British Journal of Pharmaceutical Research
13(6): 1-19, 2016, Article no.BJPR.29048
ISSN: 2231-2919, NLM ID: 101631759

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Formulation Development and Optimization of Ibuprofen Poloxamer Melt Granules Using Hydrophilic Excipients

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Authors' contributions

The project was jointly developed by authors BYG and RPD who equally worked on this project. They conducted the experiments and analyzed the data jointly. As their major advisor, the role of author RHD was to supervise them and help them to complete the project and develop meaningful manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2016/29048
Editor(s):
(1) Nawal Kishore Dubey, Centre for Advanced Studies in Botany, Banaras Hindu University, India.
Reviewers:
(1) Arno A Enose, Technology Transfer, India.
(2) Claudia Garnero, Universidad Nacional de Córdoba, Argentina.
(3) Surajpal Verma, Lovely Professional University, Phagwara, Punjab, India.
(4) T. M . Aminabhavi, Soniya College of Pharmacy, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/16822

Original Research Article

Received 20th August 2016
Accepted 2nd November 2016
Published 7th November 2016

ABSTRACT

The focus of this research work was to develop a melt granulation technique to enhance solubility, dissolution rate and associated flowability concerns of Ibuprofen. Hydrophilic excipients like xylitol and lactose anhydrous were added to the binary mixture of conventional low melting surfactant Poloxamer 407 and Ibuprofen. Physical mixtures of Ibuprofen and Poloxamer 407 were prepared in ratios of 1:0.25, 1:0.5 and 1:0.75 using a water-jacketed high shear mixer. For each ratio of Ibuprofen and Poloxamer 407, xylitol and lactose anhydrous were added separately at two levels (75 mg and 150 mg) per unit dose containing 200 mg drug. Phase solubility studies revealed linearity in drug solubility enhancement with Poloxamer 407 concentration. *In vitro* dissolution studies were carried out for drug, physical mixtures (PM) and melt granules (MG) for all ratios in de-ionized water and 0.1 N HCl (pH=1.2). Solid state characterization was performed using Fourier transform infrared spectroscopy (FTIR), modulated differential scanning calorimetry (mDSC) and

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powder X-ray diffraction (PXRD) methodologies. Powder rheology studies were performed conventionally by measuring Carr's index and Hausner's ratio. Basic flowability energy values were calculated using a powder rheometer to corroborate flowability data measured by conventional methods. Particle morphological studies were done by Scanning electron microscope (SEM) and Fluid imaging technologies. *In-vitro* dissolution studies showed approximately 7 fold drug release in water and 19 fold drug release in acidic media for MG 1:0.75 at hydrophilic excipient level of 150 mg compared to that of neat Ibuprofen in respective dissolution media. mDSC and PXRD data confirms crystalline nature of drug in the formulations. FTIR data confirms no interactions between drug and excipients used during processing. Particle morphology analysis confirms absence of rhombic Ibuprofen crystals in formulations. Dissolution rate and solubility enhancement was seen due to synergistic effects of Poloxamer 407 and hydrophilic excipients incorporated in formulations.

Keywords: Melt granulation; poloxamer; xylitol; lactose anhydrous; ibuprofen; dissolution rate enhancement; solubility; eutectic formation.

1. INTRODUCTION

The aqueous solubility and dissolution rate of a BCS class II drug moiety has been a significant factor influencing its absorption in systemic circulation. Many drugs show rate limited drug solubility affecting bioavailability [1]. Increasing dissolution rate and solubility has been one of the challenging areas of research in drug development. BCS class II drugs are poorly soluble and face delivery challenges like incomplete drug release from formulation, poor dissolution rate, poor bioavailability, variable food effects and high inter-patient variability [2]. Improvement in the dissolution rate and overall dissolution can help in overcoming this problem. Many techniques like solid dispersions [3], complexation [4], micronization, nanonization [5], cocrystallization and melt granulation [6] have been employed since the last few decades to enhance solubility and dissolution rate of drugs.

Hot melt extrusion (HME), Spray drying and Melt granulation are the commonly used methods to enhance drug solubility at a molecular level [7]. Melt granulation technique has the advantage of avoiding solvent related toxicological concerns which is a drawback for solvent based processes. Melt granulation is a size enlargement process, which involves mixing of a meltable binder with a melting point in the range of 40℃-90℃ along with the drug and other excipients. High shear mixer and Fluid bed granulator are two commonly used laboratory equipment employed for melt granulation. Appropriate selection of binders can help in designing immediate or controlled release granules. Poloxamers and PEG (polyethylene glycol) are the most commonly used hydrophilic polymers in melt granulation due to its low melting and rapid solidification properties. In addition to hydrophilic polymers, Compritol® ATO 888 [8] and Gelucire® 50/13 [9] are frequently used lipophilic polymers to formulate controlled release granules.

Poloxamers are non-ionic tri-block copolymers composed of a central hydrophobic chain of polyoxypropylene (POP) bonded to hydrophilic chains of polyoxyethylene (POE) on either side [10]. They exist as monomolecular micelles in liquid media at low concentrations and form multi-molecular aggregates at higher concentration [11]. POP block and PEO block interacts with drug substance via van der Waals forces and hydrogen bonding respectively aiding its solubilization. They are used extensively in melt granulation process because of their low melting, superior wettability and solubilization properties. Poloxamers are white, coarse prilled powder having a waxy consistency. They have inherent properties to form micelles and liquid crystalline phases aiding solubilization [12]. Commercially available racemic Ibuprofen (Fig. 1) and Poloxamer 407 (Fig. 2) were used for the present study.

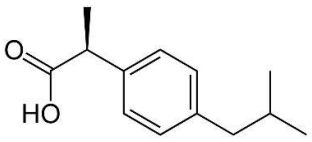

Fig. 1. Ibuprofen

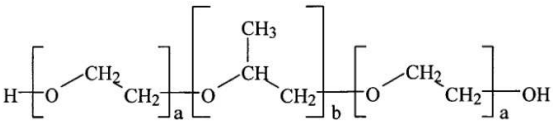

Fig. 2. Poloxamer 407

Incorporation of poloxamer in a formulation increases the dissolution rate [13], however formulations tend to be sticky which results in low yield and hinders manufacturing processes [14]. Lactose anhydrous and Xylitol were incorporated as hydrophilic fillers and adsorbents to aid dissolution and address the common flowability concerns associated with poloxamer containing granules. Above mentioned fillers were selected owing to their water solubility and adsorptive capacity. Also, they fall in a class of sugars and alcoholic-sugars respectively which have good matrix forming properties and have no known toxicity. Ibuprofen is known to be hydrophobic and resistant to wetting resulting in poor aqueous solubility [15]. The aim of current research was to ameliorate solubility, dissolution rate and flow properties of poloxamer based melt granules and evaluate the effects of xylitol and lactose anhydrous on physicochemical and performance properties of Ibuprofen-Poloxamer 407 melt granules prepared using jacketed high shear mixer.

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen was purchased from Fagron Inc. (MN, USA) and was sieved through a 595-µm sieve, when used. Lutrol® F127 NF Prill was kindly donated by BASF Corporation (NJ, USA). Lactose anhydrous and Xylitol were purchased from Letco® Medical (AL, USA).

2.2 Methods

2.2.1 UV-visible spectroscopy

Calibration curve of Ibuprofen was prepared at λ_{max} of 264 nm in triplicate using a UV-VIS spectrophotometer (Shimadzu Scientific Instruments Inc., NJ, USA). Linearity and range were studied by preparing a calibration curve, which was constructed with standard solutions ranging in concentration of 0-1000 µg/ml in ethanol. All the measurements were performed in triplicates.

2.2.2 Content uniformity

Accurately weighed samples containing an equivalent of 200 mg drug were dissolved in ethanol for all formulations to determine content uniformity of samples. Samples with particle size of 700-1000 µm were selected for all the studies. The samples were sonicated for 15 minutes and allowed to cool to room temperature (25±0.4℃). The drug solution was passed through 0.45 µm syringe filter and analyzed at a λ_{max} of 264 nm to determine drug content. All measurements were performed in triplicates.

2.2.3 Phase solubility studies

Phase solubility studies were performed to evaluate the affinity of Poloxamer 407 for Ibuprofen [16]. It aids in investigating the complexation process and stoichiometry between the drug and poloxamer 407. Studies were performed according to the method reported by Higuchi and Connors in de-ionized water and 0.1 N HCl (pH 1.2) [17]. Excess drug was added to 40 ml of the two media containing various concentrations of poloxamer (0-8 mM) in a series of 50 ml volumetric flasks and the mixture was shaken for 48 hours at room temperature (25±0.8℃). Sample aliquots were centrifuged (Beckman Coulter, Inc., USA) for 10 minutes at 3500 RPM maintaining a temperature of 25±0.5℃ during centrifugation. Supernatant liquid was diluted suitably and analyzed quantitatively at a λ_{max} of 264 nm against respective molar solutions of Poloxamer 407. Measurements were performed in triplicates to confirm low variation in measured drug concentration. The apparent stability constant (K_s) value was calculated from the phase solubility curve using equation 1 [18] and Gibbs free energy of transfer (ΔG_{tr}^0) from pure water to aqueous solutions of Poloxamer 407 was calculated using equation 2 [19], where S_i is the intrinsic solubility, R is the universal gas constant, T is temperature and S_0/S_s is the ratio of molar solubility of drug in aqueous solution of Poloxamer 407 to that in pure water.

$$K_s = \frac{\text{Slope}}{S_i*(1-\text{Slope})} \quad (1)$$

$$\Delta G_{tr}^0 = -2.303RT\ logS_0/S_s \quad (2)$$

2.2.4 Saturation solubility studies

An excess amount of the drug and all other formulations were placed in beakers containing 40 ml of de-ionized water and 0.1 N HCl (pH=1.2). Samples were stirred using a magnetic stirrer at a temperature of 25±1℃ for 48 hrs. (n=3). Aliquots of each sample were transferred to 15 ml screw cap tubes and were centrifuged (Beckman Coulter, Inc., USA) for 15 minutes at 3500 RPM maintaining a temperature of 25±1℃

during centrifugation. Centrifugation was repeated twice. Supernatant liquid was filtered through 0.45 µm syringe filters, diluted appropriately and then analyzed spectrophotometrically at a λ_{max} of 264 nm.

2.2.5 Preparation of physical mixtures (PM) and melt granules (MG)

Physical mixtures were prepared by blending the drug, polymer and adsorbents in accordance with the ratios in Table 1 in a turbula blender (Glen Mills Inc., NJ, USA) at constant speed for 10 minutes. Mixing time and speed were optimized earlier by performing preliminary trials. Melt granulation was carried out in a jacketed 1L bowl of lab scale high shear mixer (GMX-LAB Micro®, Freund-Vector Corporation, IA, USA), jacket temperature was maintained at 75℃ using an external water circulator (Julabo Inc., PA, USA). Granulation was carried out at 200 RPM (impeller speed) and 950 RPM (chopper speed) for 15 min. The post granulation, jacketed bowl temperature was set to 25.0±1.0℃ and the mixture was allowed to cool after granulation. Cooled mixtures were then pulverized with a Fitz mill (FitzPatrick®, IL, USA) and sieved through a mesh opening of 1680 µm (US mesh #12). All the samples were stored in sealed containers within a desiccator at a temperature of 25±1.0℃ for further studies.

2.2.6 Flowability/powder rheology

PMs and MGs were characterized for flow properties by measuring Carr's index and Hausner's ratio [20]. Bulk density and Tapped density were calculated by standard methods [21]. Carr's index and Hausner's ratio were calculated from values of bulk and tapped densities. Sophisticated powder flow property marker like basic flowability energy (BFE) was also measured by FT-4 powder rheometer (Freeman Technology, UK) to confirm evaluations obtained by conventional methods. BFE is a measure of a powder's flow properties when the powder is in a loosely packed state following conditioning [22]. Conditioning cycle is employed to generate a uniform packing density, before the powder is subjected to measurement tests to ensure homogeneity and repeatability. BFE measures the work done by the downward anti-clockwise motion of the rheometer blade at a tip speed of 100 mm/s to displace constant volume of conditioned powder from top to bottom of vessel [23]. Compendial tests like Carr's index and Hausner's ratio sometimes are not sensitive enough to detect minor differences in powder flow. Hence, powder rheometer studies were performed simultaneously to validate the results obtained by conventional methods.

2.2.7 Particle morphological studies

Particle size analysis of samples (n=3) for Melt granules (MG) was carried out using an electromagnetic sieve shaker (Natoli Engineering Company Inc., MO, USA) using five standard US sieves in the size range of 500-1410 µm. Real time particle characterization of suspended Ibuprofen, poloxamer, lactose anhydrous, xylitol, PMs and MGs was performed

Table 1. List of formulations

PMs/MGs	Ratio[a]	Lactose	PMs/MGs	Ratio	Xylitol
PML1	1-0.25	75 mg	PMX1	1-0.25	75 mg
PML2	1-0.25	150 mg	PMX2	1-0.25	150 mg
PML3	1-0.50	75 mg	PMX3	1-0.50	75 mg
PML4	1-0.50	150 mg	PMX4	1-0.50	150 mg
PML5	1-0.75	75 g	PMX5	1-0.75	75 mg
PML6	1-0.75	150 mg	PMX6	1-0.75	150 mg
MGL1	1-0.25	75 mg	MGX1	1-0.25	75 mg
MGL2	1-0.25	150 mg	MGX2	1-0.25	150 mg
MGL3	1-0.50	75 mg	MGX3	1-0.50	75 mg
MGL4	1-0.50	150 mg	MGX4	1-0.50	150 mg
MGL5	1-0.75	75 mg	MGX5	1-0.75	75 mg
MGL6	1-0.75	150 mg	MGX6	1-0.75	150 mg
MG1	1-0.25	-			
MG2	1-0.5	-			
MG3	1-0.75	-			

[a] *Ratios are Ibuprofen: Poloxamer 407*

using Flowcam (Fluid Imaging Technologies, ME, USA). 4X magnification was used to record images of Ibuprofen and 10X magnification along with collimator was used to record images for other samples. Samples were suspended in mineral oil to perform measurements, 800 µm sample holder was used to perform all the measurements. Aspect ratio values for formulations were calculated from an average of 50 structures observed in Flowcam. The surface morphology of Ibuprofen, Poloxamer 407, lactose anhydrous, xylitol, physical mixtures and melt granules were examined using a scanning electron microscope (Jeol JSM-6010LV, MA, USA). The powders were fixed on a brass stub using double-sided adhesive tape and made electrically conductive by coating in a vacuum ($6P_a$) with gold (6 nm/min) using Denton Ion Sputter (DESKV) for 80 s at 45 mA.

2.2.8 *In-vitro* dissolution studies

In-vitro dissolution test was performed in USP dissolution apparatus type II (Distek 2100B) using paddle speed of 50 RPM and a temperature of 37±0.2℃ in de-ionized water and 0.1 N HCl (pH=1.2). Powdered samples having an equivalent weight of 200 mg drug were filled in hard gelatin capsules to perform dissolution with the help of sinkers. All the measurements were performed in triplicate. For dissolution testing, particle size below 1000 µm was selected for all samples. 5 ml of samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes time intervals from the dissolution vessel, and an equal amount of fresh media maintained at 37±0.2℃ was replenished. Samples were filtered through Polytetrafluoroethylene (PTFE) filters and analyzed spectrophotometrically at a wavelength of 264 nm.

2.3 Statistical Analysis

Model independent methods like fit factors were used for analyzing dissolution profiles of all formulations. Model independent methods promote direct comparison of the dissolution data, and do not rely on choice of model functions that sometimes prove artificial [24]. For fit factors, difference (f_1) and similarity (f_2) factors were calculated using the equation 3 and 4 respectively as outlined in the SUPAC and IVIVC guidelines [25,26].

$$f_1 = \{\sum_{t=1}^{n}|R_t - T_t|/\sum_{t=1}^{n} R_t\} \times 100 \quad (3)$$

$$f_2 = 50 \times log_{10}\left\{\left[1 + \left(1/n\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (4)$$

2.3.1 Modulated differential scanning calorimetry (mDSC)

mDSC measurements were performed on Ibuprofen, Poloxamer 407, lactose anhydrous, xylitol, physical mixtures and melt granules using a differential scanning calorimeter (Q100, TA Instruments, USA). 5±1 mg of samples (n=3) were taken in a sealed aluminum pan with a pin hole, and heated at a scanning rate of 5℃/min from 20℃ to 110℃ and a modulation of ±1.59℃ every 60 seconds. Lactose anhydrous was heated until 250℃. An empty aluminum pan was used as reference. Change in enthalpy and melting temperature values were recorded from the thermograms.

2.3.2 Fourier transform infra-red spectroscopy (FTIR)

Attenuated Total Reflectance (ATR) FTIR spectra were recorded using a Nicolet iS5 FTIR spectrophotometer with iD5 ATR diamond accessory (Thermo Fisher Scientific, USA). Samples were scanned between 4000 and 400 cm^{-1} with an average of 64 scans and at a resolution of 4 cm^{-1} by placing them on the diamond crystal and pressing the knob on it.

2.3.3 Powder X-ray diffraction (PXRD)

Powder X-Ray diffraction patterns were recorded using a scanning diffractrometer (Model XI Cupertino, Scintag Inc., CA, USA) using Copper-Kα radiation at a wavelength of 1.54 Å with a potential of 45kV and 40 mA power. X-ray diffraction patterns were collected over the 2θ range, 5°-40° at scan rate of 0.020° min^{-1}.

3. RESULTS AND DISCUSSION

3.1 UV-Visible Spectroscopy

A linear trend line was observed at a λ_{max} of 264 nm with an equation having regression value of 0.9997.

3.2 Content Uniformity

Percent drug content recoveries of the physical mixtures and formulations were in range of 97-102% recoveries (n=3). PM and MG 1:0.75

formulations at hydrophilic excipient level of 75 mg were considered for all comparative and characterization studies.

3.3 Saturation Solubility Studies

Fig. 3 shows the enhancement of Ibuprofen solubility for both physical mixtures and melt granules in presence of hydrophilic adsorbents lactose anhydrous and xylitol. Adsorbents increased the total surface area of drug exposed to media promoting wetting and dissolution.

3.4 Phase Solubility Studies

This methodology helps in understanding and studying the solubilization stoichiometry of Ibuprofen with an increase in poloxamer 407 concentration. The intrinsic solubility of the drug (S_0) was found to be 47.93 µg/ml and 23.93 µg/ml in de-ionized water and 0.1 N HCl (pH 1.2) respectively. Phase solubility studies shows an A_L type of profile for drug attributed to a linear increase in drug solubility with increased poloxamer 407 levels (Figs. 4a and 5a). The apparent stability constant value computed from the phase solubility profile was 21.95 mM^{-1} and 60.34 mM^{-1} in de-ionized water and 0.1N HCl (pH 1.2) respectively suggesting formation of weak water soluble complexes [27]. The Drug solubility enhancement could be attributed to the formation of micelles at concentrations of Poloxamer 407 above its critical micellar concentration (CMC) of 2.8 µM [28,29]. As per mass action model of micellization, hydrophobic drug binds with self-aggregating surfactant molecules reversibly [30]. Fig. 4b and 5b shows us that values of ΔG^{o}_{tr} were negative at all the levels of poloxamer 407. Change in Gibb's free energy values highlights whether drug solubilization in aqueous solution of carrier is favorable or unfavorable, where negative values indicates favorable conditions [31]. Gibb's free energy of transfer (ΔG^{o}_{tr}) values decreased with increase in Poloxamer 407 concentration construing spontaneous nature of solubilization at higher levels of surfactant.

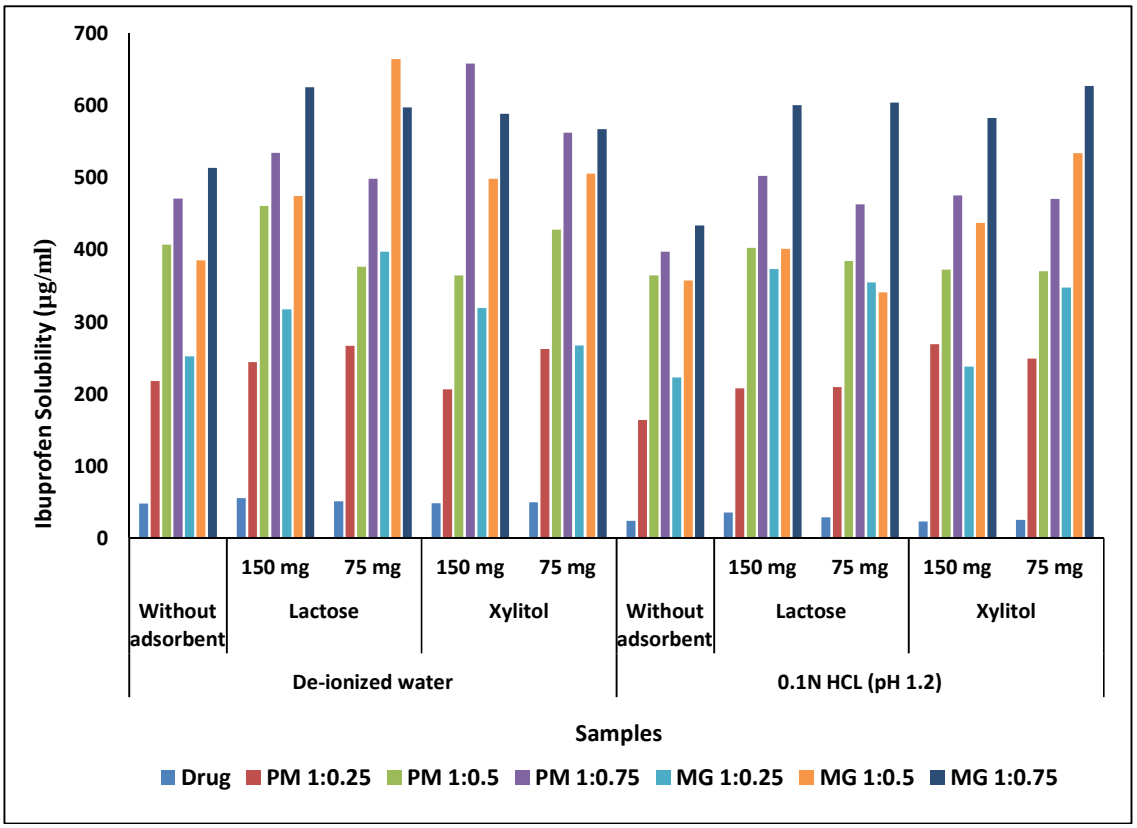

Fig. 3. Saturation solubility studies in de-ionized water and 0.1N HCl (pH 1.2)

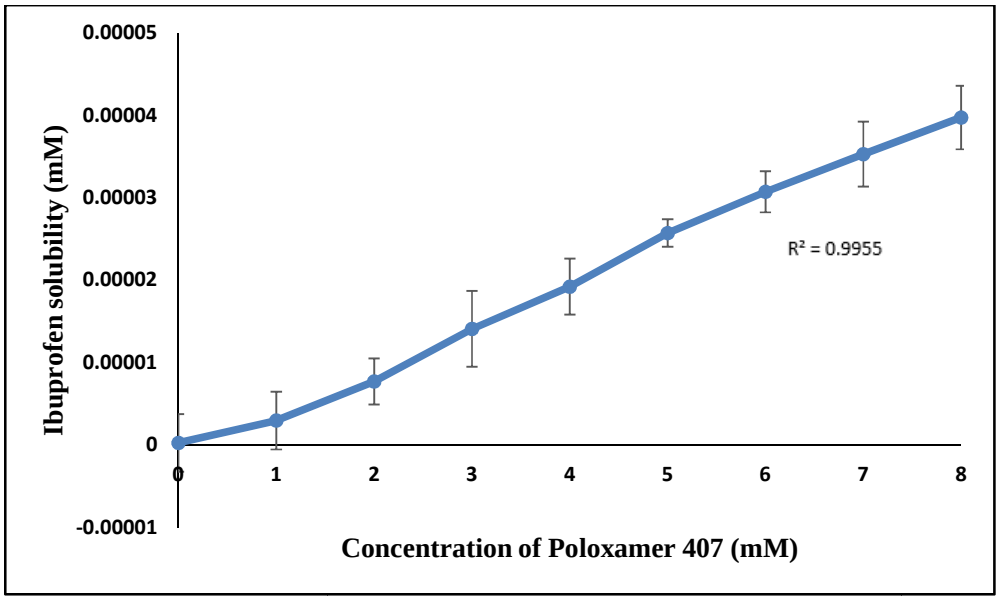

Fig. 4a. Phase solubility diagram in de-ionized water

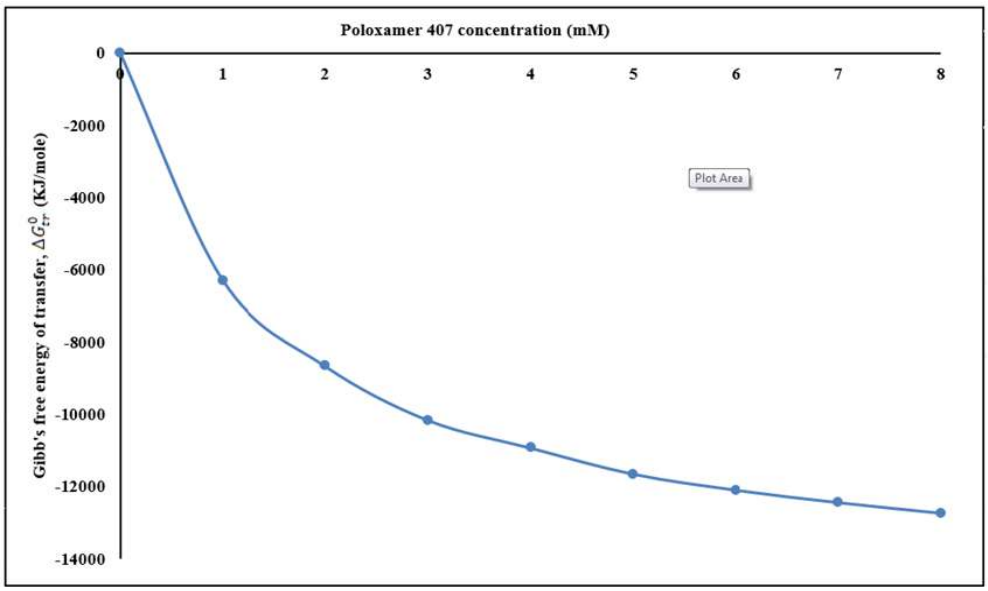

Fig. 4b. Change in Gibb's free energy of transfer of Ibuprofen with respect to Poloxamer 407 concentration in de-ionized water

3.5 Flowability/Powder Rheology

The average particle sizes of the granules were in the range of 700-1000 microns. Formulations containing lactose showed relatively larger granules compared to ones with xylitol. Table 2 shows the comparison of powder flow parameters to investigate the effect of excipients on flowability of formulations. Bulk and tapped density increased with the poloxamer content indicating higher agglomeration and densification. Carr's index values indicate better flowability for all the granulation. Rheology results suggested better flowability for xylitol and lactose containing granules with low poloxamer content. Melt granules containing lactose and xylitol showed better flowability, compared to granules devoid of any of these hydrophilic excipients. Poloxamer at higher concentrations have a tendency to form waxy granules,

incorporation of lactose anhydrous and xylitol reduces the waxy consistency of mixtures by adsorption and dilution effect. Flowability of MG improves with increase in amount of hydrophilic excipients incorporated in formulations. BFE value which is a measure of energies associated with flow of powder increased with the poloxamer content for all formulations. However, BFE values decreased for formulations which incorporated hydrophilic excipients xylitol or lactose anhydrous. Addition of these excipients to formulations thus showed that lower expenditure of energy was associated with their flow suggesting better powder flow properties. FT-4 rheometer results corroborated with results obtained by conventional methods (Carr's indices and Hausner ratio values) [32].

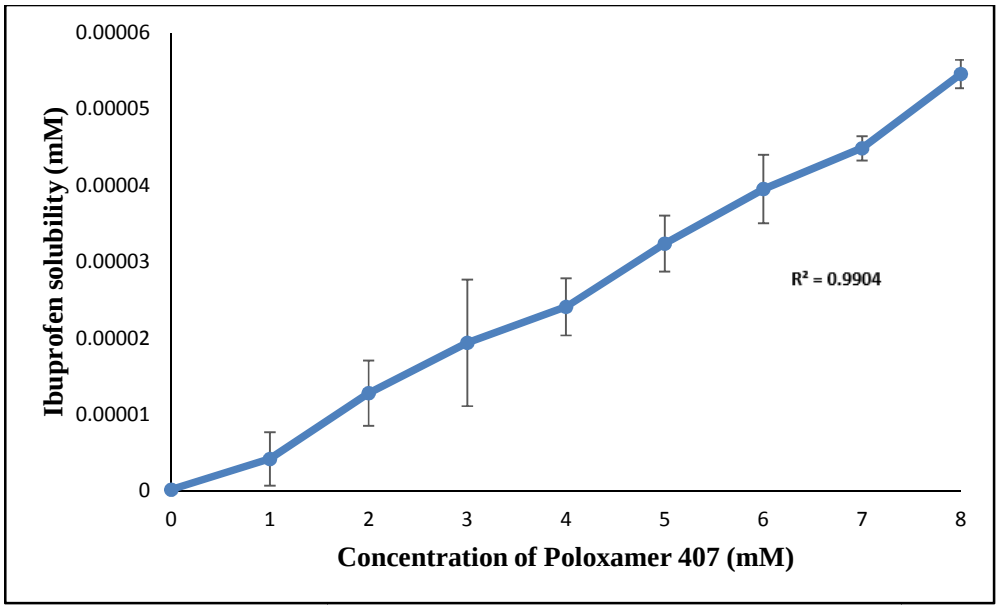

Fig. 5a. Phase solubility diagram in 0.1N HCl (pH 1.2)

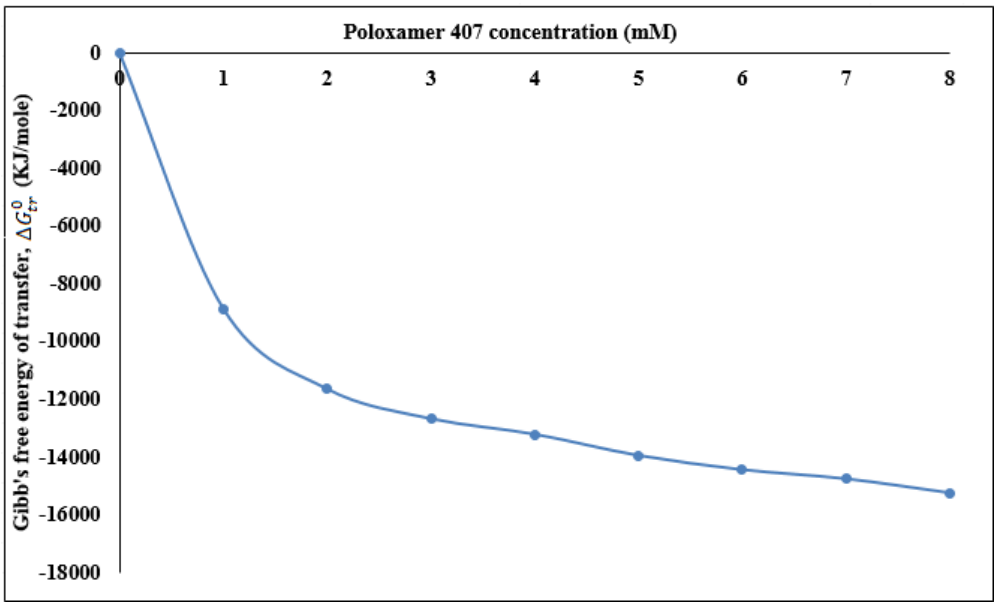

Fig. 5b. Change in Gibb's free energy of transfer of Ibuprofen with respect to Poloxamer concentration in 0.1N HCl (pH 1.2)

Table 2. Powder rheological evaluation

Formulations	Carr's index	Hausner's ratio	BFE (mJ)
MG1	33.75 ± 0.26	1.34 ± 0.001	235.28 ± 12.35
MG2	22.44 ± 0.85	1.22 ± 0.011	527.07 ± 8.57
MG3	22.86 ± 1.02	1.23 ± 0.003	677.9 ± 6.59
MGL1	10.17 ± 0.67	1.10 ± 0.024	149.61 ± 9.51
MGL2	6.35 ± 0.24	1.06 ± 0.002	163.04 ± 11.64
MGL3	11.67 ± 0.91	1.12 ± 0.018	247.63 ± 5.11
MGL4	6.06 ± 0.18	1.06 ± 0.006	224.42 ± 13.54
MGL5	22.03 ± 1.53	1.22 ± 0.033	291.55 ± 7.94
MGL6	14.7 ± 0.46	1.15 ± 0.027	314.2 ± 7.25
MGX1	13.11 ± 0.66	1.13 ± 0.002	187.79 ± 12.36
MGX2	9.23 ± 0.19	1.09 ± 0.041	194.65 ± 13.24
MGX3	9.67 ± 0.34	1.10 ± 0.079	315.83 ± 10.73
MGX4	7.35 ± 0.27	1.07 ± 0.035	256.29 ± 8.62
MGX5	14.75 ± 1.13	1.15 ± 0.086	378.17 ± 9.38
MGX6	13.04 ± 0.78	1.13 ± 0.008	281.03 ± 15.48

Table 3. Comparison of aspect ratios for melt granule formulations

	Formulations						
	Ibuprofen	**MGL1**	**MGL2**	**MGL3**	**MGL4**	**MGL5**	**MGL6**
Aspect Ratio	0.52 ± 0.11	0.68 ± 0.16	0.72 ± 0.09	0.69 ± 0.11	0.78 ± 0.13	0.73 ± 0.14	0.81 ± 0.08
		MGX1	**MGX2**	**MGX3**	**MGX4**	**MGX5**	**MGX6**
		0.59 ± 0.21	0.66 ± 0.18	0.71 ± 0.12	0.72 ± 0.09	0.76 ± 0.16	0.75 ± 0.13

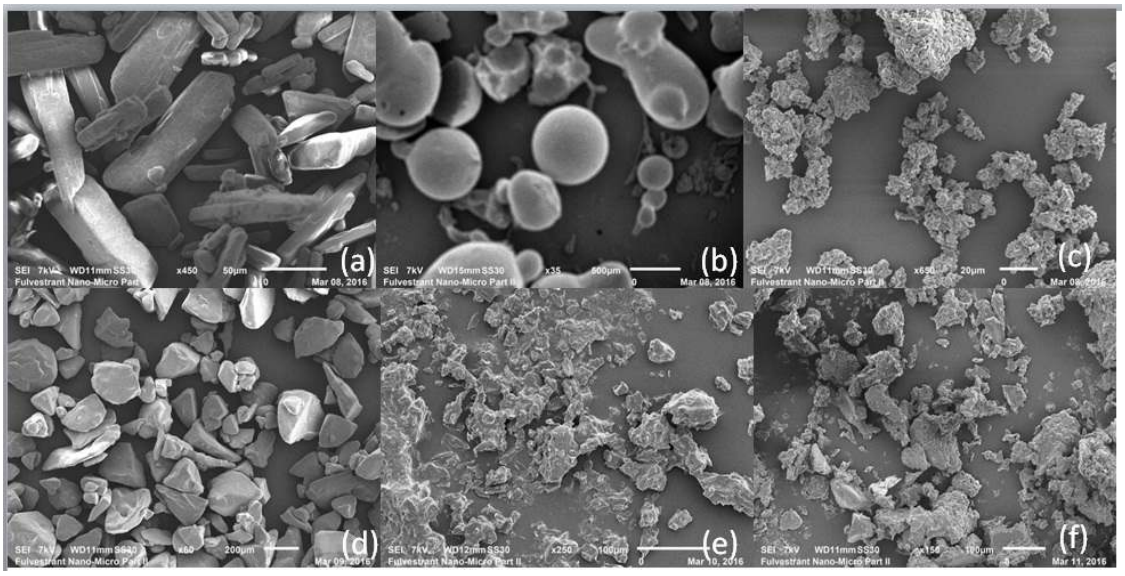

Fig. 6. SEM studies of a) Ibuprofen; b) Poloxamer 407; c) Lactose anhydrous; d) Xylitol; e) MG 1:0.75 (Lactose anhydrous-75 mg); f) MG 1:0.75 (Xylitol-75 mg)

3.6 Particle Morphological Studies

Fig. 6 shows characteristic structures of each individual component and of melt granulated formulations to study change in morphology of Ibuprofen. Ibuprofen showed inherently characteristic rhombic shaped crystals, xylitol showed crystalline structures, lactose anhydrous

showed irregular shaped particles and poloxamer showed spherical morphology. Characteristic structures of each individual component were observed in PMs (not shown here), MGs however showed irregular shaped structures devoid of any characteristic rhombic shaped crystals of Ibuprofen. MGs showed better flowability profile compared to the drug which can be inferred upon better aspect ratio values of formulations relative to Ibuprofen crystals. Table 3 shows aspect ratio values of MGs in range of 0.65-0.9 compared to an average value of 0.52 for Ibuprofen. In ideal conditions, a completely spherical particle will have an aspect ratio of 1.

3.7 *In-vitro* Dissolution Studies

Dissolution studies were carried out in de-ionized water and 0.1N HCl (pH=1.2) since these dissolution mediums were more prominent in differentiating dissolution rate enhancement at different levels of excipients. Figs. 7a, 7b, 7c and 7d show dissolution profiles of formulations with hydrophilic excipients at level of 75 mg in de-ionized water and pH 1.2. Amount of lactose anhydrous and xylitol in a given formulation did not have a significant effect on the drug release. Dissolution profiles for formulations at both weight fractions (75 mg and 150 mg) of hydrophilic excipients were similar (not shown here). However, it was observed that the dissolution rate was enhanced with the surfactant proportion in a formulation. Formulations with poloxamer ratio of 0.75 showed the maximum dissolution rate enhancement. Approximately, a 7 fold drug release in water and 19 fold drug release in acidic media was observed for MG 1:0.75 at hydrophilic excipient level of 150 mg compared to drug release of drug alone in respective dissolution media (From Fig. 3). This increase in drug release could be attributed to rapid and enhanced hydration of hydrophilic excipients and poloxamer, promoting wetting and dissolution of the hydrophobic drug moiety. Enhancement in solubility and rate of dissolution could thus be related to the wetting effect and reduced agglomeration of drug particles [33]. Standard deviations were not shown in the dissolution profiles since the standard deviation for all formulations were in the range of ± 1.5 and the error bars were smaller than markers used in figures.

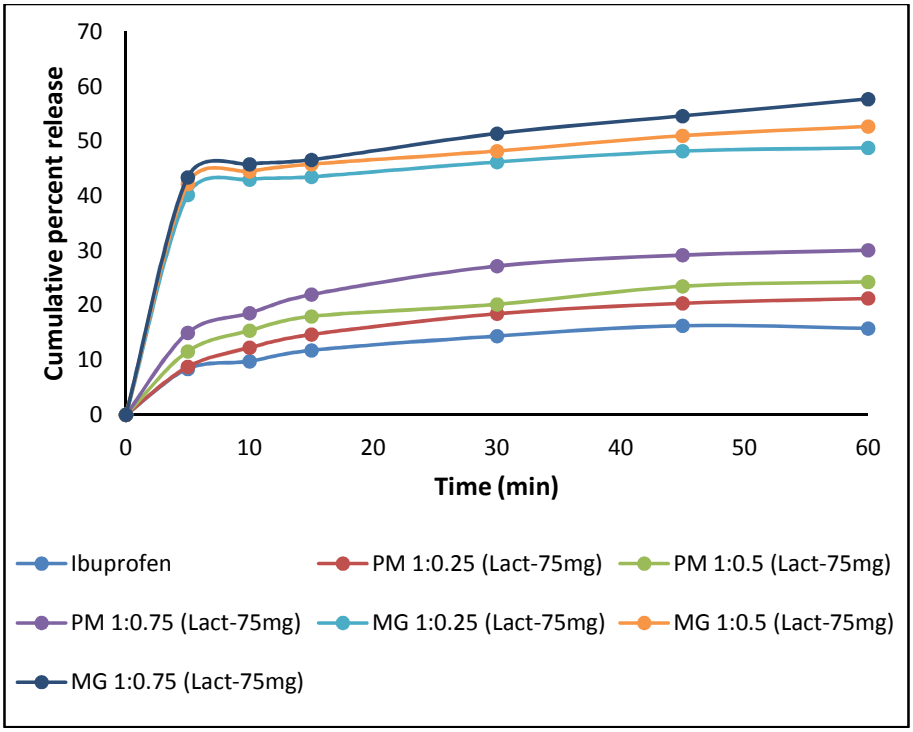

Fig. 7a. Dissolution profiles of Ibuprofen, physical mixtures and melt granules at lactose anhydrous level of 75 mg in de-ionized water

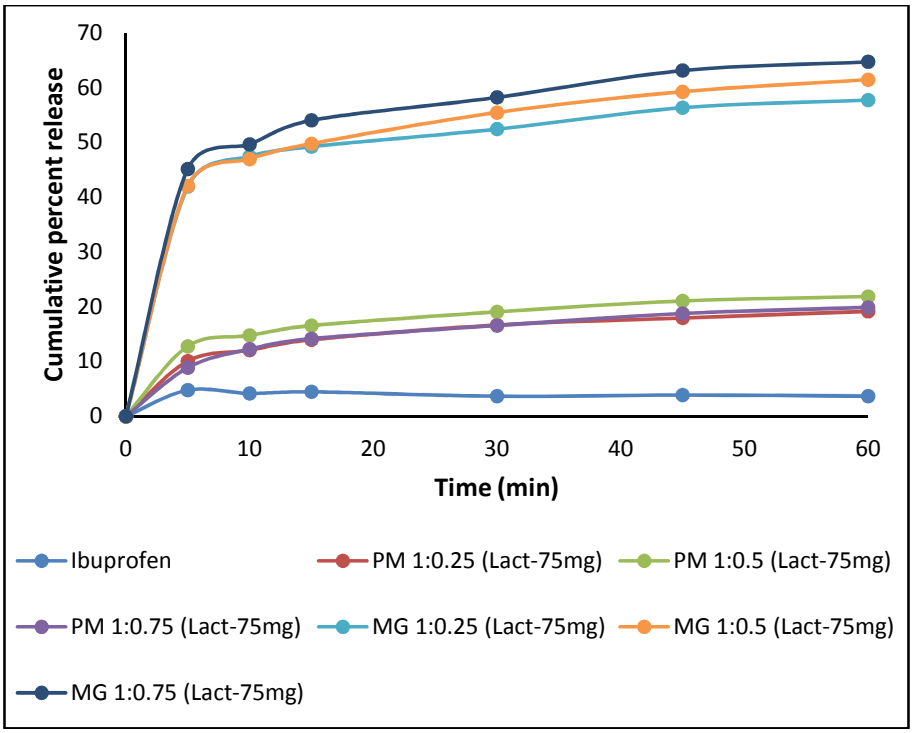

Fig. 7b. Dissolution profiles of Ibuprofen, physical mixtures and melt granules at lactose anhydrous level of 75 mg in 0.1N HCl (pH 1.2)

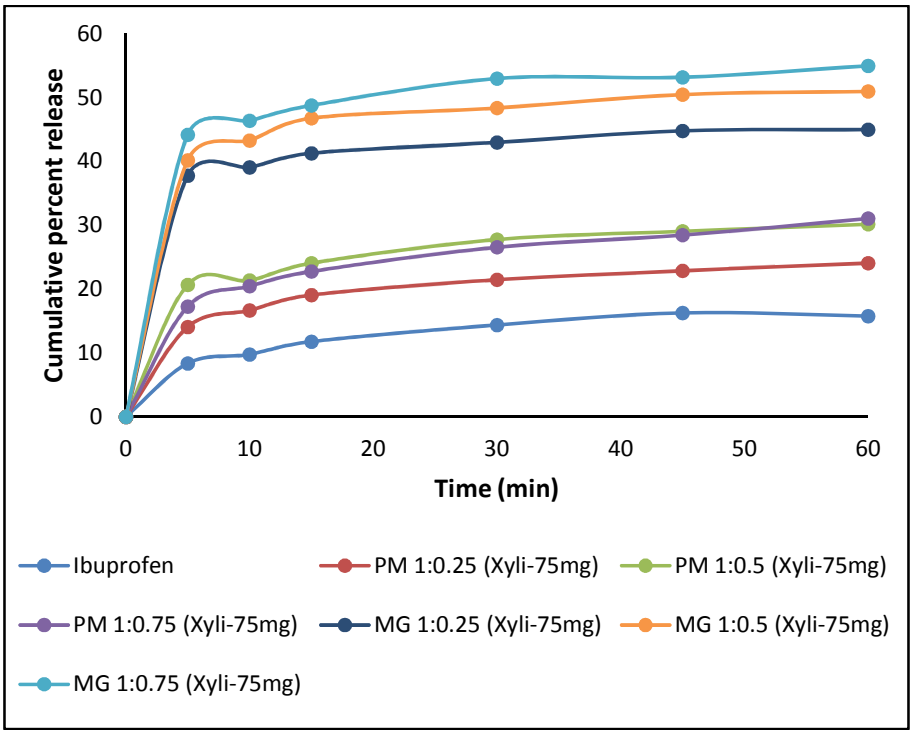

Fig. 7c. Dissolution profiles of Ibuprofen, physical mixtures and melt granules at xylitol level of 75 mg in de-ionized water

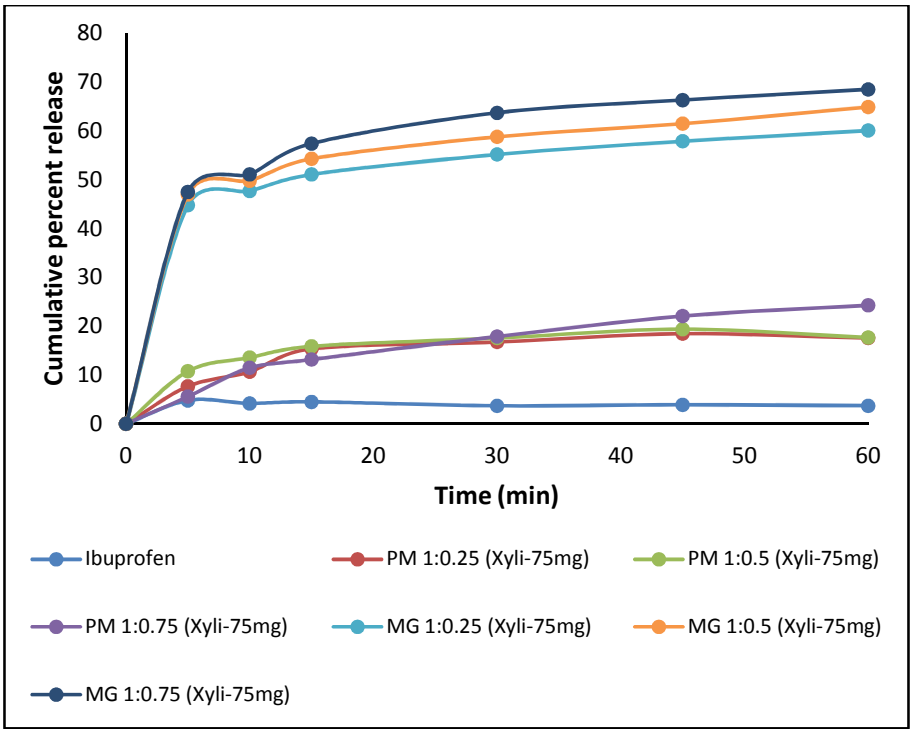

Fig. 7d. Dissolution profiles of Ibuprofen, physical mixtures and melt granules at xylitol level of 75mg in 0.1N HCL (pH 1.2)

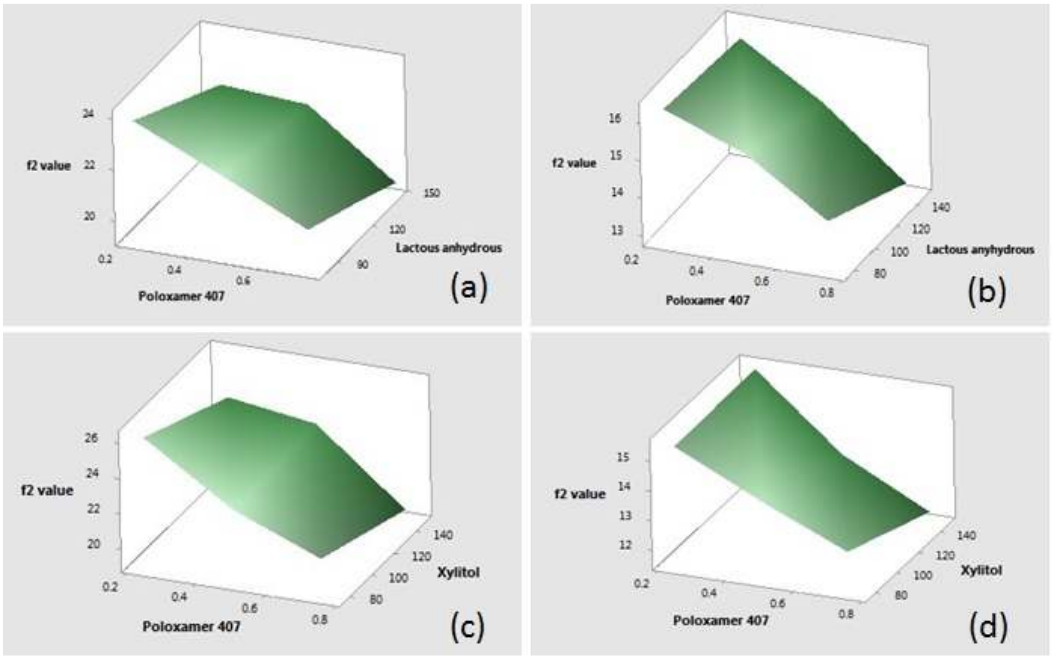

Fig. 8. Surface plots of, effect of Poloxamer 407 a) and lactose anhydrous on f_2 values in de-ionized water. b) and lactose anhydrous on f_2 values in 0.1N HCl (pH 1.2) c) and xylitol on f_2 values in de-ionized water. d) and xylitol on f_2 values in 0.1N HCl pH 1.2

3.8 Statistical Analysis

In pairwise analysis, f_1 and f_2 factors were determined for both PMs and MGs. Conventionally, f_1 value between 0-15 and f_2 value in the range of 50-100 suggests similarity between dissolution profiles of formulations and the drug [34]. Calculated f_1 and f_2 factors however shows dissolution profiles of formulations being significantly different in comparison to the drug. Fig. 8 shows relationship of f_2 factors with respect to amount of poloxamer and hydrophilic excipients incorporated in formulation. f_2 factors deviates from similarity with increase in concentration of poloxamer and adsorbents. f_1 values for all the formulations deviated from similarity as well with increase in concentrations of excipients.

3.9 Modulated Differential Scanning Calorimetry (mDSC)

Ibuprofen shows an onset of melting at 72.69℃ and its heat of fusion is 123.01 ± 1.26 J/g. mDSC thermograms of Poloxamer 407 shows a sharp endothermic peak at 51.73 ± 0.59℃, whereas lactose anhydrous and xylitol shows a sharp endothermic peak at 235 ± 1.14℃ and 96.41 ± 0.87℃ respectively. Binary mixtures of Ibuprofen and Poloxamer 407 were prepared at different ratios to understand the effect of Poloxamer 407 levels on the thermal behavior of Ibuprofen. Eutectic formation was seen at concentration of around 30% w/w drug in binary mixture as reported in previous study [35]. Also, decreased intensity of its melting transition corresponds to decrease in percent crystallinity which was observed as the concentration of Poloxamer 407 increased (11). Figs. 9a and 9b shows overlay of thermograms of formulations PML5, MGL5 and PMX5, MGX5. It shows the effect of lactose anhydrous and xylitol on thermal properties of the drug. There was a significant shift in the melting point of Ibuprofen in presence of the excipients along with reduction in ΔH values which was possibly due to eutectic formation. On the other hand, Fig. 9c and 9d shows the overlay of thermograms of formulations MGL1, MGL3, MGL5 and MGX1, MGX3, MGX5 to study effect of increasing levels of poloxamer on the drug endotherm in presence of similar amount of lactose anhydrous and xylitol in a formulation. Decreased intensity of Ibuprofen endotherm at higher ratios of poloxamer is seen, that can be attributed to decrease in particle size, dilution effect and formation of eutectic mixture.

3.10 Fourier Transform Infra-red Spectroscopy (FTIR)

Infrared spectra of Ibuprofen shows two well defined transmittance peaks at 1721 cm^{-1} (carbonyl stretching) and another around 3000 cm-1 (aromatic C-H stretching). Poloxamer shows absorption peaks at 1100 cm^{-1} and around 3000 cm^{-1}. Lactose anhydrous and xylitol show characteristic peaks at 2280 cm^{-1} and 3400 cm^{-1} respectively. Spectra of MGs were similar to addition spectra of individual components, which shows absence of any interaction between Ibuprofen and excipients (Figs. 10a and 10b). A decrease in intensity of characteristic Ibuprofen peaks was however observed with increasing concentration of poloxamer, lactose anhydrous and xylitol in MGs which can be inferred to dilution effect of Ibuprofen at higher concentration of excipients (Figs. 10c and 10d). There were no significant peaks other than that of the formulation components in FTIR spectra of samples indicative of no chemical interactions between drug and excipients.

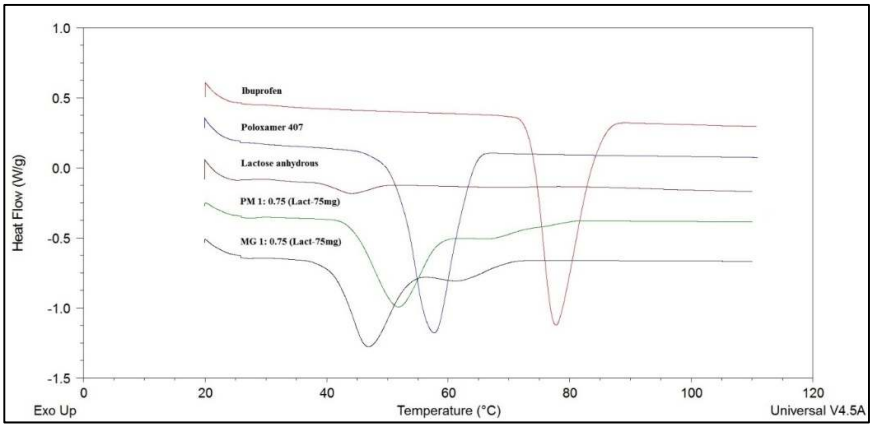

Fig. 9a. mDSC overlay of Ibuprofen, Poloxamer 407, lactose anhydrous, PML5 and MGL5

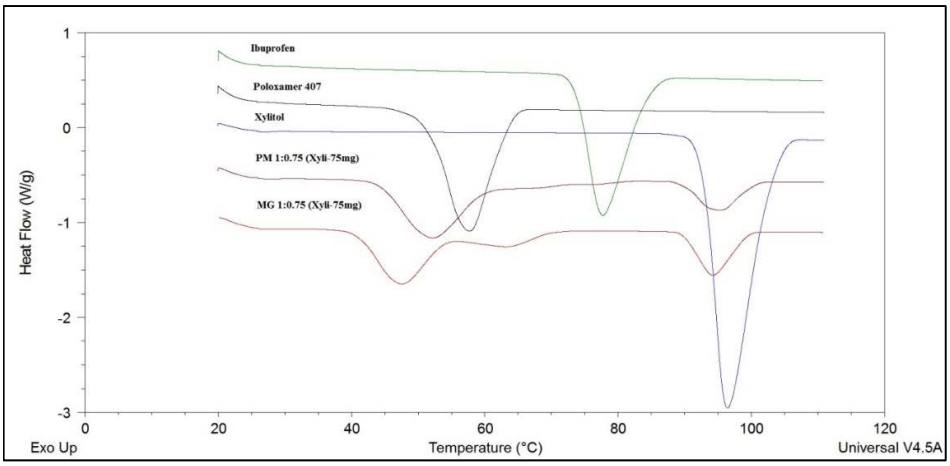

Fig. 9b. mDSC overlay of Ibuprofen, Poloxamer 407, xylitol, PMX5 and MGX5

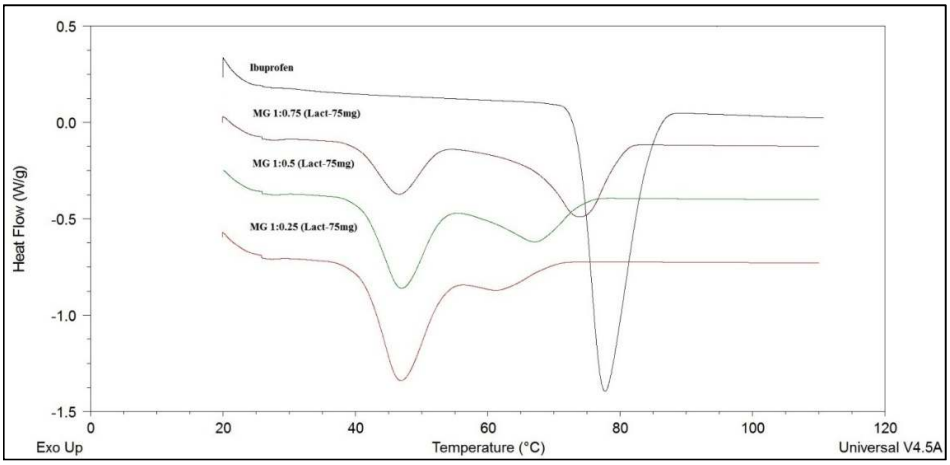

Fig. 9c. mDSC overlay of Ibuprofen, MGL1, MGL3 and MGL5

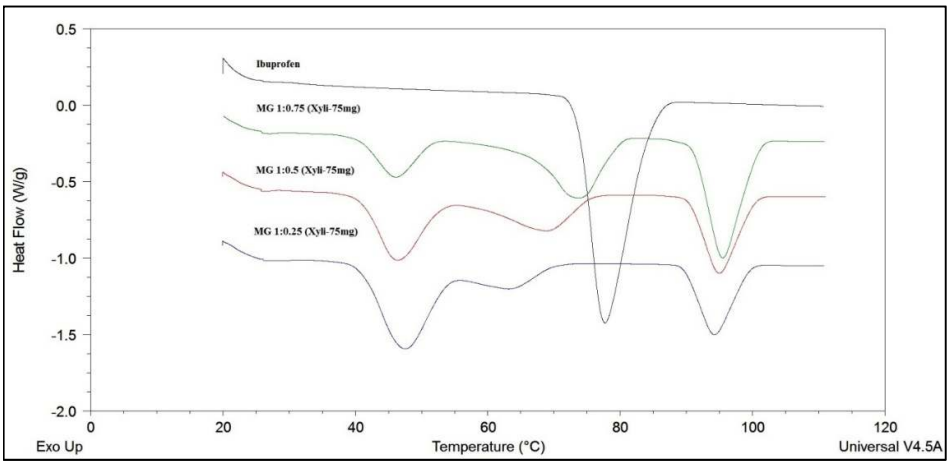

Fig. 9d. mDSC overlay of Ibuprofen, MGX1, MGX3 and MGX5

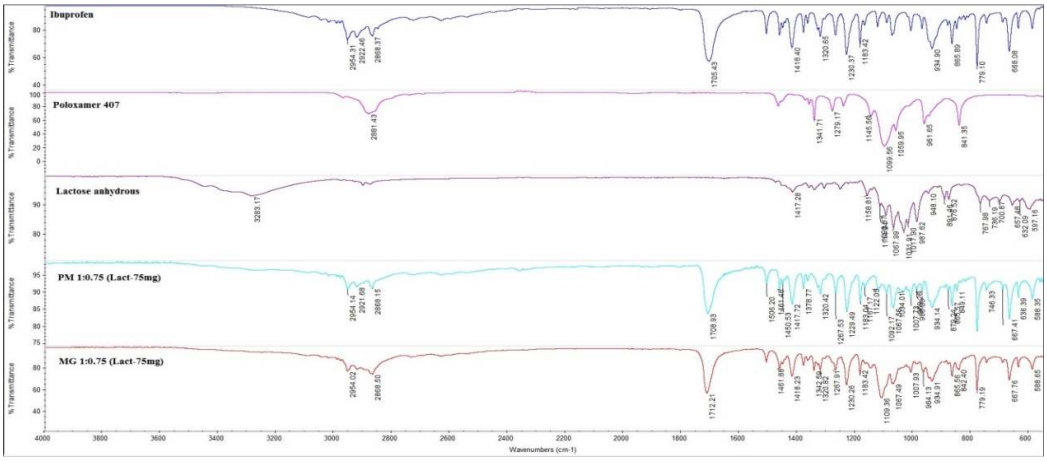

Fig. 10a. FTIR spectra of Ibuprofen, Poloxamer 407, lactose anhydrous, PML5 and MGL5

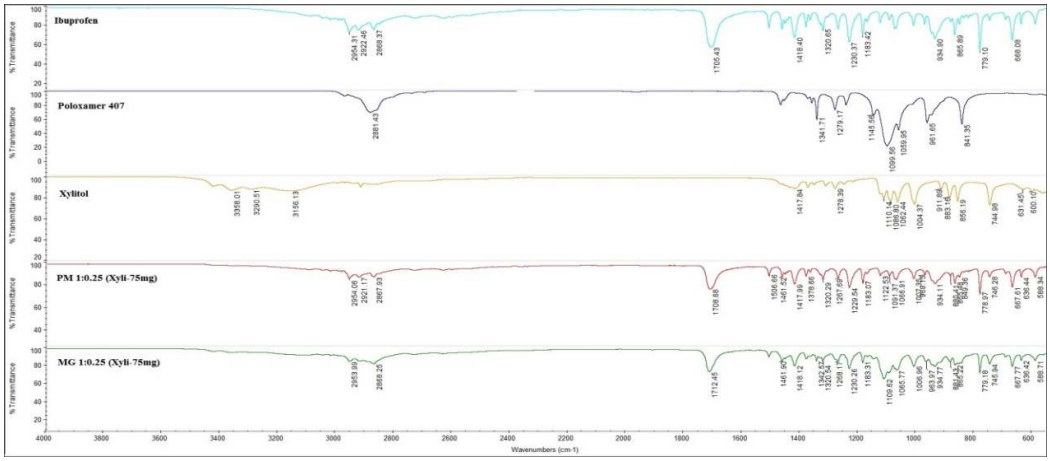

Fig. 10b. FTIR spectra of Ibuprofen, Poloxamer 407, xylitol, PMX5 and MGX5

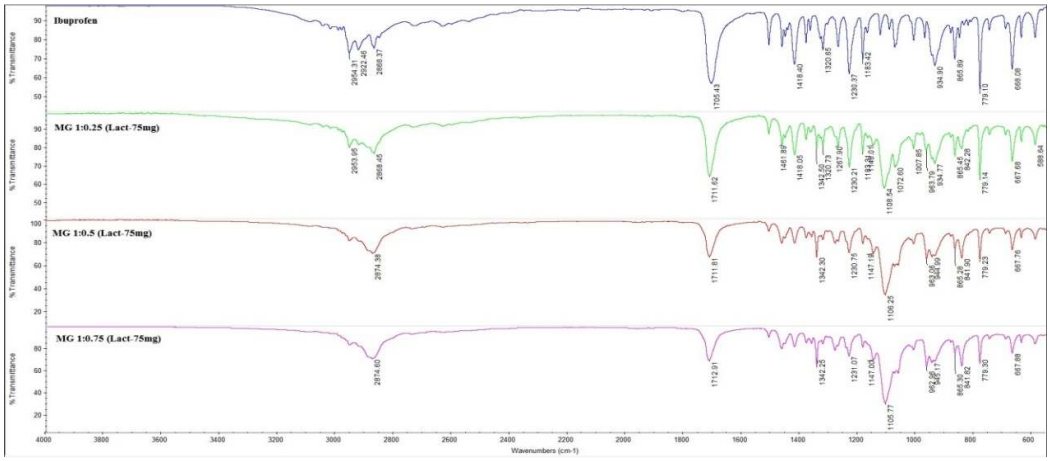

Fig. 10c. FTIR spectra of Ibuprofen, Poloxamer 407, MGL1, MGL3 and MGL5

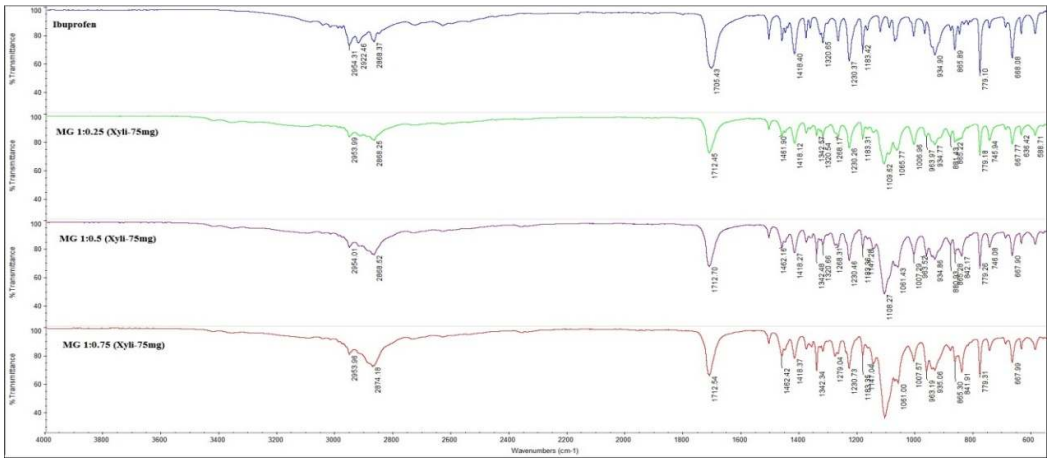

Fig. 10d. FTIR spectra of Ibuprofen, Poloxamer 407, MGX1, MGX3 and MGX5

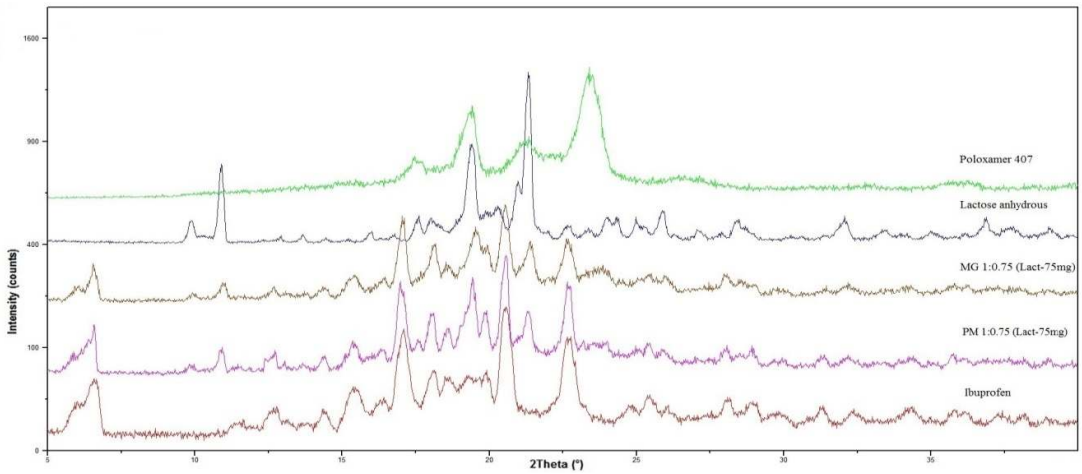

Fig. 11a. Overlay of PXRD patterns of Ibuprofen, Poloxamer 407, lactose anhydrous, PML5 and MGL5

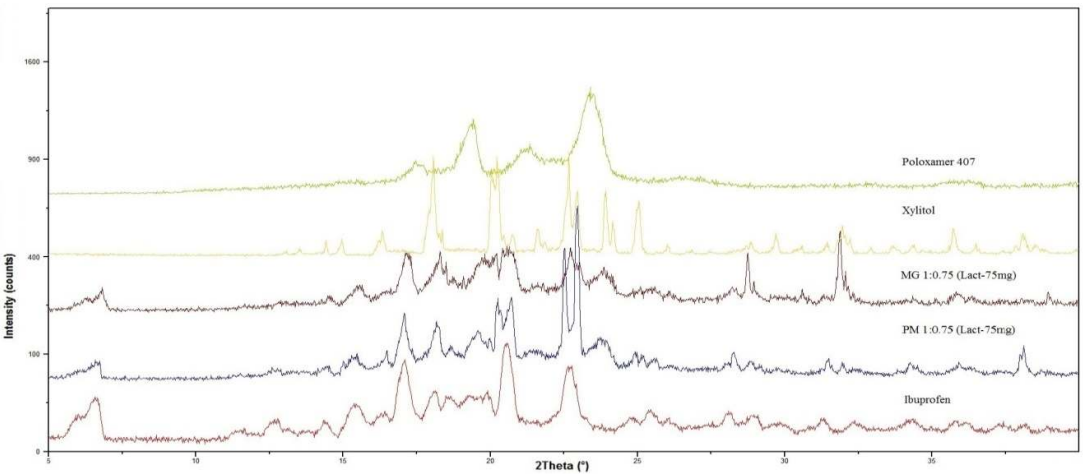

Fig. 11b. Overlay of PXRD patterns of Ibuprofen, Poloxamer 407, xylitol, PMX5 and MGX5

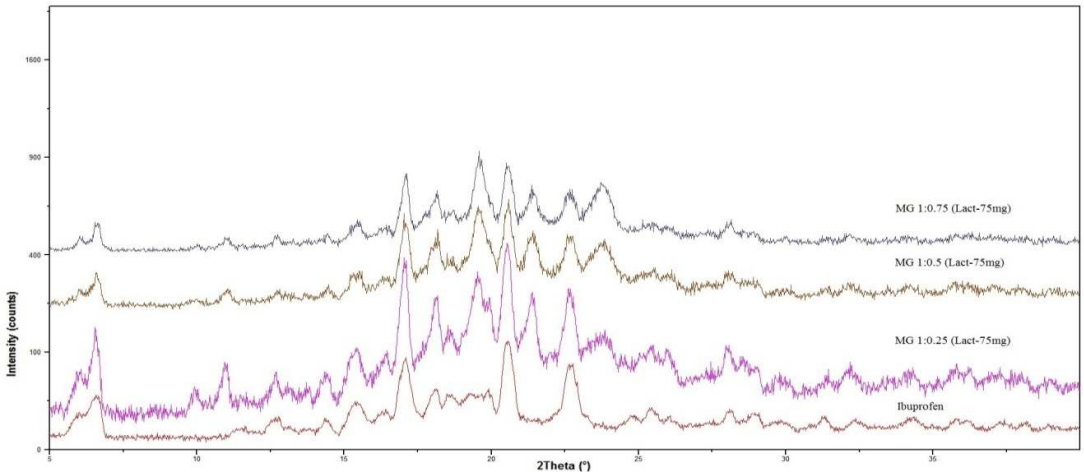

Fig. 11c. Overlay of PXRD patterns of Ibuprofen, Poloxamer 407, MGL1, MGL3 and MGL5

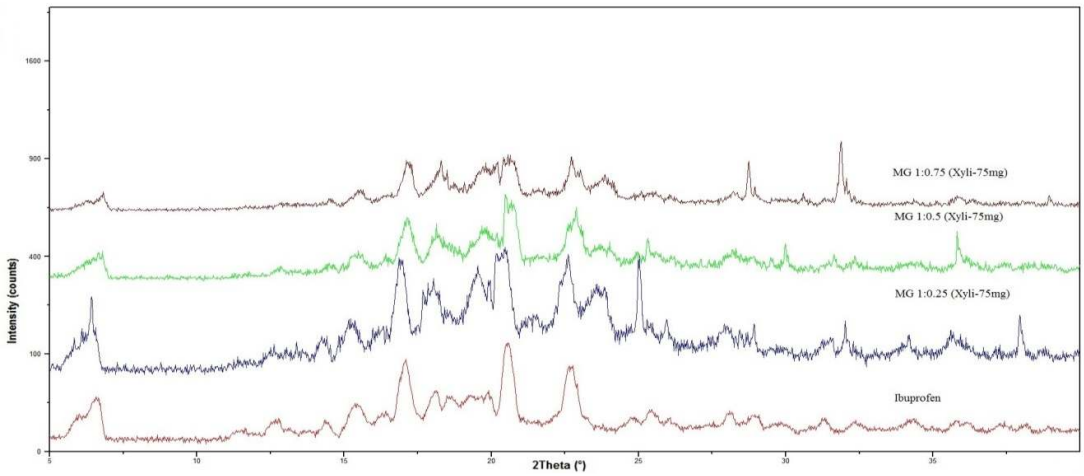

Fig. 11d. Overlay of PXRD patterns of Ibuprofen, Poloxamer 407, MGX1, MGX3 and MGX5

3.11 Powder X-ray Diffraction (PXRD)

Diffractogram of untreated Ibuprofen displayed intense and sharp peaks at 2θ values of 22.73°, 20.50° and 17.08° affirming its crystalline nature. X-ray diffraction analysis were performed on physical mixtures and melt granules to check the crystallinity of all the developed formulations (Fig. 11). The characteristic peaks of the Ibuprofen were seen in all the formulations, however attenuated intensities were observed for melt granules at higher concentration of poloxamer. It can be ascertained from the XRD observations that the enhanced dissolution rate of melt granules is due to reduction in crystallinity of Ibuprofen caused by formation of eutectic mixture and due to dilution effect in presence of hydrophilic excipients [2]. Increase in dissolution rate of Ibuprofen is thus achieved in form of melt granules, by sustaining its most stable crystalline form.

4. CONCLUSION

Melt granulation technique has been successfully employed to develop a robust formulation which enhances dissolution rate and thus bioavailability for BCS class II drugs. This alteration in dissolution profile can be due to finer Ibuprofen particles adsorbed over hydrophilic excipients resulting in a higher surface area of drug exposed to dissolution media. Thus, according to Noyes-Whitney's equation higher dissolution rate was observed due to increase in exposed surface area of Ibuprofen. The synergistic effects of finer Ibuprofen particles, poloxamer surfactant

properties and hydrophilic character of excipients results in overall dissolution rate enhancement. Flowability concerns associated with Ibuprofen and granules containing poloxamer has been counterbalanced by using hydrophilic excipients which plays a dual role of promoting wetting of drug and aiding flowability of formulation. The objective of developing a formulation with enhanced dissolution properties along with freely flowing powder was investigated in the current study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors are thankful to Division of Pharmaceutical Sciences, Long Island University to provide an opportunity to conduct the above research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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