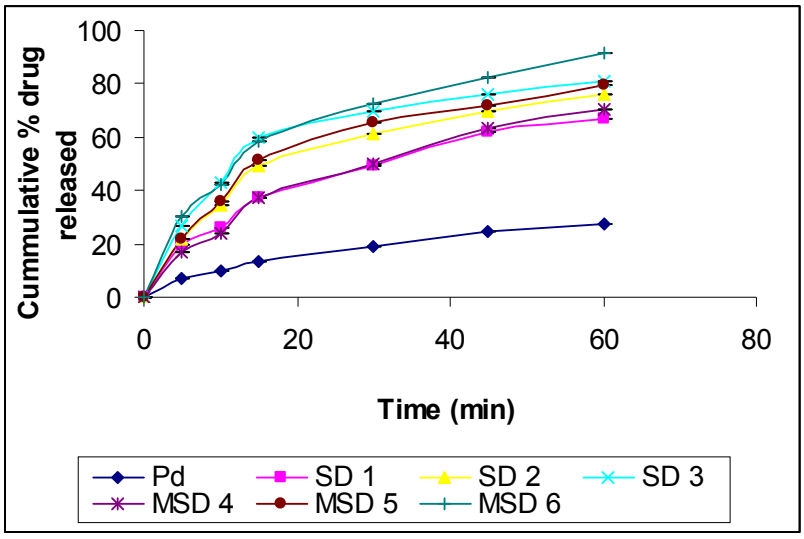

Figure 2: Comparative dissolution profiles of drug v/s different batches of solid dispersions

The data obtained from drug release studies from different batches of solid dispersion was analyzed using various mathematical models for predicting the drug release kinetics. The kinetic models used were zero order, first order, Higuchi, Korsmeyer- Peppas and hixon crowel. All batches followed Higuchi model. It revealed that release mechanism could be diffusion from a matrix system. Model fitting of data from formulations prepared by melting and microwave assisted method are summarized in **table 3**

Table 3: Drug release kinetics treatment of data obtained from formulation batches prepared by melting method and by microwave assisted method

Formul-ation code	DRUG RELEASE KINETICS MODELS				
	Zero order	First order	Higuchi	Peppas	Hixon Crowel
	R value ± S.D.	R value ± S.D.	R value ±S.D.	R value ± S.D.	R value ± S.D.
SD 1	0.947±0.628	0.498±0.016	**0.993±0.001**	0.922±0.055	0.972±0.036
SD 2	0.900±0.900	0.388±0.049	**0.972±0.02**	0.815±0.043	0.953±0.062
SD 3	0.840±0.155	0.412±0.009	**0.940±0.003**	0.841±0.008	0.926±0.095
MSD 4	0.950±0.609	0.533±0.012	**0.991±0.000**	0.917±0.007	0.977±0.023
MSD 5	0.891±0.253	0.458±0.011	**0.970±0.000**	0.875±0.008	0.952±0.062
MSD 6	0.923±0.340	0.427±0.009	**0.978±0.000**	0.888±0.076	0.961±0.051

(n = 3, data represent mean of three observations)

Differential Scanning Calorimetry

The solid state characteristics of solid dispersions were investigated using DSC to find out crystallinity of meloxicam. The DSC thermohram of meloxicam and of its solid dispersions (batch SD 3 and MSD 6) are shown in **figure 3.** Meloxicam showed endotherm at 263ºC. The thermogram of poloxamer 188 showed peak at 53.75ºC. This peak represents its melting point.

Thermograms of physical mixture and solid dispersions (batch SD 3 and MSD 6) showed absence of sharp endothermic peak of drug.

Thermograms of physical mixtures and solid dispersions demonstrated two endothermic transactions. The first sharp peak was observed very close to the melting point of polymer; whereas the second minor transaction peak of very low intensity corresponds to the melting temperature of drug. The peak gradually shifted to the lower temperature, losing its sharp and distinctive appearance.

Melting endotherm of drug was not found in the thermograms of solid dispersions. It seems that during the formation of solid dispersions, the drug changed from crystalline phase to amorphous phase. This phenomenon may be responsible for higher solubility observed with solid dispersions with respect to pure drug.

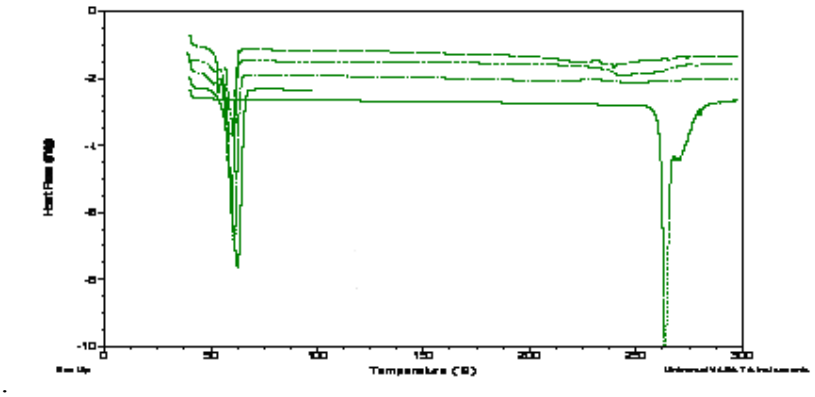

Figure 3: Comparison of thermograms of meloxicam, Poloxamer 188, Physical mixture, batch SD 3 and MSD 6

X-Ray Diffraction analysis of solid dispersions

The XRD patterns of meloxicam and different batches of solid dispersions are shown in **figure 4**. The diffraction pattern of the pure drug showed its highly crystalline nature, as indicated by the numerous distinctive peaks. The lack of numerous distinctive peaks of drug in the solid dispersions indicated that high concentration of drug was dissolved in the solid state carrier matrix in an amorphous structure. Crystallinity was determined by comparing some representative peak heights in diffraction pattern of solid dispersions with those of the reference. The relationship used for calculation of crystallinity was relative degree of crystallinity (RDC).where RDC = I_{sam}/ I_{ref}, where I_{sam} is peak height of the sample under investigation and I_{ref} is peak hight at the same angle for the reference with the highest intensity. Pure drug peak at 25.88° (2θ) was used for calculating RDC values of different batches of SDs. The RDC values of batch SD3 and MSD 6 were 0.496 and 0.447 respectively. These values suggest that meloxicam present in the solid dispersions would be mostly in amorphous state with only a few partially crystallized molecules.

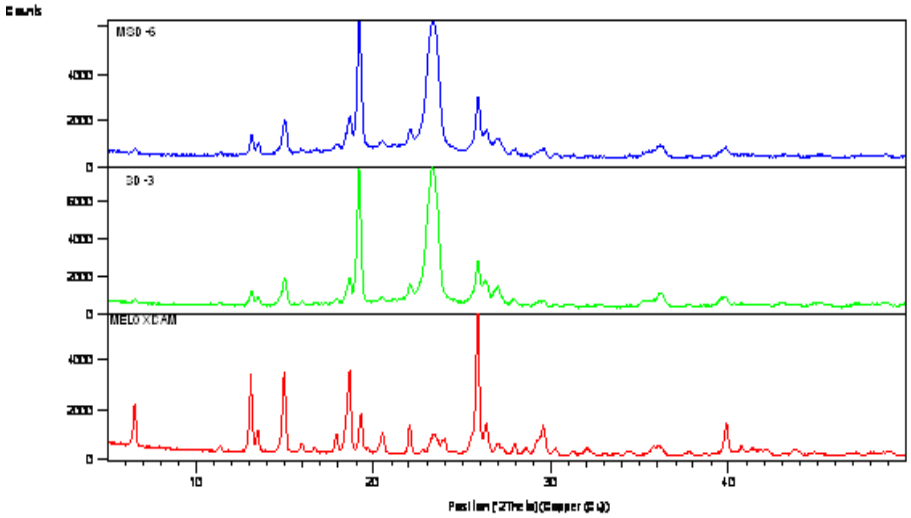

Figure 4: Comparison of XRD diffraction pattern of meloxicam, batch SD 3 and MSD 6

Stability studies

Drug Content

After 3 months of storage in the stability chamber, residual drug content of samples stored at 40ºC/75% RH was calculated and the results are shown in **table 4.** No significant changes were observed in the assay values determined by using UV-Visible spectrophotometer.

Table 4: Residual drug content of solid dispersions of meloxicam prepared by melting method & microwave assisted method stored at 40ºC/75% RH

Batch No.	Residual Drug Content (%) ± S.D.		
	After 1st month	After 2nd month	After 3rd month
SD 1	88.76 ± 0.326	88.01 ± 2.91	86.56 ± 0.359
SD 2	81.12 ± 0.085	79.91 ± 0.396	79.10 ± 0.324
SD 3	77.43 ± 4.31	76.68 ± 0.261	75.49 ± 2.39
MSD 4	86.13 ± 1.25	85.89 ± 2.91	84.17 ± 1.87
MSD 5	83.49 ± 0.329	82.21 ± 0.263	82.06 ± 2.06
MSD 6	76.12 ± 0.896	75.03 ± 0.981	73.43 ± 2.23

(n = 3, data represent mean of three observations)

Dissolution studies

The comparative dissolution profiles of the solid dispersions (batch SD 3 and MSD 6) stored for 1 to 3 months at 40°C/75 % RH. with initial samples are shown in **figure 5** and **6**.

From the above dissolution profiles of the stability samples of solid dispersions (SD 3 and MSD 6), it was observed that their dissolution profile were found to be almost similar after 3 months

stability as that of initial dissolution profiles. This indicated that the stability conditions of high temperature and high humidity i.e. 40ºC/75% R.H had not much affected the dissolution profiles.

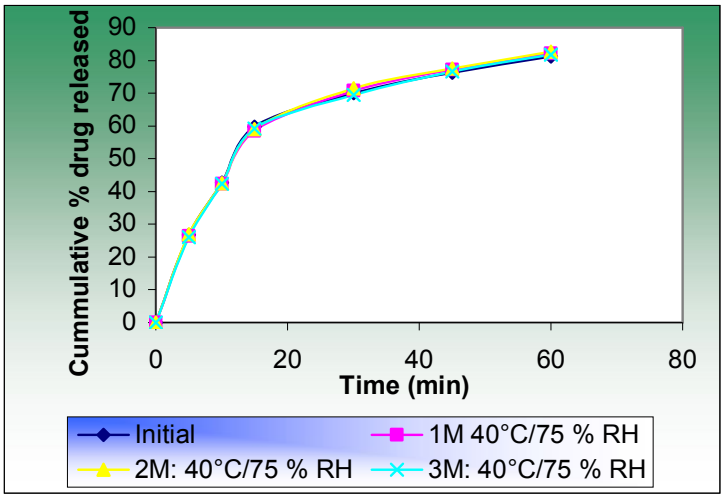

Figure 5: Comparative dissolution profiles of SD 3 (Initial v/s 1st, 2nd and 3rd month samples)

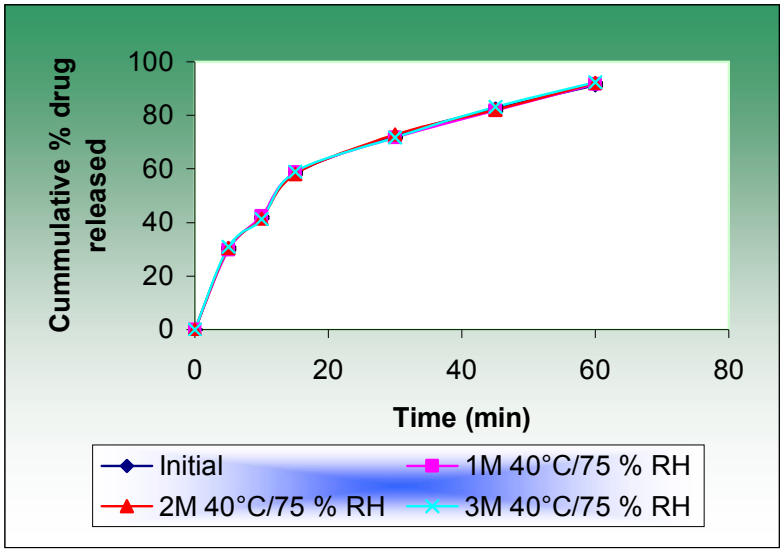

Figure 6: Comparative dissolution profiles of MSD 6 (Initial v/s 1st, 2nd and 3rd month samples)

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