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Valuing Best Poloxamer Carrier for Meloxicam Solid Dispersions by novel microwave fusion: Designing and Characterization

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Abstract

Present research activity is to establish the best Poloxamer carriers for making solid dispersions (SD) with Meloxicam. The main aim of this investigation is to find the best among the better Poloxamer carriers viz., Poloxamer-108, Poloxamer-188, Poloxamer-237, Poloxamer-338 and Poloxamer-407 for making SD by novel microwave fusion technique. Four portions of Meloxicam: Poloxamer in various ratios (1:1, 1:2, 1:4 and 1:6) are used for making SD by microwave fusion technique later compressed using 8 station tablet compression machine. The SD and tablet formulations are evaluated for physicochemical characterization. All the prepared batches found to have satisfactory specifications as per pharmacopoeia. The authors concluded that Poloxamer-188 is found to be the best carrier among the Poloxamer carriers used for making Meloxicam SD.

Keywords: Meloxicam, Poloxamer, microwave, solid dispersions, tablets

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1. INTRODUCTION

The researchers made many attempts to elevate the solubility of a range of low soluble drugs. The poor water solubility has a negative impact by obstructing the absorption of the drug from the gut. As dissolution has a direct impact on the bioavailability of drugs, inadequate and variable bioavailability. Drug solubility enhancement of orally given drugs and expecting bioavailability of poorly water-soluble drugs stands first preference in dosage form development.

Amongst the various approaches for enhancing low solubility drugs, solid dispersion (SD) technique is gaining the attraction for its simple and economical strategy [1-3]. Meloxicam (MXM) is of BCS class II, non-steroidal anti-inflammatory drug (NSAID) used to relieve patients with pain and inflammation[4].

The traditional heating method for making SD does not give a uniform distribution of heat and it may provide uneven temperature for melting. But, the electromagnetic irradiation produced in the microwave oven stretches prompt and undeviating heating for polymers with low heat conductivity[5-7]. So, a microwave oven is used to melt the SD blend.

Amar et al., 2017, succeeded in hiking the solubility of MXM using Poloxamer 188 by melting technique[8]. Amina et al., 2014 prepared MXM SDs using Poloxamer-407 by solvent evaporation method and achieved enhancement in MXM release[9]. Mowafaq et al, 2009, also made attempts in elevating the solubility of MXM using Poloxamer 188 using the kneading method[10]. Zahra et al., 2017 made successful attempts in increasing the solubility of MXM using Poloxamer 188 by direct compression method[11].

This research work is aimed to multiply the solubility of MXM by making SD using Poloxamer carriers i.e., Poloxamer- 108 [12], Poloxamer- 188 [13], Poloxamer- 237 [14], Poloxamer- 338 [15] and Poloxamer- 407 [16] and finding out the best Poloxamer among them as a solubility increasing carrier.

The authors made an extensive search in literature and revealed that no attempts have made in hiking the solubility of MXM by microwave melting technique. So, an attempt has made too so.

2. MATERIALS AND METHODS

Meloxicam (MXM) was requested from Zydus Cadila, Ahmedabad, India. Poloxamer- 108, Poloxamer- 188, Poloxamer- 237, Poloxamer- 338 and Poloxamer- 407, Microcrystalline Cellulose, Talc, and Magnesium stearate were gained from SD Fine Chemicals, Mumbai, India, and double distilled water was utilized when anticipated.

2.1 Solubility studies

MXM pure drug was assessed for solubility in 0.1N HCl, water, pH 4.5 Acetate buffer, pH 6.8 and pH 7.4 Phosphate buffers[17].

2.2 Drug-Excipient compatibility studies

The DSC and FTIR studies were performed to assess the interface among the MXM and carriers used in the study.

2.2.1 Differential Scanning Calorimetry (DSC)

Pure MXM and 1:1 ratio of MXM: Poloxamer carriers were exposed to the analysis which is scanned at a range of 50-300°C (DSC-50, Shimadzu, Japan).

2.2.2 Fourier-Transform Infrared (FTIR) spectroscopic study

The interactions of MXM with SD blend were studied by FTIR spectroscopy. The FTIR spectra of the MXM alone and in combination with carriers were recorded using an FTIR spectrometer (Bruker) by scanning at 4000-400 cm^{-1} range.

2.3 Fabricating Solid Dispersions

MXM SD was made using a microwave oven. Various portions of MXM and Poloxamer were taken (Table 1) into a glass beaker and kept in a microwave oven (model no. CATA- 3T, Mumbai, India). Only one beaker was kept at a time for a fusion in the microwave oven. The blend was wide-open to microwave energy for 10 min, later the mixture was maintained at room temperature to solidify. The SD so formed

were took and kept in a glass desiccator for 24 h, afterword powdered in a mortar and pestle and passed through an 80# sieve. The various formulations of MXM SD represented in table 1.

Table 1. Drug (MXM): Carrier (Poloxamer) ratios in various formulations

Drug: Carrier	Ratio	Formulation Code
MXM: Poloxamer 108	1:1	MP108-1
	1:2	MP108-2
	1:4	MP108-3
	1:6	MP108-4
MXM: Poloxamer 188	1:1	MP188-1
	1:2	MP188-2
	1:4	MP188-3
	1:6	MP188-4
MXM: Poloxamer 237	1:1	MP237-1
	1:2	MP237-2
	1:4	MP237-3
	1:6	MP237-4
MXM: Poloxamer 338	1:1	MP338-1
	1:2	MP338-2
	1:4	MP338-3
	1:6	MP338-4
MXM: Poloxamer 407	1:1	MP407-1
	1:2	MP407-2
	1:4	MP407-3
	1:6	MP407-4

2.4 Evaluation of solid dispersions

The given constraints were tested for MXM SD

2.4.1 Flow properties

The SD were assessed for flow properties[18-20] viz., angle of repose, true and tapped densities, Carr's Index, Hausner's ratio.

2.4.2 Percent yield

The % retrieval of SD was stanch after comprehensive amputation of dampness. So, % retrieval scheming comprises the weight of dehydrated SD to some of the weight of drug in the preparation[21].

$$\% \text{ Yield} = \frac{\text{Actual weight of the SD}}{\text{Total weight of drug and excipients}} \text{X}100$$

2.4.3 Preparation of tablets

The SD equivalent to MXM was prepared by direct compression[22] into tablet dosage form, after mingling with essential quantities of various contents (table 2) by using 8 station tablet compression machine (Karnavati Engineering, Ahmedabad, India).

Table 2. Formulation of SD tablets

Ingredients	Quantity per tablet
SD equivalent to MXM	125
Lactose	50
Starch	15
Micro Crystalline Cellulose	50
Magnesium stearate	5
Talc	5
The weight of the tablets	250

2.5 Evaluation of SD Tablets

2.5.1 Morphological characteristics

In this study, tablets were verified for size and shape.

2.5.2 Thickness

Tablets were examined for its thickness using vernier Caliper (Qumos Enterprises, Mumbai, India). These trials were made in triplicates.

2.5.3 Hardness

The force obligatory to disruption the tablets were noted by Pfizer tablet hardness tester (Pfizer, Mumbai, India). These tests were performed in triplicates.

2.5.4 Uniformity in weight

20 tablets from each batch weighed separately with an electronic digital balance (Citizen, CY-104, Mumbai, India) for mean weight and equated with the singular tablet weights. The % weight alteration was interpreted with IP specifications (Limit ± 7.5% of average weight).

2.5.5 Friability

This was executed with Roche Friabilator. 10 tablets pre weighed ($W_{initial}$) and moved into a friabilator, run at 25 rpm for 4 min and post weight (W_{final}) was dogged. The loss on friability was revealed by the equation[23].

$$F = \frac{\text{W initial} - \text{W final}}{\text{Winitial}} \text{X100}$$

2.5.6 Uniformity of drug content

Randomly 5 tablets were selected, crushed and powder having 15 mg of MXM was dissolved in 10 mL of Methanol and volume was made to 100 mL with pH 6.8 buffer. The solution was clarified, and from this 1 mL was taken and capacity prepared to 100 mL with phosphate buffer (pH 6.8). The MXM was dogged spectrophotometrically at 362 nm using UV- spectrophotometer. The same procedure was adopted for all the prepared tablets [24].

2.5.7 Meloxicam calibration curve

The process of finding MXM by UV spectrophotometer at 362 nm was standardized and MXM obeyed Beer-Lambert's law in 2-10 µg/mL concentration[25].

2.5.8 Dissolution RATE/In-Vitro drug release

The dissolution specifications were as below[26]

- Unit speed: USP XXIII dissolution test apparatus
- Dissolution medium and volume: 0.1M HCl and 900 mL
- Temperature: 37±0.5°C
- Paddle rpm: 50
- Sampling breaks and volume: 5 min and 10mL
- Absorbance measured at 362 nm

2.6 Kinetic modelling of drug release

The contrivance of the drug discharge was analysed and rate kinetics[27, 28] of the dosage form was obtained with the formulae shown in table 3.

Table 3. Kinetic models and their corresponding formula

Model	Formula
Zero-order	Cumulative % drug released Vs. Time
First order	Log cumulative % drug remaining Vs. Time
Hixson Crowell's	$\sqrt[3]{\text{Drug remaining}}$ Vs. time

3. RESULTS AND DISCUSSIONS

3.1 Drug-Excipient compatibility

The characteristic endothermic peak of formulations, corresponding to MXM was broadened and shifted toward lower temperature, indicating the distribution of a drug in a carrier is uniform indicating complete miscibility of the MXM in Poloxamer (Fig.1).

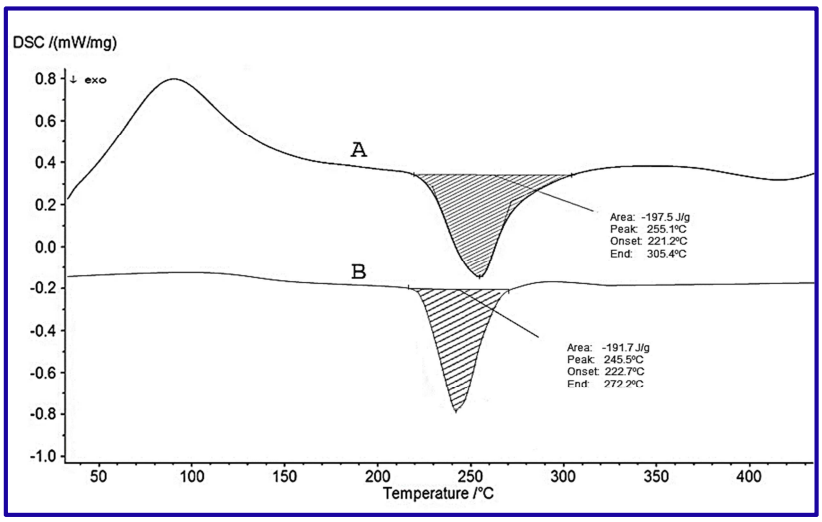

Fig.1: DSC thermograms of MXM and Poloxamer bases

The FTIR spectra indicate no change in the position of the absorption bands spectra of MXM and its combination with carrier mixture. The FTIR spectrum of MXM was the superposition of drug and carrier (Fig.2).

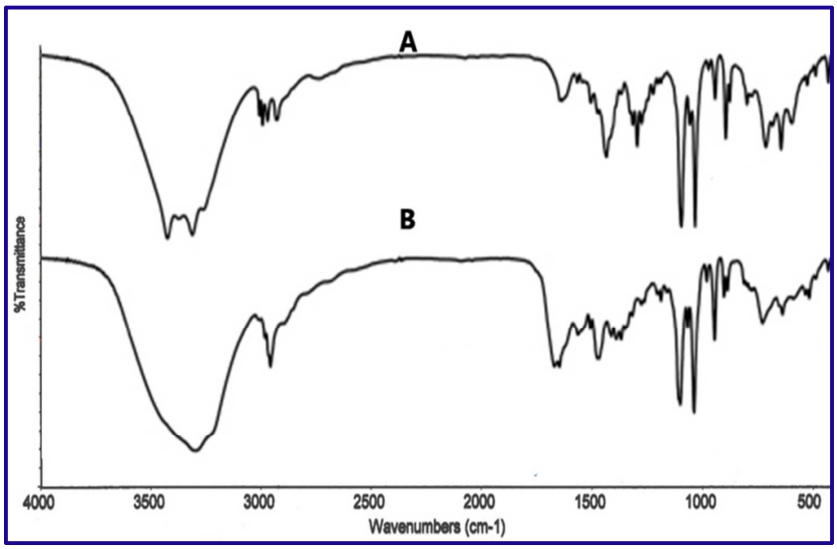

Fig.2: FTIR spectrum of MXM with Poloxamer

3.2 Flow properties

The fabricated MXM SD showed very good flow properties as the angle of repose ranged from 24.20±0.14 to 31.78±0.15^{o}). The compressibility Index was between 2.13±0.02 to 9.27±0.05, indicating good compression properties while tableting. Additionally, the Hausner's ratio was less than 1.25 indicating very good flow of SD. The flow of fabricated MXM SD were revealed in table 4.

Table 4. Flow parameters

Formulation	Flow properties				
	Angle of repose (^{0})	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
MP108-1	24.20±0.14	0.409±0.04	0.451±0.14	9.31±0.01	1.10
MP108-2	25.39±0.07	0.405±0.15	0.419±0.14	3.34±0.02	1.03
MP108-3	31.78±0.15	0.377±0.21	0.403±0.14	6.45±0.01	1.06
MP108-4	28.98±0.01	0.393±0.10	0.428±0.14	8.17±0.02	1.08
MP188-1	26.34±0.01	0.401±0.01	0.442±0.14	9.27±0.05	1.10
MP188-2	25.45±0.09	0.490±0.05	0.531±0.14	7.72±0.04	1.08
MP188-3	29.28±0.11	0.524±0.09	0.548±0.14	4.37±0.01	1.04
MP188-4	27.95±0.12	0.458±0.07	0.468±0.14	2.13±0.02	1.02
MP237-1	30.28±0.04	0.298±0.10	0.323±0.14	7.73±0.03	1.08
MP237-2	28.27±0.06	0.458±0.11	0.474±0.14	3.37±0.01	1.03
MP237-3	29.84±0.09	0.395±0.18	0.425±0.14	7.05±0.02	1.07
MP237-4	25.07±0.07	0.451±0.19	0.489±0.14	7.77±0.01	1.08
MP338-1	26.05±0.10	0.511±0.07	0.544±0.14	6.06±0.07	1.06
MP338-2	26.01±0.09	0.478±0.06	0.498±0.14	4.01±0.02	1.04
MP338-3	24.84±0.04	0.454±0.03	0.489±0.14	7.15±0.02	1.07
MP338-4	30.51±0.14	0.569±0.08	0.584±0.14	2.56±0.05	1.02
MP407-1	30.54±0.06	0.385±0.09	0.401±0.14	3.99±0.06	1.04
MP407-2	28.45±0.02	0.396±0.02	0.428±0.14	7.47±0.04	1.08
MP407-3	29.35±0.04	0.474±0.03	0.501±0.14	5.38±0.03	1.05
MP407-4	27.97±0.05	0.465±0.08	0.487±0.14	4.51±0.05	1.04

Values in mean ±SD; Trials (n=3)

3.3 Post compression parameters

The prepared MXM tablets were observed to have a uniform in size, shape, off white in colour, odorless with the smooth surface. The thickness of prepared formulations, uniformity of weight, hardness, friability, percent yield and drug content uniformity (see Table 5). The weight loss on friability (< 1%) and the hardness (>4 Kg/cm^2) represents that the tablets have acceptable mechanical forte. The yield was found to good (>90%) and the drug content was also found to be uniform. These values listed in Table 5.

Table 5. Physical Characteristics of SD

Formulation	Physical parameter					
	Uniformity of weight (mg)	Hardness (cm^2)	Thickness (mm)	Friability (%)	Yield (%)	Assay (%)
MP108-1	255.0±3.25	8.5±0.15	4.59±0.03	0.47±0.01	98.9±2.25	97.8±2.36
MP108-2	255.1±1.84	5.2±0.12	4.53±0.08	0.61±0.05	98.5±2.15	96.6±1.25
MP108-3	252.9±5.26	5.5±0.09	4.58±0.04	0.52±0.01	98.7±0.84	98.2±4.15
MP108-4	254.2±1.08	5.6±0.08	4.53±0.07	0.06±0.02	95.5±2.11	96.5±2.21
MP188-1	254.5±0.94	6.5±0.16	4.52±0.08	0.59±0.01	96.8±0.31	98.2±0.95
MP188-2	252.5±1.25	5.3±0.13	4.51±0.01	0.25±0.04	95.8±3.26	96.8±1.22
MP188-3	252.2±2.25	5.7±0.09	4.50±0.09	0.18±0.02	98.6±4.84	97.2±4.15
MP188-4	252.7±3.26	5.2±0.08	4.50±0.06	0.02±0.01	96.5±0.11	97.7±2.21
MP237-1	252.8±5.26	6.5±0.11	4.52±0.05	0.21±0.07	96.6±2.31	97.9±2.25
MP237-2	254.2±8.25	8.3±0.21	4.53±0.02	0.24±0.05	97.8±2.35	99.5±0.68
MP237-3	254.7±9.65	7.5±0.09	4.50±0.05	0.59±0.01	98.6±4.25	98.5±3.25
MP237-4	252.3±4.57	5.9±0.08	4.52±0.03	0.09±0.02	94.7±2.36	99.5±2.68
MP338-1	251.8±2.65	6.7±0.14	4.53±0.02	0.52±0.05	98.5±1.05	98.3±1.27
MP338-2	252.2±3.26	5.8±0.08	4.52±0.09	0.28±0.02	95.6±2.36	97.5±2.15
MP338-3	251.9±5.41	7.6±0.07	4.51±0.04	0.56±0.03	92.8±0.11	97.2±2.21
MP338-4	252.3±8.54	5.2±0.03	4.50±0.05	0.17±0.07	98.6±1.84	97.8±3.25
MP407-1	253.6±7.84	6.5±0.09	4.50±0.01	0.50±0.05	90.5±0.11	99.5±2.68
MP407-2	252.4±1.52	8.7±0.07	4.52±0.07	0.45±0.02	96.6±0.31	98.3±1.84
MP407-3	252.5±2.55	4.9±0.08	4.53±0.09	0.58±0.01	95.8±1.25	96.5±1.28
MP407-4	254.8±0.62	6.2±0.09	4.52±0.11	0.59±0.02	98.6±0.61	98.2±0.59

Values in mean ±SD; Trials (n=3)

3.4 Solubility studies

The solubility of MXM SD was found to be increased contrast to pure MXM drug in all solubility media. Among the solvents used the SD tablets found to have good solubility in 0.1M HCl. The solubility of tablets was appreciated in distilled water and 0.1N HCl (see fig.3, 4 and 5).

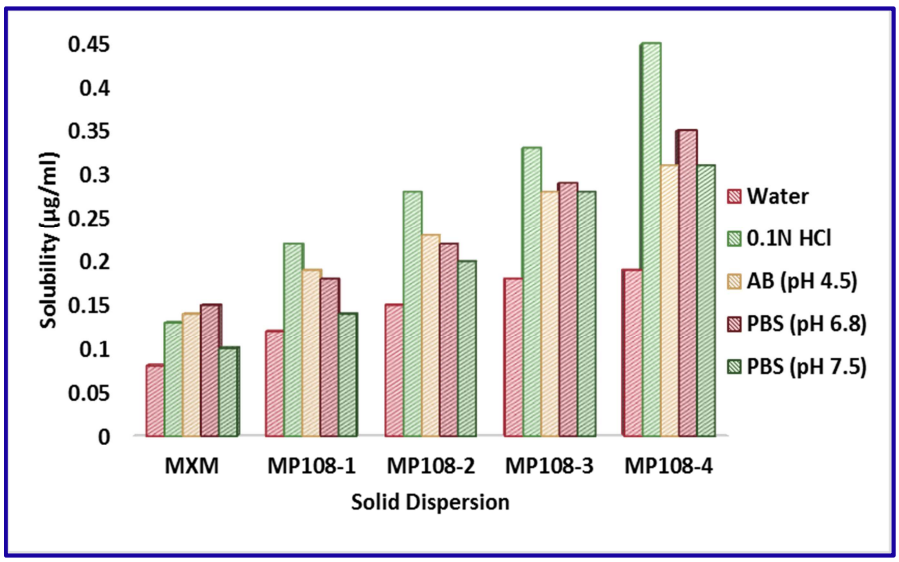

Fig.3: Solubility of MXM and Poloxamer-108 SD in various media

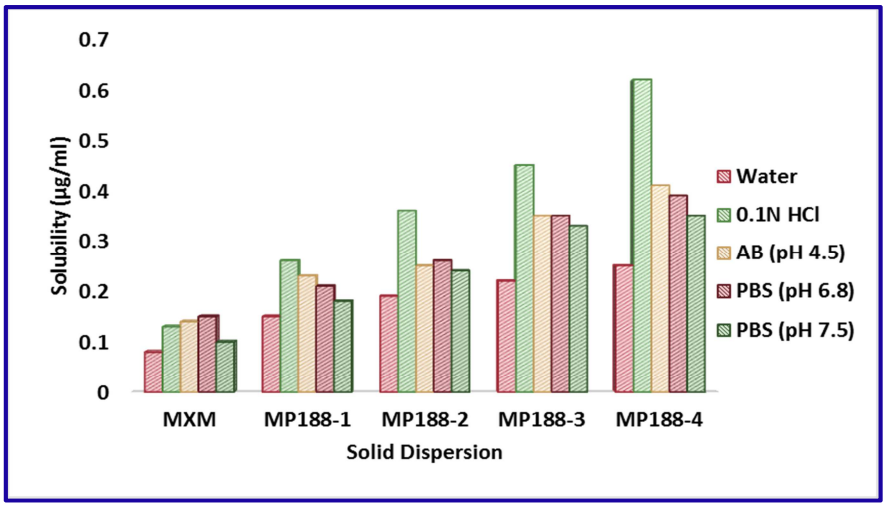

Fig.4: Solubility of MXM and Poloxamer-188 SD in various media

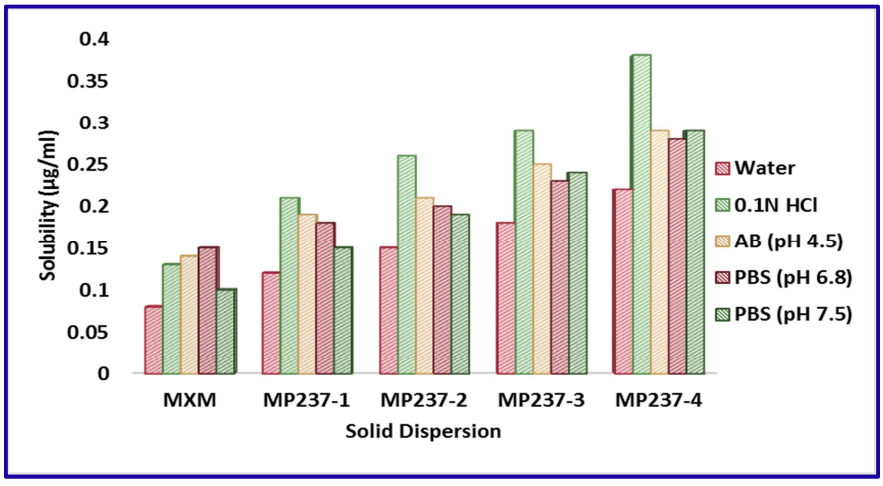

Fig.5: Solubility of MXM and Poloxamer-237 SD in various media

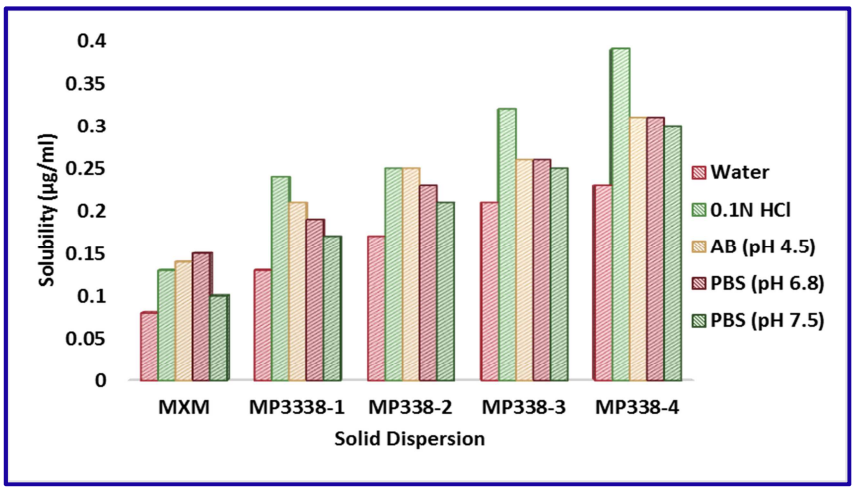

Fig.6: Solubility of MXM and Poloxamer-338 SD in various media

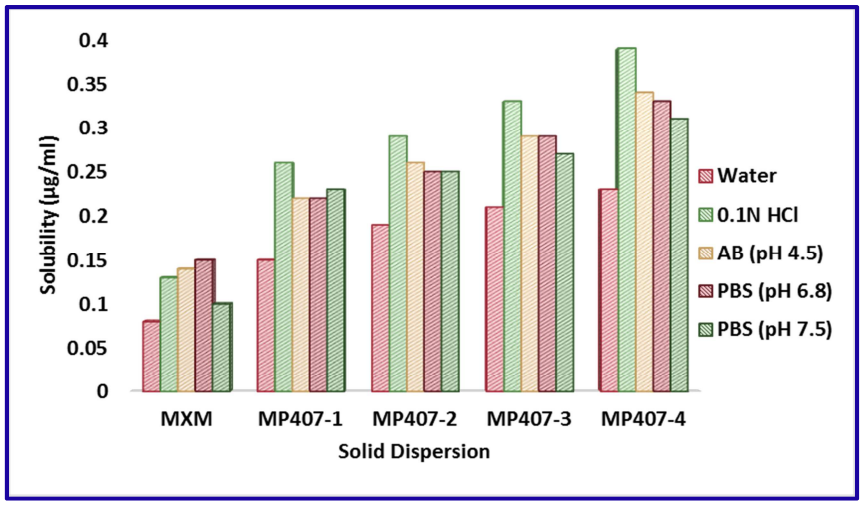

Fig.7: Solubility of MXM and Poloxamer-407 SD in various media

3.5 Analytical data

MXM followed Beer's Lamberts law at the concentration of (2 to 10 µg/mL). The regression (R^2) value was found to be 0.99. The estimation of MXM was determined by plotting a calibration curve of MXM (fig.8).

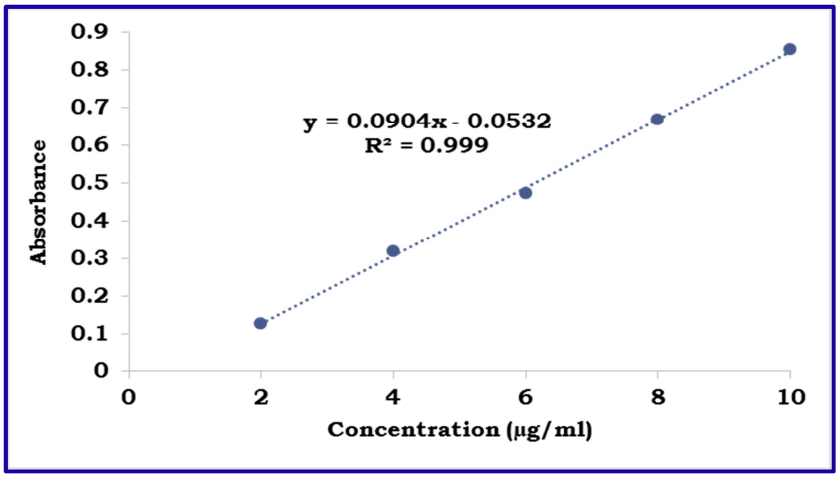

Fig.8 Calibration curve for the estimation of MXM

3.6 In vitro dissolution data

The dissolution of tablets was found good in formulations containing MXM: Poloxamer ratios 1:6 with all carriers viz., Poloxamer- 108, Poloxamer- 188, Poloxamer- 237, Poloxamer- 338 and Poloxamer- 407 (Fig.9). The reason behind is good surfactant property of Poloxamer-188 equated to other Poloxamers.

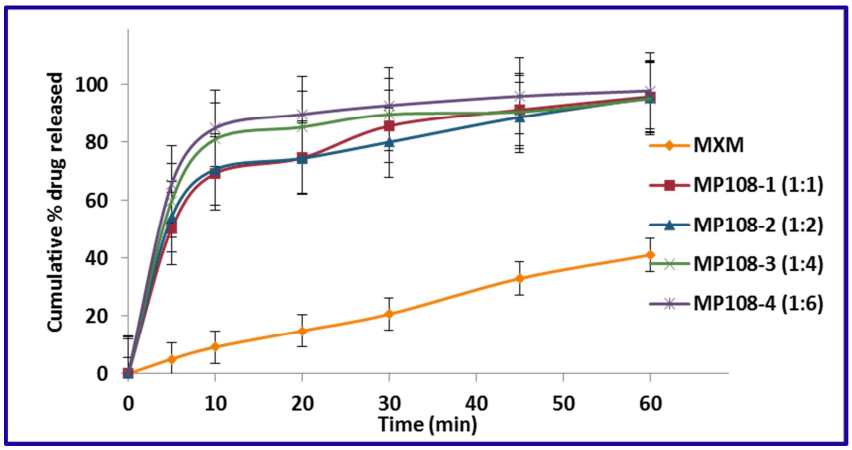

Fig.9: *In vitro* dissolution profile of MXM with Poloxamer 108

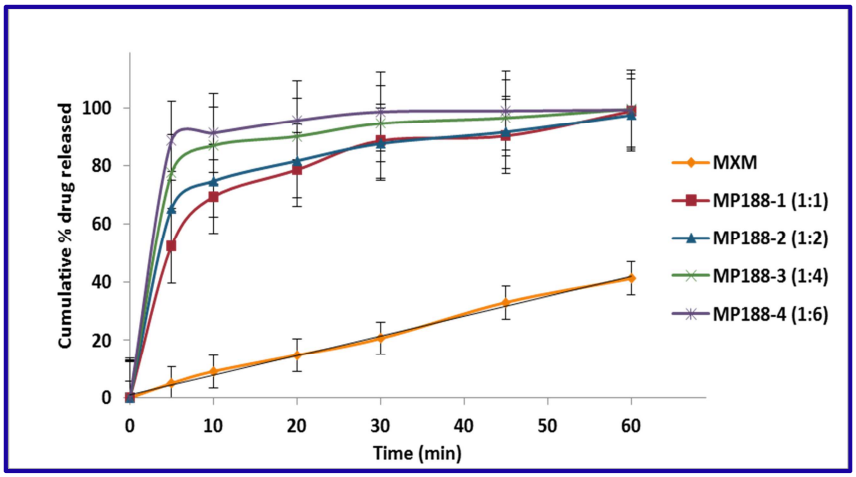

Fig.10: *In vitro* dissolution profile of MXM with Poloxamer 188

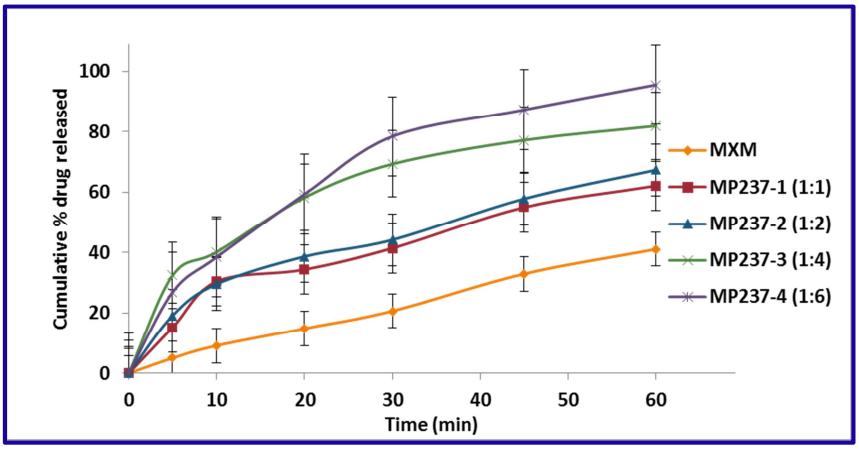

Fig.11: *In vitro* dissolution profile of MXM with Poloxamer 237

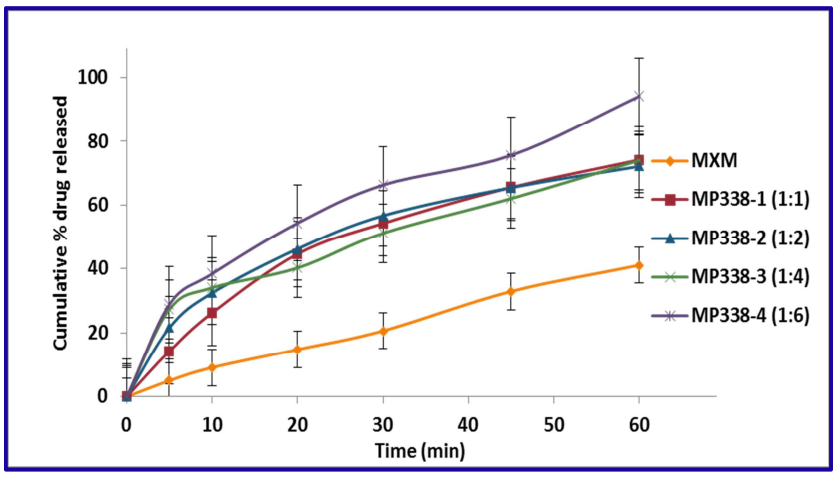

Fig.12: *In vitro* dissolution profile of MXM with Poloxamer 338

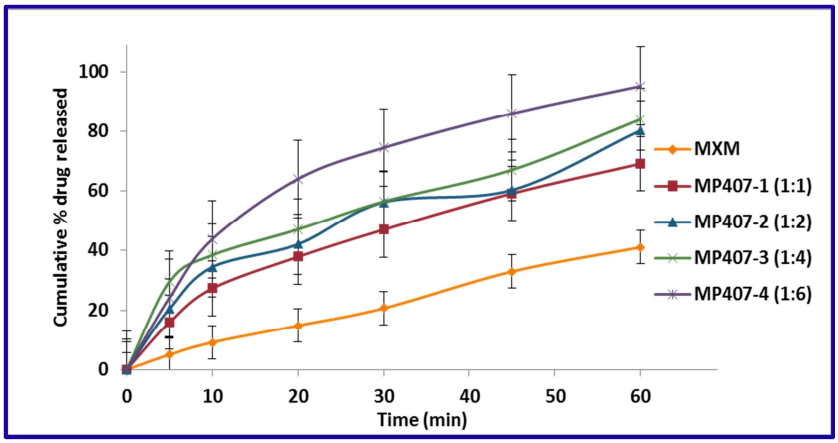

Fig.13: *In vitro* dissolution profile of MXM with Poloxamer 407

3.7 KINETIC ANALYSIS

The MXM release pattern from tablets was determined by kinetic treatment *of in vitro* drug dissolution data. The correlation (R^2) values were revealed in table 6. First order and Hixson Crowell's plots were revealed in fig.14 and 15.

The regression (R^2) value was found to be 0.4651, 0.3249, 0.8808 and 0.9046 for zero order; 0.8837, 0.8217, 0.9913 and 0.9284 for first order; 0.8786, 0.8847, 0.9622, and 0.9903 for Hixson Crowell's models for formulations MP108-4, MP188-4, MP237-4, MP338-4 and MP407-4.

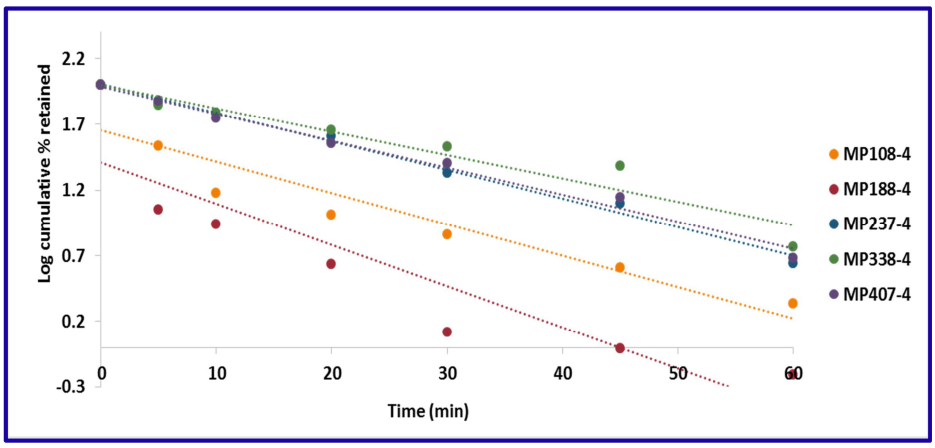

Fig.14: First order plots for SD

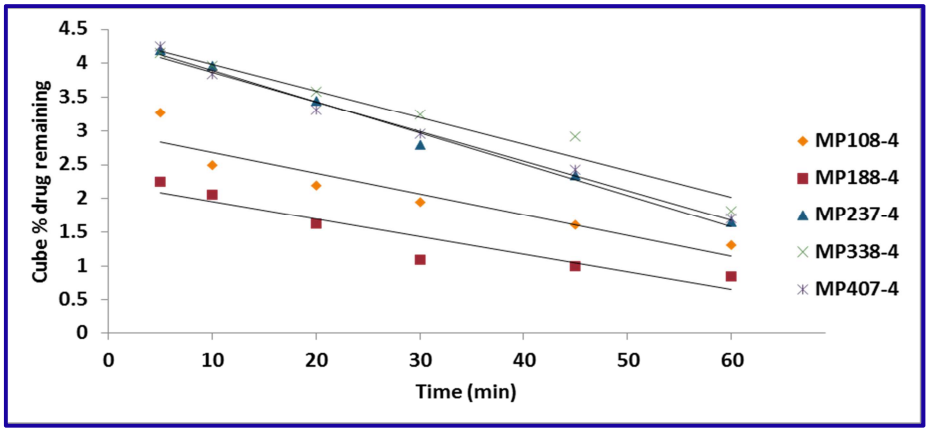

Fig.15: *Hixson Crowell's* plots for SD

Table 6. Kinetic data of MXM SD

Formulation	Zero order		First order		Hixson Crowell's	
	Y	R^2	y	R^2	Y	R^2
MP108-4	1.0779x + 49.062	0.4651	-0.0239x + 1.6575	0.8837	-0.0307x + 2.992	0.8786
MP188-4	0.938x + 59.036	0.3249	-0.0315x + 1.4118	0.8217	-0.0261x + 2.2186	0.8847
MP237-4	1.4891x + 19.001	0.8808	-0.0218x + 2.0056	0.9913	-0.0395x + 4.384	0.9622
MP338-4	1.3588x + 18.109	0.9046	-0.0179x + 2.0022	0.9284	-0.0463x + 4.363	0.9903

4. CONCLUSIONS

The investigational finding revealed that SD with Poloxamer-188 (MP188-4) containing drug: carrier ratio (1:6) was satisfactory solubility and drug dissolution compare to others formulation. The extensive work concludes that among the Poloxamer carriers (Poloxamer-108, Poloxamer-188, Poloxamer-237, Poloxamer-338, and Poloxamer-407), Poloxamer-188 was found to be the best Poloxamer among the tested carriers of preparing SD.

5. CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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