International Journal of Bioengineering & Biotechnology
2018; 3(2): 14-23
http://www.openscienceonline.com/journal/ijbb

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Design and Development of Polymer Based Micro-Composite Scaffold as a Platform for Drug Delivery System

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To cite this article

Vishal Vijay Pande, Vipul Prahladbhai Patel, Sanjay R. Arote, Pramila S. Bhawar, Dhanashri Devendra Borawake, Vishal Vitthal Halnor. Design and Development of Polymer Based Micro-Composite Scaffold as a Platform for Drug Delivery System. *International Journal of Bioengineering & Biotechnology.* Vol. 3, No. 2, 2018, pp. 14-23.

Received: March 21, 2018; **Accepted**: April 2, 2018; **Published**: June 5, 2018

Abstract

Present study was taken up to develop scaffolds from biodegradable polymeric system and also to develop a new and simple method for preparation of scaffold. Number of drug delivery systems are available today but there is no ideal drug delivery system which full-fill all requirements. Hence scaffold is ideal drug delivery system which gives more advantages over conventional drug delivery systems. Scaffolds loaded with Meloxicam were prepared by using quasi emulsion solvent diffusion method using Polylactic co-glycolic acid (PLGA) and Polylactic acid (PLA) biodegradable polymer which is non toxic in nature. The synthesized scaffolds we reanalyzed for particle size, production yield, entrapment efficiency, zeta potential, Fourier transform infrared spectroscopy (FT-IR), Scanning electron microscopy (SEM), X-ray diffraction analysis (XRD), Brunauer-Emmett-Teller (BET) analysis. The FT-IR spectroscopy shows characteristics peak for pure Meloxicam and scaffold. The SEM analysis confirms porous network of scaffold. Surface area of scaffold for drug entrapment was studied by BET analysis and shows the good surface area available for drug entrapment. Entrapment efficiency of scaffold was 91.15% and practical yield was 45.37%. The in-vitro dissolution study for scaffold shows high drug release up to 90%cumulative drug release (CDR) than pure drug which show upto 50% CDR after 6 hrs thus it shows that increased in solubility and dissolution of pure Meloxicam entrapped in scaffold.

Keywords

Scaffold, Tissue Engineering, Drug Delivery System, Meloxicam

1. Introduction

Scaffolds are artificial extracellular matrices which are capable of supporting cell growth and three-dimensional tissue formation, thus being important components for tissue engineering. [1] Scaffolds are used to deliver cells, drugs and genes into the body which are either implant or inject. Different forms of polymeric scaffolds for cell and drug delivery are available such as:

a. Typical three-dimensional porous matrix
b. Nanofibrous matrix
c. Thermo sensitive sol-gel transition hydrogel
d. Porous microsphere

Scaffolds are used for drug delivery in tissue engineering as this structure is highly porous to allow tissue growth. [2] For cell attachment, cell proliferation, differentiated function and cell migration scaffold provides a suitable substrate. Biodegradable scaffolds are being investigated as a way to regenerate bone without the need for an auto or allograft to

meet the challenge of regenerating bone lost to disease or trauma. [3] Because of the poor blood circulation in the osseous defect sites a level of drugs such as antibiotics, antimicrobials, and growth factors, need to be supplied to the affected regions. In order to be effective as a drug delivery system, the carrier needs to full fill the requirements of safety, greater efficacy, predictable therapeutic response, controlled release period and prolonged release period. Several carriers have been developed to encapsulate drugs, such as biodegradable polymers (synthetic or natural) and bioactive ceramics, in the form of particulates, membranes, and porous matrix. Among those, hydroxyapatite (HA) scaffold has enhanced interest as a drug delivery carrier due to its osteoconductivity and biocompatibility. [4-7] the conventional methods of supplying a patient with pharmacologic active substances suffer from being very poorly selective, so that damage can occurs to the healthy tissues and organs, different from the intended target. In addition, high drug doses can be required to achieve the desired effect. Hence highly porous scaffold is an ideal drug delivery system. Due to excellent biocompatibility with living body and bioactivity calcium phosphate, ceramic scaffold are widely used as biomedical implant materials. [8] for the preparation of porous structures with regular porosity the technique used are particulate leaching, freeze-drying, supercritical fluid technology, thermally induced phase separation, rapid prototyping, powder compaction, sol-gel, and melt moulding. For the fabrication of porous scaffolds from advanced biomaterial for healing bone defects represents a new approach for tissue engineering in biomedical research. One of the interdisciplinary and multidisciplinary field is tissue engineering that aims at the development of biological substitutes which improve, restore or maintain tissue function. [9] Scaffold are utilized effectively as a part of different fields of tissue designing [10].

2. Materials and Method

2.1. Material

Meloxicam was obtained as a gift sample from Microlabs India, Bangalore, DMSO (Dimethyl sulphoxide) and PLGA and PLA, Tri-ethyl citrate Camphor, dichloromethane were supplied by Research-labs Fine Chemicals Industries, Mumbai.

2.2. Method

Before formulation of scaffold preformulation study was carried out for identification and confirmation of drug as well as to study drug excipients interaction

2.3. PreformulationStudy

2.3.1. Identification and Confirmation of Drug

Confirmation of drug carried out by using UV spectroscopy, Infrared Spectrophotometer (FT-IR), Differential Scanning Calorimeter (DSC) and melting point.

2.3.2. UV Spectroscopy

Meloxicam (0.01 g) was dissolve in 100 ml of pH 1.2 acid buffer, pH 6.8 buffer, pH 7.4 buffer, dimethyl sulphoxide (DMSO), distilled water, carbon tetrachloride and methanol to form stock solution of 100 µg/ml of each. Aliquots of 0.5 ml from each stock solutions representing 5 µg/ml of drug were transferred to 10 ml volumetric flask and volume was adjusted to the mark with respective solvent. The resultant dilutions then scanned by using UV spectrophotometer (Shimadzu 1650) at 400-200 nm in pH 1.2 acid buffer, pH 6.8 buffer, pH 7.4 buffer, DMSO, distilled water, carbon tetrachloride and methanol.

2.3.3. FT-IR Spectroscopy

The pure Meloxicam characterized by FT-IR spectrophotometer. The samples scanned in the spectral region between 4000-400cm^{-1}. Solid powder samples were oven dried at around 300°C. Finely crushed, mixed with the liquid paraffin oil (1:10 ratio by weight) and scanned it. The software used for the data analysis.

2.3.4. Differential Scanning Calorimetric (DSC)

The molecular state of the pure drug evaluated by performing DSC analysis. The DSC curve of the samples obtained by Differential Scanning Calorimeter (Lab mettlerstar SW 10.00). Each sample placed in aluminum pan and then crimped with aluminum cover. The heating and cooling rates were 10°C/min and all measurements performed over temperature range 40-400°C.

2.3.5. Melting Point

Melting point of drug meloxicam was determined using "Thiele's tube apparatus", few crystals of the compound were placed in a thin walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end. The capillary, which contains the sample and thermometer suspended so they heated slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point. The presence of relatively small amount of impurity detected by a lowering as well as widening in the melting point range.

2.4. Drugs-Excipients Interaction Study

2.4.1. Fourier Transform Infrared (FT- IR) Spectroscopy

IR spectroscopy used to determine the molecular interaction between drug and excipients. FT-IR spectral measurement of pure meloxicam, and polymer PLA (Polylactic acid) and PLGA (Polylactic co-glycolic acid) and physical mixture taken at ambient temperature. All the spectra acquired scanned between 400 and 4000 cm^{-1}.

2.4.2. Differential Scanning Calorimetric (DSC)

Physical mixture of drug and excipients filled in the

prewashed vial and sealed. The sealed vial kept at 37±0.5°C for 28 days in stability chamber. At the end of 28 days, vials removed from stability chamber and investigated for interaction study. In this study thermogram of drug, excipient sand physical mixtures obtained by differential scanning calorimeter (Mettler Toledo). Each sample placed in aluminum pan and then crimped with aluminum cover. The heating and cooling rates were 10°C/min and all measurements performed over temperature range 40-400°C.

Table 1. *Formula for scaffold preparation.*

Sr No	Ingredient	Quantity
1	PLA	2gm
2	PLGA	2gm
3	Tri-ethyl citrate	0.2 ml
4	Camphor	0.5%
5	SLS	1%
6	Dichloromethane	5ml
7	Water	200ml

PLA - Polylactic acid, PLGA - Polylactic co-glycolic acid, SLS - Sodium layurl sulfate

2.5. Method of Preparation of Scaffold

Scaffold was prepared by using quasi emulsification solvent diffusion method because of feasibility, ease of preparation and reproducibility of proposed method. PLGA and Meloxicamwere dissolving in dichloromethane with aid of sonication tri-ethyl citrate which acts as an plasticizer. Camphor was acts as a pore forming agent and SLS which acts as a surfactant was added in to same solution and poured in to external phase which comprises of PLA in distilled water with continuous stirring for 5 hrs for removal of organic solvent and camphor. After 5hrs the solution was filtered using filter paper and washed with water and dried in oven at 40-50°C. Drying ensures removal of remaining dichloromethane and camphor.

3. Results and Discussion

3.1. Preformultion Study of Drug

3.1.1. UV Spectroscopy

Meloxicam solution scanned at 400 nm to 200 nm, an absorbance maximum was observed at 361 nm, 356 nm, 360nm, 364, 348 nm 359 nm and 360 respectively inpH 1.2 acid buffers, phosphate buffers pH 6.8, phosphate buffer pH 7.4, dimethyl sulphoxide, distilled water, carbon tetrachloride and methanol respectively. It shows that drug is stable at every buffer solution, pH as well as constant lambda max shows that drug does not undergoes any chemical interaction or conformational changes.

3.1.2. Infrared Spectroscopy

FT-IR Spectroscopy of pure Meloxicam carried out for the confirmation of the drug. The principal peaks corresponds to the structural features of meloxicam are found due to presence of C-H stretch at 1465 cm^{-1}, carbonyl C=O stretchat 1725 cm^{-1}, O-H stretch at 3200 cm^{-1}, C=C stretch at 1650 cm^{-1}, C-SO-O stretch at 1225 cm^{-1} and C-S stretch at 715 cm^{-1}, N-H stretching at 3700 cm^{-1}, Ar-H stretching at 3100 cm^{-1}, S-H stretching at 2700 cm^{-1}, C=N stretching at 1660 cm^{-1}

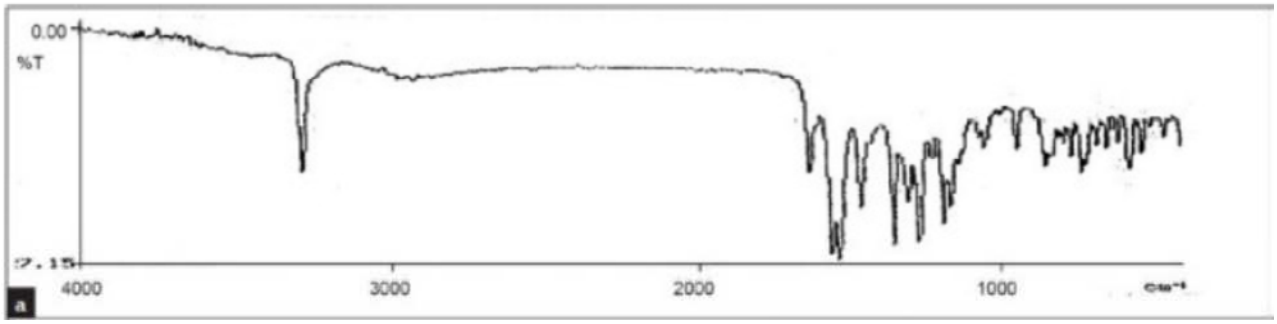

Figure 1. *IR spectra of pure mlx (Meloxicam).*

3.1.3. Differential Scanning Calorimetry (DSC)

The melting point of meloxicam detected at scan rate of 10°C/min.

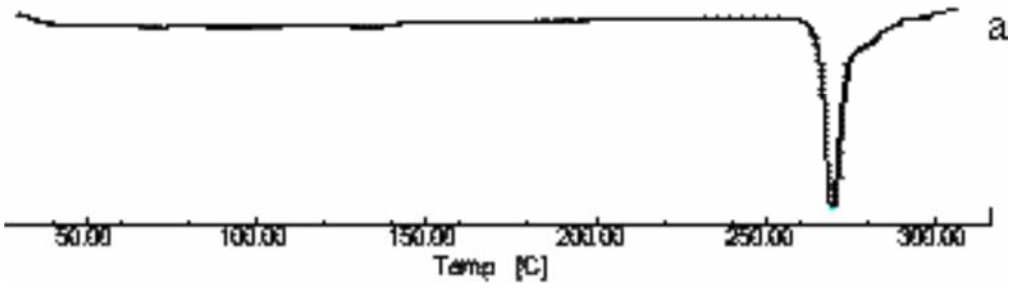

Figure 2. *DSC thermogram of Meloxicam.*

The DSC thermogram meloxicam was shows that, a sharp endothermic peak at 278.78°C corresponding to its melting and decomposition. Reported peak temperature was 265-301°C.

3.1.4. Melting Point

Melting point of drug determined by capillary method, it was 253°C where as reported melting point for Meloxicam is 254-256°C. It indicates that Meloxicam is in pure form.

3.2. Drug-Excipient Interaction Study

3.2.1. Fourier Transforms Infrared (FT-IR) Spectroscopy

Drug- excipients checked using FT-IR spectrophotometer. The IR spectra of Meloxicam and physical mixture given in follows displayed the peaks for functional groups.

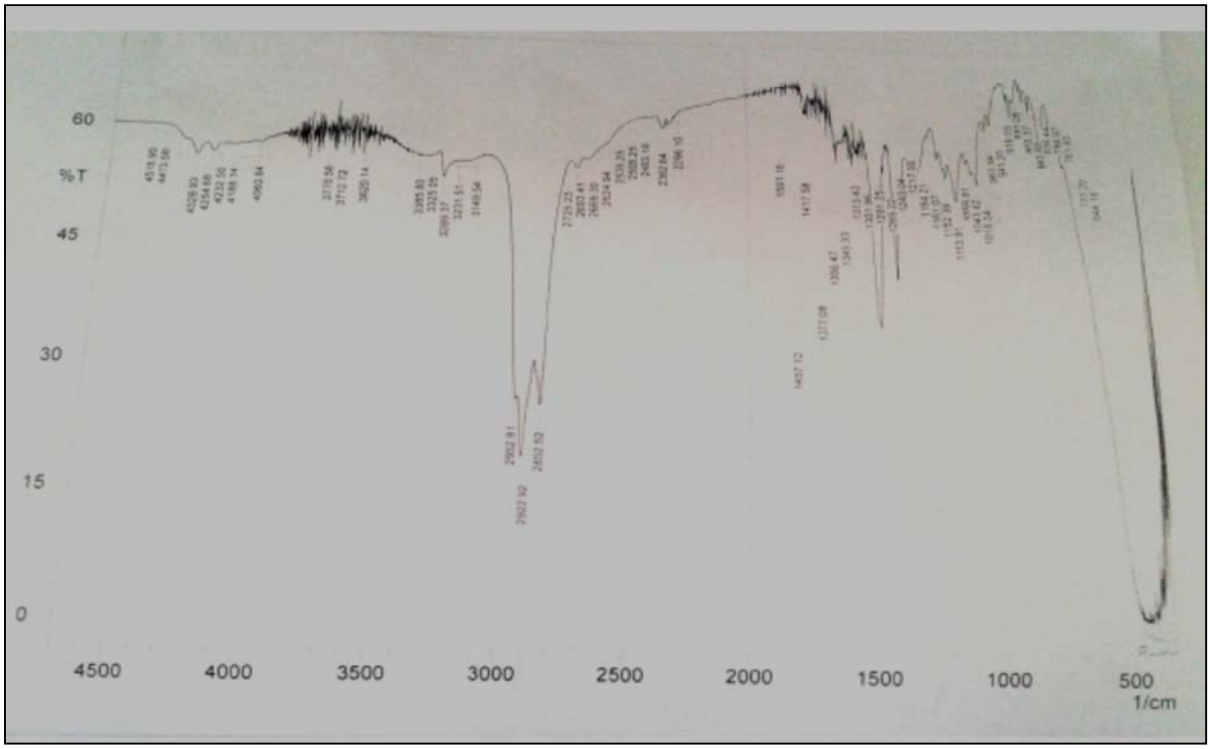

Figure 3. *IR spectra of physical mixture (Meloxicam + Polylactic co-glycolic acid and Polylactic acid).*

There is no significant change in absorbance band hence drug polymer are compatible with each other. FT-IR Spectroscopy of pure Meloxicam carried out for the confirmation of the drug. The principal peaks corresponds to the structural features of meloxicam are found due to presence of C-H stretching at 1465 cm^{-1}, carbonyl C=O stretchingat 1725 cm^{-1}, O-H stretching at 3200 cm^{-1}, C=C stretching at 1650 cm^{-1}, C-SO-O stretching at 1225 cm^{-1} and C-S stretching at 694 cm^{-1}, N-H stretching at 3717 cm^{-1}, Ar-H stretching at 3100 cm^{-1}, S-H stretching at 2700 cm^{-1}, C=N stretching at 1660 cm.

3.2.2. Differential Scanning Calorimetry (DSC)

The melting point of Meloxicam and mixtureMeloxicam plusExcipients detected by differential scanning calorimetry at heating rate of 20°C/min. The DSC of A. Meloxicam gives sharp endothermic peak at 256°C gives purity of drug. The DSC of B: Physical mixture containing Meloxicam and PLA and PLGA gives lower shift of peaks means drug was present in mixture without any incompatibility with other excipients.

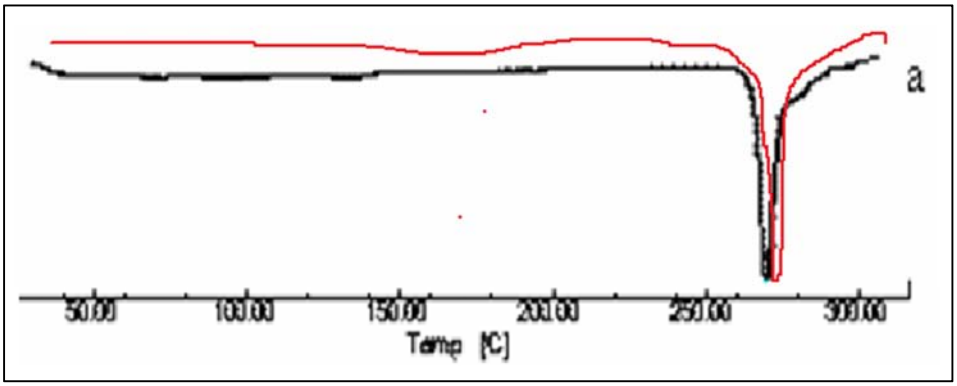

Figure 4. *Differential scanning calorimetry spectra of pure drug and scaffold.*

3.3. Characterization and Evaluation of the Formulation (Scaffold)

3.3.1. Particle Size Analysis

The average particle size of scaffold as shown

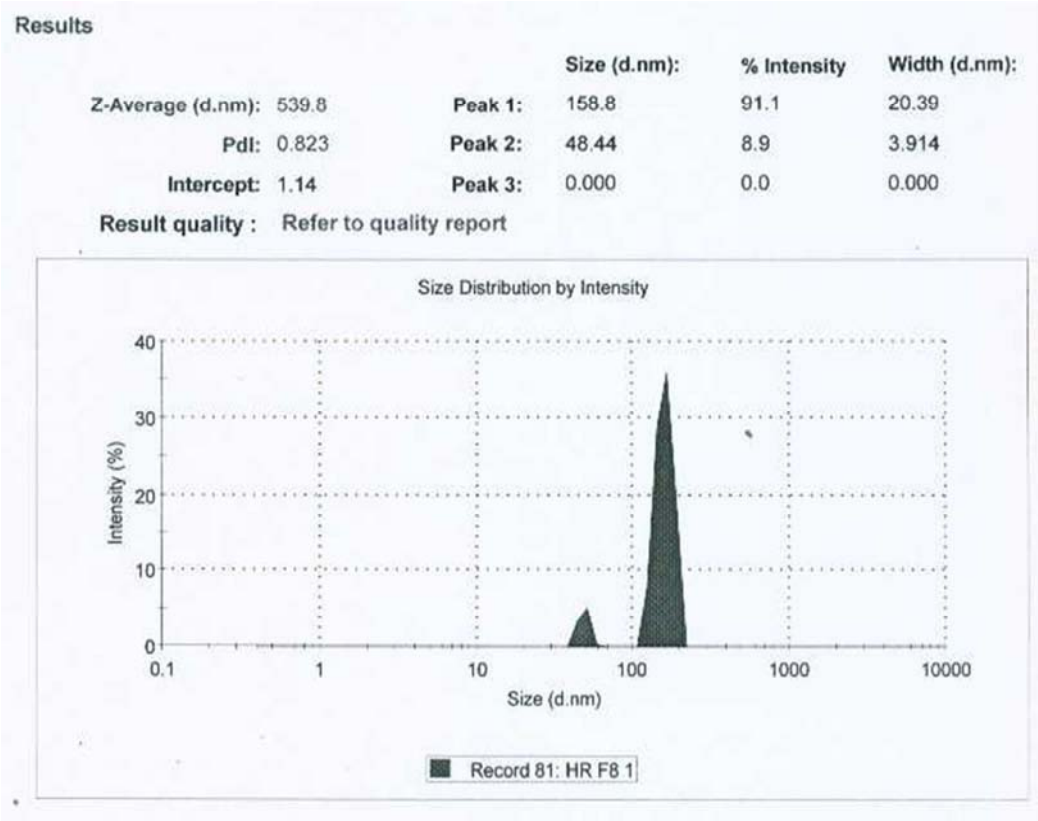

Figure 5. *Particle size of scaffold.*

Scaffold shows particle size 539.8 nm is in micro-meter range.

3.3.2. Zeta Potential (Particle Charge Distribution)

The zeta potential of ideal drug delivery system is in between -8 to -30 mv. And optimized scaffold formulation shows zeta potential -10.4 mv hence these drug delivery system was stable drug delivery system. And suitable for meloxicam delivery.

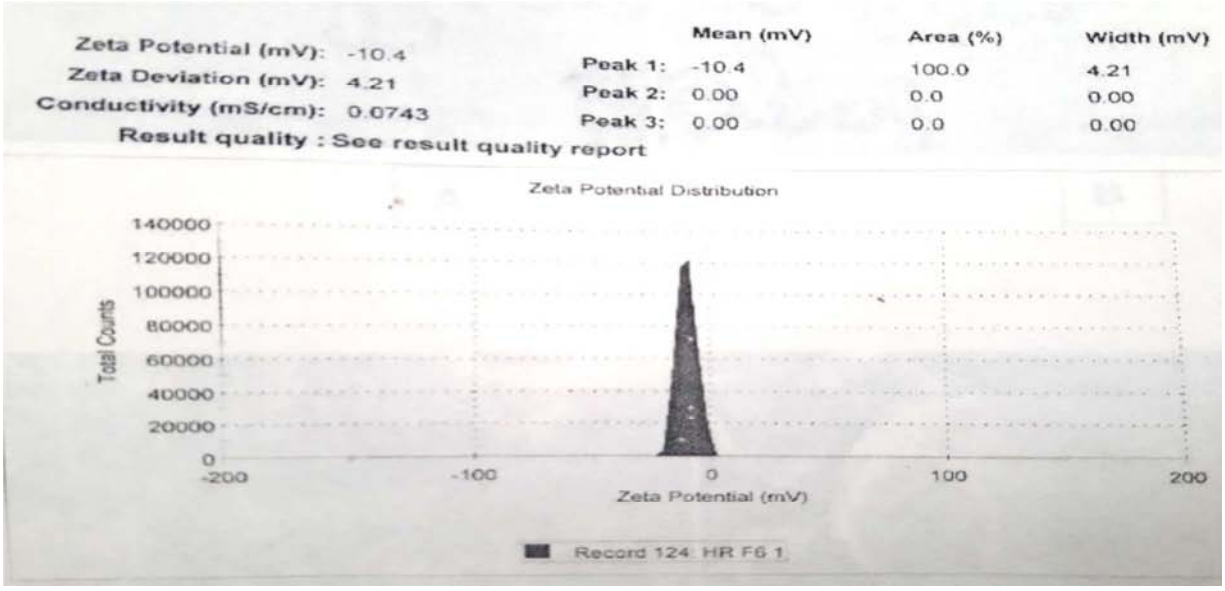

Figure 6. *Zeta potential of scaffold.*

3.3.3. Scanning Electron Microscopy

This Scanning Electron Microscopy carried out to study the surface morphology of particles. It found scaffold revealed a highly porous surface. The SEM picture of plane scaffold shows porous structure of scaffold hence it is very suitable for drug loading and drug delivery. Scaffold having high drug loading efficiency because of porous structure.

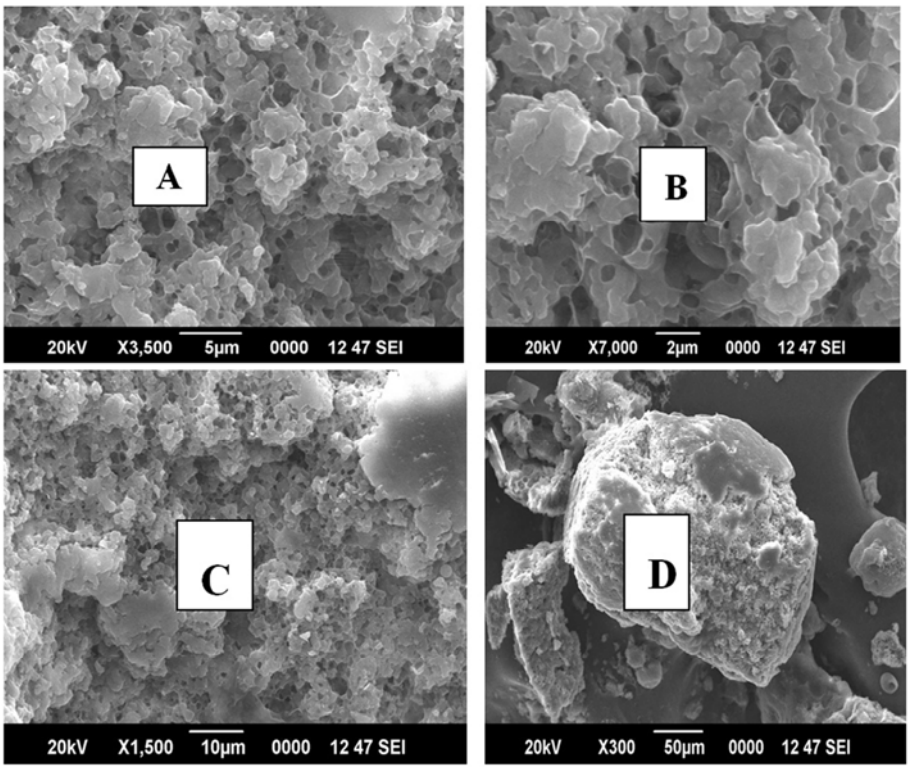

Figure 7. *SEM images of scaffold A) 5µm B) 2µm, C) 10µm, D) 50µm.*

3.3.4. BET Analysis of Scaffold

The BET surface area of scaffold was found to be 2.7875m^2/gm. It is significant for loading of drug into the scaffold.

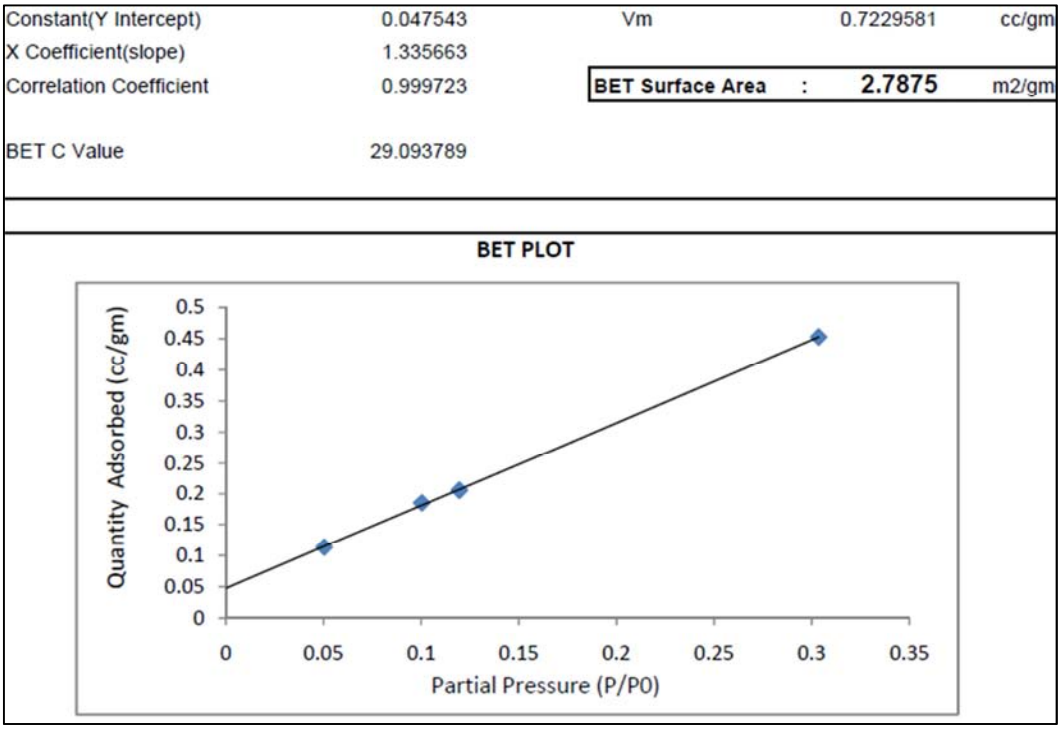

Figure 8. *BET surface area analysis.*

3.3.5. X Ray Diffraction Analysis (XRD)

X ray diffraction study for plane scaffold and scaffold loaded with meloxicam was studied. Plane scaffold shows broad peak in the range of 10-30°. And the scaffold loaded with meloxicam shows the similar peak broadning in the given range with slight sharp peak for meloxicam present on surface. There is no significant change in XRD pattern of plane scaffold and drug loaded scaffold. Hence from these we can conclude that there is no drug interaction observed in a formulation.

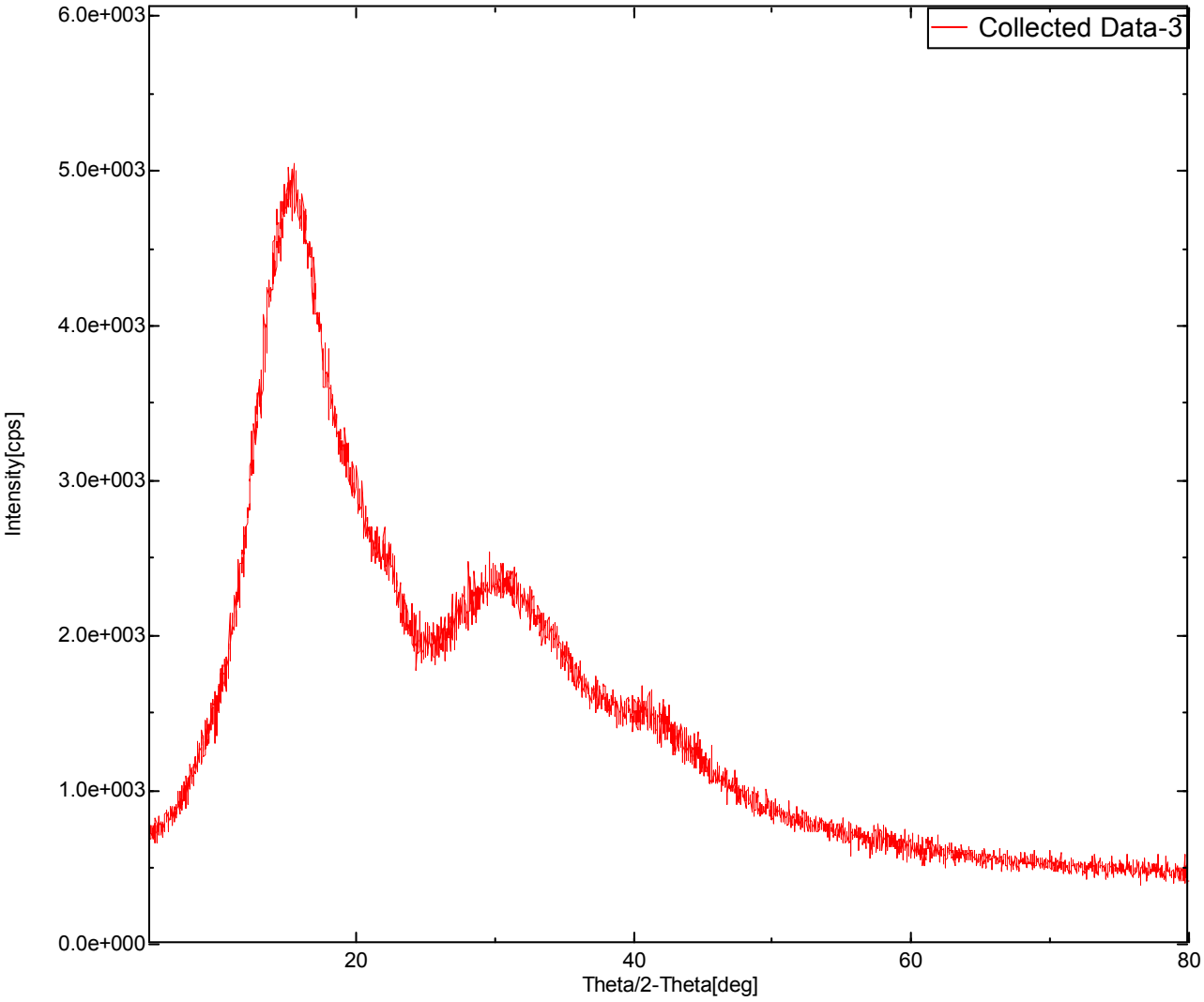

Figure 9. *XRDimage of drug loaded scaffold.*

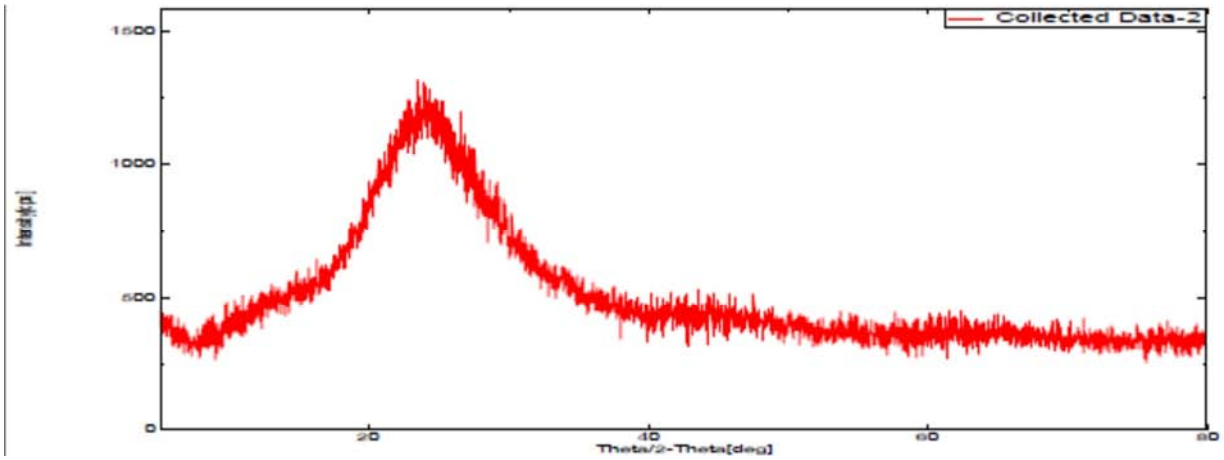

Figure 10. *XRD image of plain scaffold.*

3.3.6. Fourier Transform Infrared Spectroscopy (FT-IR)

The IR spectrum of scaffold formulation show peak for O-H stretching, N-H stretching, C=O stretching, C-SO-S stratching, C==C stretching, S-H stretching, Ar-h, stretching, C=N Stretching, C=S stretching, C-H bending at 3178cm^{-1}, 3734 cm^{-1}, 1730 cm^{-1}, 1217 cm^{-1}, 1647 cm^{-1}, 2725 cm^{-1}, 3134 cm^{-1}, 1669 cm^{-1}, 793 cm^{-1}, 1456 cm^{-1} respectively. There is no significant change in peak intensity of functional group in scaffold and in pure Meloxicam. Hence drug and excipients are compatible with each other and does not show any drug interaction.

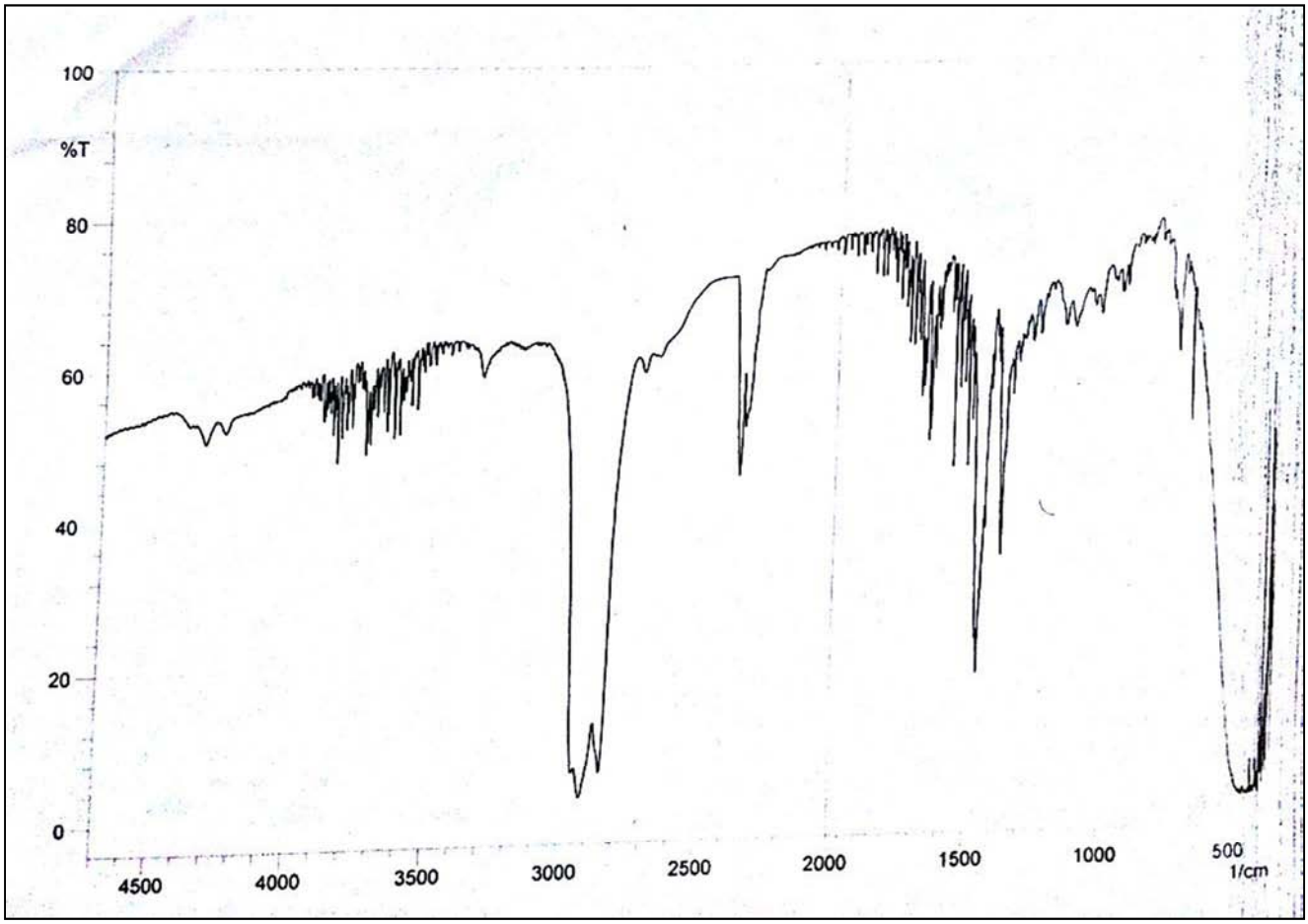

Figure 11. *IR spectra of scaffold.*

3.3.7. Differential Scanning Calorimetry

DSC study of pure drug meloxicam and scaffold was studied pure drug shows endothermic peak at 260°which shows pure drug presence. Scaffold also shows the endothermic peak at 262°. There is no significant change in both DSC spectra hence no significant interaction occurs in scaffold preparation.

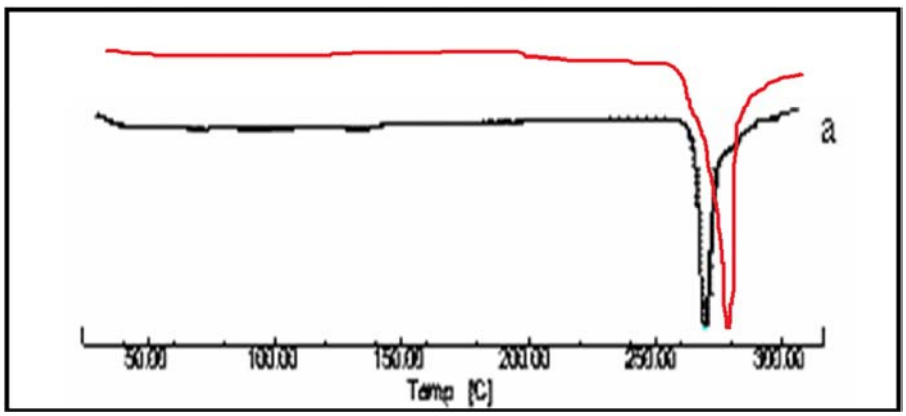

Figure 12. *DSC spectra of pure meloxicam and scaffold.*

3.3.8. Production Yield

Production yield of scaffold was determined by calculating initial weight of raw material materials and the last weight of scaffold obtained. Production yield obtained was 45.37%

$$\text{percentageyield} = \frac{\text{practicalmassofscaffold}}{\text{theoroticalmass (polymer + drug)}} \text{X100}$$

3.3.9. Entrapment Efficiency

Obtained Entrapment efficiency was 91.15% by using following formula

$$\text{Entrapment efficiency} = \frac{\text{actual drug content in scaffold}}{\text{theorotical drug contents}} \text{X } 100$$

3.3.10. Saturated Solubility

The Noyes Whitney equation described the dependency of the saturation solubility in comparing the solubility of two particles with different radius. As the particle size decreases, it improves the saturation solubility. However, if Ostwald ripening or aggregation appeared, the radius would increase and the solubility would adversely affect. The solubility of pure drug found to be 0.1568 mg/mL in aqueous and it was significantly increased in scaffold to 1.9 mg /ml Therefore, it was hypothesized that decreasing the particle size to increase the surface area for dissolution and thereby increase the bioavailability of Meloxicam. It is shown in following table.

Table 2. *Saturation solubility study of pure drug meloxicam and scaffold in mg/ml.*

Sr. no	Solvent	Pure MLX (mg/ml)	Drug loaded scaffold (mg/ml)
1	Water	0.1568	1.900
2	PH 1.2	0.189	0.23
3	PH 6.8	0.57	1.49
4	PH 7.4	0.7	0.98
5	CCL4	2.43	3.56
6	Methanol	4.89	7.89
7.	DMSO	21.45	30.82

MLX - Meloxicam, DMSO - Dimethyl sulphoxide, CCL4- Carbon tetra chloride

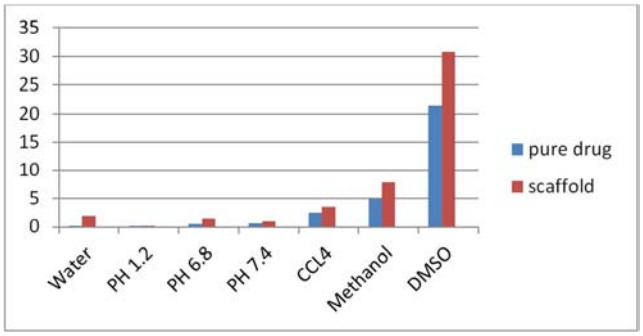

Figure 13. *Saturation solubility of pure mlx and scaffold loaded with mlx.*

3.3.11. In-vitroDissolution Study

In-vitro dissolution study was carried out using paddle type dissolution test apparatus. Test results show dissolution study of pure drug meloxicam and scaffold loaded with meloxicam pure meloxicam shows less drug release up to 4-5 hrs. But when dissolution study for scaffold was taken it shows high drug release than pure drug which is responsible for increasing solubility and dissolution of pure scaffold. The graph for the comparison in-vitro percent release profile of pure drug Meloxicam with scaffold shown in figure.

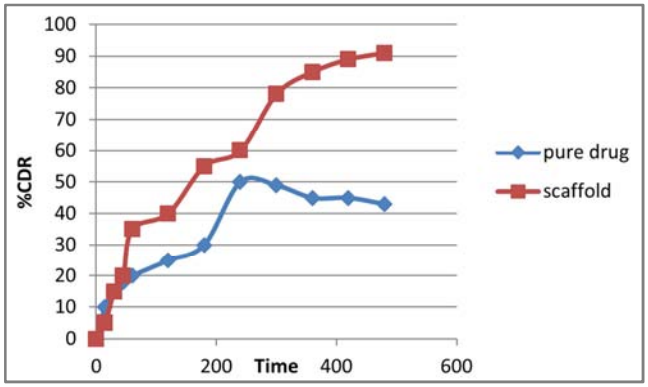

Figure 14. *%CDR of pure meloxicam and mlx scaffold.*

It shows that there is less dissolution of pure Meloxicam after 5-6hrs but scaffold shows high dissolution. The hydrophobic property of the drug prevented its contact with the dissolution medium causing it to float on the surface, and consequently hindering its dissolution. In all the cases, percent release scaffold was much greater than pure Meloxicam.

4. Conclusion

In the present study attempt was made to synthesize a polymer based micro-composite for the delivery of meloxicam as a corgo. The dissolution study of scaffold shows high drug release than pure drug which is responsible for increasing solubility and dissolution of pure scaffold. Solubility of pure drug found to be 0.1568 mg/mL in aqueous and it was significantly increased in scaffold to 1.9 mg /ml. Surface area of scaffold was found to be 2.7875m^2/gm. scaffold shows particle size 539.8 nm is in micro-meter range.

Conflict of Interest

There is no any conflict of interest.

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