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# Development and evaluation of *Artemisia vulgaris* mucilage based polymeric network for controlled drug delivery

**Ushna Laraib[1], Ume Ruqia Tulain*[1], Alia Erum[1], Muhammad Ajaz Hussain[2], Nadia Shamshad Malik[3], Ayesha Rashid[4], Samia Kausar[1] and Hira Ijaz[5]**

[1]College of Pharmacy, University of Sargodha, Sargodha, Pakistan
[2]Department of Chemistry, University of Sargodha, Sargodha, Pakistan
[3]Department of Pharmacy, Capital University of Science and Technology, Islamabad, Pakistan
[4]Department of Pharmacy, The Women University Multan, Multan, Pakistan
[5]Department of Pharmacy, University of Faisalabad, Faisalabad, Pakistan

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**Abstract**: The present study was conducted to fabricate and compare pH-sensitive polymeric networks of *Artemisia vulgaris*- Methacrylic acid using free radical polymerization conventional method and microwave-assisted method. Potassium persulphate and N' N'- Methylene bisacrylamide were employed as an initiator-crosslinker system. Swelling studies were performed at pH 1.2, 4.5, 6.8 and 7.4. Concentrations of polymer and monomer along with radiation dose were optimized as a function of swelling. Porosity and gel fraction were calculated for all samples. FTIR study confirmed the formation of cross-linked networks. Results of SEM indicated that the microwave irradiated polymeric network had a more porous structure. DSC and XRD study indicated the entrapment of drug inside the polymeric networks in amorphous form. In comparison to the conventional method, the polymeric network prepared by the microwave-assisted method exhibited high swelling ratios, porosity, thermal stability and drug release. These results signify microwave radiations as an effective alternative to the conventional heating method.

**Keywords**: Polymeric network, pH-sensitive, microwave irradiated, conventional, lornoxicam.

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## INTRODUCTION

Over the years the demand for safe and more effective pharmaceutical products has increased and thus has turned into a major zone of research. Novel systems are being investigated for enhancing drug delivery and improving medical instruments (Pillay *et al.*, 2013). The oral route is preferred for administrating drugs as it is simple, suitable, and convenient. Nevertheless, orally administered drugs are subjected to an unfavorable environment throughout the process of absorption. For example, the presence of digestive enzymes in the gut, specifically stomach and small intestine, can degrade them. Also, the value of pH is different in various regions of the gastrointestinal tract (GIT) which can lead to the hydrolysis and oxidation of the drugs (Liu *et al.*, 2017).

Polymers consist of large chains of macromolecules along with different types of functional groups. These can be customized for a variety of applications by mixing them with other substances of high and low molecular weights. Both synthetic as well as natural polymers are being utilized in the pharmaceutical and food items (Singh, Sharma and Malviya, 2011). Natural polymers have got great attention and have more attractive applications as they are easily available and can be modified chemically. In the pharmaceutical industry, they are used as binders, diluents, disintegrants and thickeners and are being utilized in the production of various dosage forms such as microspheres, nanoparticles, ophthalmic solutions and suspensions, etc. They also have applications in cosmetics, paint and paper industry. Natural polymers, for example, gums and mucilages are preferred over other synthetic/semisynthetic excipients due to their bio-compatibility and low toxicity (Bahadur *et al.*, 2017)

Artemisia species are used throughout the world for their different kinds of medicinal properties e.g. anti-inflammatory, antimicrobial, antioxidant, antimalarial, etc (Karabegovic *et al.*, 2011). *Artemisia vulgaris* belongs to the Asteraceae family. Infusion of its aerial parts is used as a traditional medicine in the treatment of many diseases (Correa-Ferreira *et al.,* 2014).

Hydrogels can be described as three-dimensional (3-D) polymeric networks made up of a polymer backbone, water, and a crosslinking agent. These polymeric networks are hydrophilic in nature and can imbibe water/physiological fluids (Krol *et al.*, 2016). Hydrogels can be cross-linked physically or chemically. This cross-linking not only prevents these polymeric networks from dissolving despite absorbing substantial amount of water and/or biological fluids but also facilitates the release of active agents in a defined manner by immobilizing them (Rizwan *et al.*, 2017; Saboktakin, 2010).

Microwave has appeared as an effective source of thermal energy and constitutes a unique system of heating

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**Corresponding author:* e-mail: umeruqia.tulain@uos.edu.pk

materials in a variety of ways. A new technique emerging in the area of polymer science is ‘microwave assisted free radical polymerization’ for grafting of biomaterial in the presence or absence of a catalyst (Singh, Nath and Guha, 2011). The cross-linking rate increases significantly under microwave radiations due to increased polymerization as compared to conventional thermal method (Jovanovic and Adnadjevic, 2010). The microwave heating method is fast, easy to operate and highly reproducible method that does not require inert conditions as compared to conventional method (Makhado *et al.*, 2017).

Hydrogels that undergo significant changes in their structure, swelling properties, mechanical strength and permeability in response to a variety of stimuli e.g. pH, light, temperature, pressure, electric current, etc. are called stimuli-responsive hydrogels (Kulkarni and Sa, 2008). pH-sensitive polymeric networks have been the prime focus of researchers that swell while moving from acidic to mildly basic environment in the gastrointestinal tract. The small intestine is deemed to be an ideal location for the delivery of substances that are sensitive to gastric environment (Hibbins *et al.*, 2017).

Hydrogels are mostly used to deliver hydrophilic drugs. Loading of hydrophobic drugs is limited in hydrogel matrices. It presents the main problem as most of the marketed drugs and drugs under research are hydrophobic (Larraneta *et al.*, 2018). Loading of hydrophobic drugs into hydrogels can increase their aqueous solubility and extended-release of these drugs can be achieved (McKenzie *et al.*, 2015). Lornoxicam (model drug) is an NSAID that belongs to BCS class 2 (low solubility, high permeability). It has a short half-life (3-5 hours) and to maintain plasma levels it is prescribed in divided doses twice or thrice a day (Sunil *et al.*, 2012). To reduce the dosing frequency and to achieve sustained levels of the drug in blood, a controlled release formulation of lornoxicam is preferable (Usman *et al.*, 2016).

The present study aimed to synthesize pH-sensitive polymeric networks of *Artemisia vulgaris*-MAA via conventional water bath and microwave-assisted methods. *Artemisia vulgaris* mucilage was used as a natural polymer to synthesize polymeric network drug carriers. Also, microwave radiations were successfully used to synthesize crosslinked polymeric networks in a short duration. Polymeric network prepared by microwave-assisted method exhibited better swelling, porosity, thermal stability, and drug release properties as compared by the conventional water bath method. Prepared polymeric networks also showed pH-sensitive properties and have the potential to be used as a carrier for controlled delivery of lornoxicam for achieving patient compliance.

## MATERIALS AND METHODS

Seeds of *Artemisia vulgaris* were purchased from the local food market of Sargodha, Pakistan. Methacrylic acid (MAA), sodium hydroxide (NaOH), potassium dihydrogen phosphate ($KH_2PO_4$) and potassium per sulfate (KPS) were obtained from Sigma Aldrich, Germany. N’ N’-Methylene bisacrylamide (MBA) was purchased from Fluka, Switzerland. Hydrochloric acid, n-Hexane and absolute Ethanol were obtained from Riedel-de Haen, Germany. Lornoxicam was accepted as a gift from Saffron Pharmaceuticals, Faisalabad, Pakistan.

### *Extraction of Artemisia vulgaris mucilage*

Seeds of *Artemisia vulgaris* were soaked in distilled water. Mucilage extracted from seeds was separated by some mechanical method. Extracted mucilage was then washed with n-hexane to set it free from fats and waxes (if any). After washing the mucilage was spread on a steel tray and kept in the oven to dry at 60°C. Finally, the dried mucilage was ground to a fine powder and stored in an airtight container in a desiccator under vacuum (Haseeb *et al.*, 2016).

### *Synthesis of polymeric networks /Hydrogel*

Polymeric networks of *Artemisia vulgaris*-MAA were synthesized via free-radical polymerization technique, using a conventional water bath and microwave-assisted method.

### *Conventional water bath method*

A weighed amount of extracted *Artemisia vulgaris* mucilage was suspended in distilled water at 70°C and stirred continuously to obtain a mucilaginous solution. Then KPS was added to it and stirred for another 10 min for generation of radicals. Finally, the mixture was allowed to cool at room temperature. A separate solution of MBA in methacrylic acid was prepared and added to the above mixture under magnetic stirring. Distilled water was used to adjust the final weight. The prepared solution was then kept in a water bath and the temperature was raised to 80°C gradually. After the termination of the reaction, copolymers obtained were then cut into discs of 5mm thickness using a blade. For the removal of unreacted monomer, the discs were washed with ethanol and water solution (30:70). After this, the discs were dried in an oven at 50°C until a constant weight was achieved. These discs were then kept in airtight containers in order to be used for further characterization (Shabir *et al.*, 2017; Tulain *et al.*, 2018). The composition of formulations prepared by the thermostatic water bath method is given in table 1.

### *Microwave-assisted method*

Based on mechanical strength C2 was chosen as optimum formulation. The same amounts of polymer and monomer were used for comparison with the thermostatic water

**Table 1**: Composition of formulations prepared by conventional water bath method

| Formulation code | *Artemisia vulgaris* mucilage extract (g/100g) | Methacrylic acid (g/100g) | Initiator (g/100g) | Crosslinker (g/100g) |
|---|---|---|---|---|
| C1 | 1 | 40 | 0.4 | 0.4 |
| C2 | 2 | 40 | 0.4 | 0.4 |
| C3 | 2 | 35 | 0.4 | 0.4 |
| C4 | 2 | 30 | 0.4 | 0.4 |

**Table 2**: Composition of formulations prepared by microwave assisted method

| Formulation code | Exposure time (min) at 300 W | *Artemisia vulgaris* mucilage extract (g/100g) | Methacrylic acid (g/100g) | Initiator (g/100g) | Crosslinker (g/100g) |
|---|---|---|---|---|---|
| M1 | 5 | 2 | 40 | 0.4 | 0.4 |
| M2 | 10 | 2 | 40 | 0.4 | 0.4 |

**Table 3**: Drug loaded in *Artemisia vulgaris*-MAA formulations prepared by conventional water bath (C2) and microwave heating method (M1)

| Formulation code | Lornoxicam loaded mg/0.3g disc | |
|---|---|---|
| | By Weight Method ±S.E.M | By Extraction Method ±S.E.M |
| C2 | 34.4 ± 1.3 | 31.5 ± 1.5 |
| M1 | 50.3 ± 1.9 | 47.7 ± 2.0 |

**Table 4**: Similarity and difference factor values for dissolution profiles of polymeric networks prepared by different methods (C2 & M1)

| C2 vs M1 | Difference factor ($f_1$) | Similarity factor ($f_2$) |
|---|---|---|
| | 24.14 | 48.74 |

**Table 5**: Correlation co-efficient ($R^2$) and release exponent (n) of various kinetic models

| Formulation code | pH | Release model | | | | | |
|---|---|---|---|---|---|---|---|
| | | Zero order | First order | Higuchi | Korsmeyer-Peppas | | Hixon Crowell |
| | | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n | $R^2$ |
| C2 | 1.2 | 0.9714 | 0.5077 | 0.9974 | 0.9978 | 0.553 | 0.4855 |
| | 7.4 | 0.9849 | 0.8668 | 0.9934 | 0.9982 | 0.673 | 0.8007 |
| M1 | 1.2 | 0.9745 | 0.4626 | 0.9973 | 0.9983 | 0.541 | 0.4279 |
| | 7.4 | 0.9813 | 0.6966 | 0.9926 | 0.9959 | 0.646 | 0.5558 |

bath method. The reaction mixture was set in a locally available microwave oven (Dawlance, Korea). It was first exposed to radiations for 5 min at 100W, then after 1 min interval, it was again irradiated for 5 min at 180W and again after 1 min interval, it was finally irradiated at 300 W for different periods. Obtained copolymer cylinders were cut into discs and washed as described in the method mentioned above (Iqbal *et al.*, 2017). Formulations prepared by the microwave method are given in table 2.

### Swelling studies

Swelling studies of all prepared formulations were conducted at pH 1.2, 4.5, 6.8 and 7.4. The swelling ratio, equilibrium swelling and pulsatile swelling behavior were measured.

### Swelling ratio (q) determination

Dried discs were placed in 100ml solutions of pH 1.2, 4.5, 6.8 and 7.4 at 37°C. Swollen samples were removed, dried with filter paper and weighed at regular intervals. The swelling ratio(q) was determined by using equation 1:

$$q = W_s / W_d \qquad (1)$$

Where 'q' represents the dynamic swelling ratio, '$W_s$' is swollen gel's weight given at time t and '$W_d$' indicates the weight of sample at $t_0$ (Tulain *et al.*, 2018).

### Equilibrium swelling determination (% ES)

For equilibrium swelling, samples were allowed to remain in the same solutions. Percentage equilibrium swelling (% ES) or percentage equilibrium water content (EWC %) of each formulation was computed using equation 2:

$$ES\,(\%) = (M_{eq}-M_o) / M_{eq} \times 100 \qquad (2)$$

Where '$M_{eq}$' denotes the mass of the sample at equilibrium state and '$M_o$' is the mass of dry sample (Ranjha *et al.,* 2011).

### Pulsatile swelling

To evaluate pulsatile swelling behavior, the dry disc was placed in a solution of pH 7.4 to swell. After this, the disc was taken out and placed in a solution of pH 1.2 to de-swell. It was again placed in pH 7.4 solution to swell followed by de-swelling at pH 1.2 (Ijaz *et al.,* 2018).

### *Gel fraction determination*

Freshly prepared discs (non-washed) were taken and oven dried to achieve a constant weight ($W_o$) at 50°C. For the removal of unreacted monomer, the discs were extracted with de-ionized water for 72 hrs and were then again oven dried at 50°C to attain a constant weight ($W_1$). The gel fraction was determined for each disc using the following equation (Ranjha *et al.*, 2016; Pandey and Amin, 2013):

$$\text{Gel fraction } (\%) = (W_1/W_0) \times 100 \qquad (3)$$

Where '$W_0$' and '$W_1$' denote the weights of dried discs before and after extraction respectively.

### *Porosity measurement*

For measuring porosity, the solvent replacement procedure was employed. Dried discs of polymeric networks were first weighed and then dipped in absolute ethanol overnight. After that, the discs were blotted using a filter paper and were again weighed. The porosity was calculated using the following equation:

$$\text{Porosity} = (M_h - M_d) / \rho V \qquad (4)$$

Where '$M_d$' is the mass of dried disc before dipping and '$M_h$' is the mass of disc after dipping in absolute ethanol. '$\rho$' denotes the density of absolute ethanol and 'V' represents the volume of the hydrogel (Jalil *et al.*, 2017).

### *Drug loading*

A 0.1% (w/v) solution of lornoxicam in phosphate buffer (USP) of pH 7.4 was prepared. Copolymer discs were immersed in the drug solution for 24 hours. After that, the discs were taken out and washed with distilled water. Finally, the drug-loaded polymeric discs were oven dried at 50°C until a constant weight was achieved (Ijaz *et al.,* 2018).

### *Determination of drug loading*

The total amount of the drug loaded into polymeric networks was calculated by weight and extraction methods (Khan and Ranjha, 2014). In the weight method, the following formulas were used to determine drug loading and percentage drug loading in polymeric networks:

$$\text{Amount of drug} = W_D - W_d \qquad (5)$$

$$\%\text{ Drug loading} = [(W_D - W_d)/ W_d] \times 100 \qquad (6)$$

Here, $W_d$ and $W_D$ represent the weights of dried discs before and after dipping in drug solution respectively.

In the extraction technique, repeated extraction of drug-loaded discs of polymeric networks with phosphate buffer (USP) of pH 7.4 was done. Every time 25ml of fresh buffer was used until no drug remained in solution. Drug contents were then analyzed at 374 nm. Quantity of drug in all parts was computed as the total amount of drug loaded (Khan and Ranjha, 2014).

### *Fourier transform infrared spectroscopic (FTIR) analysis*

FTIR spectra of pure polymer, pure drug, monomer, and prepared polymeric networks before and after drug loading were recorded using IR Prestige-21 spectrophotometer (Shimadzu, Japan). Potassium bromide (KBr) was used to prepare tablets of samples which were then scanned in region of 400-4000cm$^{-1}$ (Vijan *et al.*, 2012).

### *Scanning electron microscopic (SEM) analysis*

The surface morphology of polymeric networks was examined using scanning electron microscopy (SEM). Samples were placed on an aluminum mount and then sputtered with gold-palladium. Then a high beam of accelerating electrons at 10kV was applied to scan the samples and produce images (Bukhari *et al.*, 2015).

### *Thermal analysis (TGA and DSC)*

Thermo-gravimetric analysis (TGA) and differential scanning calorimetric (DSC) analysis were done for the evaluation of thermal changes in pure drug, loaded, and unloaded polymeric networks. This was performed at a temperature range of 20°C to 600°C under the nitrogen atmosphere. The heating rate was uniform i.e. 20°C/min (Minhas *et al.*, 2016).

### *X-ray diffraction analysis (XRD)*

X-ray diffractograms of pure drug and synthesized polymeric networks before and after drug loading were recorded using an X-ray diffractometer (Panalytical, Germany). Copper Kα radiation was generated at a voltage (40kV) and current (35mA). The range of differential angle was 10-80° (2θ) (Ahuja *et al.*, 2011).

### *In-vitro drug release measurement*

The *in vitro* release studies of prepared loaded hydrogels were carried out using a USP dissolution apparatus II. The dissolution mediums used were 0.1 N HCl and phosphate buffer of pH 7.4. The temperature was maintained at 37± 0.5°C and the speed of paddle was adjusted at 50 rpm. About 5 ml samples were withdrawn from the dissolution medium at 0.5, 1, 2, 4, 6, 8, 10, 14, 18, 22 and 24 hrs and replaced with an equal volume of fresh dissolution buffer. The samples were filtered, suitably diluted and finally analyzed via a UV spectrophotometer at 374 nm and the cumulative drug release was calculated (Karna *et al.,* 2012; Tyagi and Kori, 2014; Atyabi *et al.,* 2010).

### *Percentage of drug release*

Following formula was used to calculate percentage drug release:

$$\%\text{ release} = (W_t / W_\infty) \times 100 \qquad (7)$$

Here '$W_t$' represents the amount of drug release at any time t and '$W_\infty$' shows the total amount of drug absorbed into polymeric matrix (Sokker *et al.*, 2009).

***Assessment of release kinetics***

*Model-independent approach*

The model-independent approach was applied to compare the dissolution profiles of polymeric networks prepared by different techniques. It is based on the evaluation of fit factors ($f_1$, $f_2$) (Moore and Flanner, 1996). The difference factor ($f_1$) is a measure of percent error between the curves of two profiles (Eq.8) while similarity factor ($f_2$) is logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between two curves (Eq. 9).

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \qquad (8)$$

$$f_2 = 50 \log[\{1 + \frac{1}{n} \sum_{j=1}^{n} (R_j - T_j)^2\}^{0.5} \times 100] \qquad (9)$$

Where n shows the sample number while $R_j$ and $T_j$ represent the mean percent dissolved of reference and test formulation at time j respectively. Generally, if $f_1$ is between 0-15 and $f_2$ is between 50-100, the two profiles are considered similar (Costa and Lobo, 2001; Cascone, 2017).

***Model dependent approach***

The model-dependent approach was applied to determine the release kinetics of lornoxicam. Korsmeyer-Peppas, Higuchi, Hixon-Crowell, Zero-order and First-order models were applied to evaluate the mechanism of drug release. These models are represented by following equations:

Zero-order kinetics: $Q_t = K_o t$ (10)
First order kinetics: $\ln(100 - Q_t) = \ln 100 - K_1 t$ (11)
Higuchi model: $Q_t = K_H t^1/_2$ (12)
Hixon-Crowell model: $(100 - Q_t)^{1/2} = 100^{1/3} - k_{HC}\, t$ (13)

Where $Q_t$ represents the percentage of drug released at time t while $K_o$, $K_1$, $K_H$, and $K_{HC}$ represent Zero-order, First-order, Higuchi, and Hixon-Crowell release rate constants respectively.

Korsmeyer-Peppas model: $Q_t/Q_e = k_{KP}\, t^n$ (14)

Where $Q_t/Q_e$ indicates the fraction of released drug from the sample at time t and $k_{KP}$ represents the release rate constant. 'n' represents the release exponent. When the value of n is 0.45 the order of release is Fickian. When n = 1, it corresponds to case II transport. The mechanism of diffusion is non-Fickian when 0.45 <n<1 (Dash *et al.*, 2010).

## STATISTICAL ANALYSIS

Microsoft Excel (2013) was used to calculate all means, S.E.M and percentages. Whereas DD solver was applied for measurement of release kinetics.

## RESULTS

This study was conducted to fabricate and compare pH-sensitive polymeric networks of *Artemisia vulgaris*-Methacrylic acid using free radical polymerization conventional method and microwave-assisted method. Prepared polymeric networks were characterized by swelling behaviour mentioned in Figures from 1-6 Porosity and gel contents showed in figs. 7 and 8 and instrumental analysis has been depicted in Figures 9-20. Drug release had been characterized and depicted in fig. 21. In comparison to the conventional method, the polymeric network prepared by the microwave-assisted method exhibited high swelling ratios, porosity, thermal stability and drug release. These results signify microwave radiations as an effective alternative to the conventional heating method.

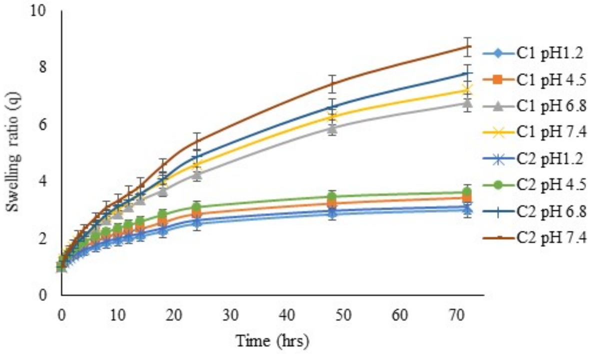

**Fig. 1**: Influence of polymer concentration on dynamic swelling ratio in pH 1.2, 4.5, 6.8 and 7.4

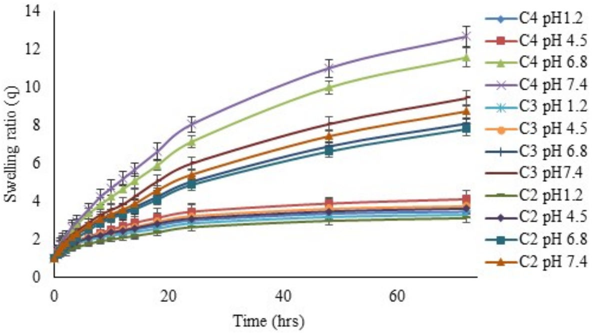

**Fig. 2**: Influence of monomer concentration on dynamic swelling ratio in pH 1.2, 4.5, 6.8 and 7.4

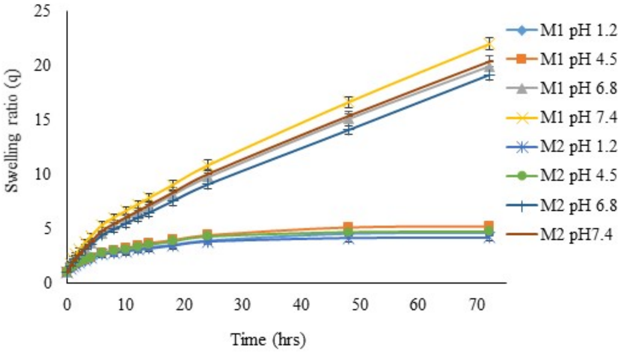

**Fig. 3**: Influence of radiation dose on dynamic swelling ratio in pH 1.2, 4.5, 6.8 and 7.4

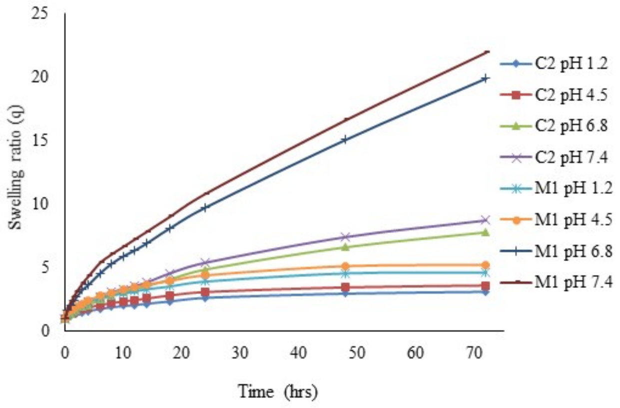

**Fig. 4**: Comparative swelling ratios of polymeric networks prepared by conventional heating (C2) and microwave assisted method (M1)

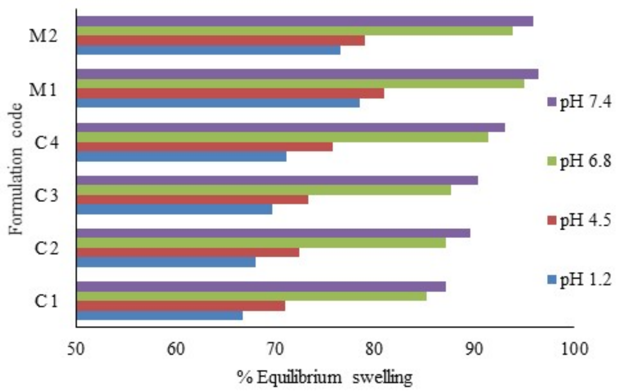

**Fig. 5**: Percent equilibrium swelling of all formulations prepared by conventional heating method and microwave assisted method

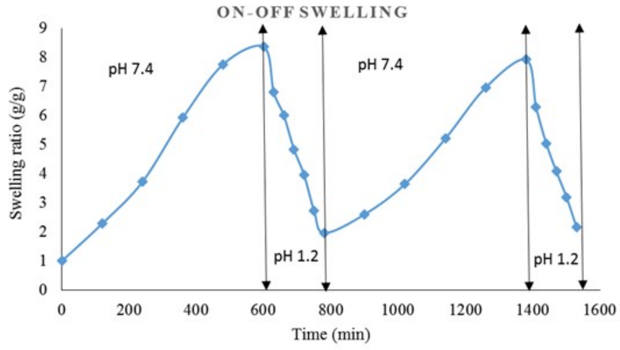

**Fig. 6**: On-off swelling behavior of *Artemisia vulgaris*-MAA polymeric network at pH 1.2 and 7.4

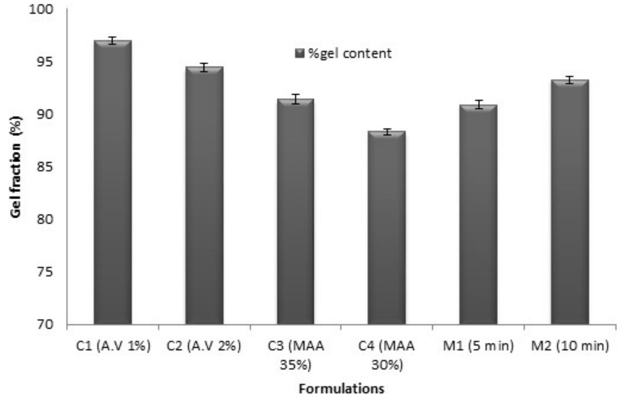

**Fig. 7**: Percent gel fraction of all *Artemisia vulgaris*-MAA formulations

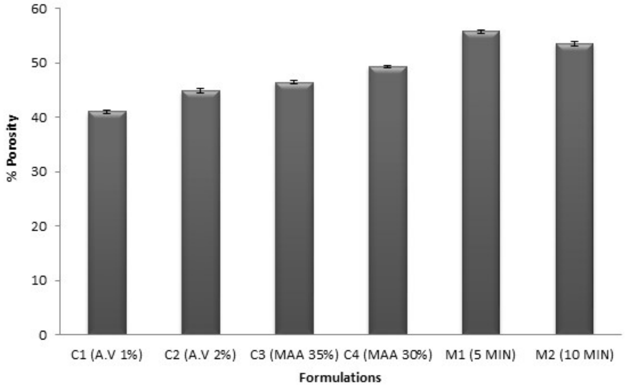

**Fig. 8**: Porosity measurement of all *Artemisia vulgaris*-MAA formulations

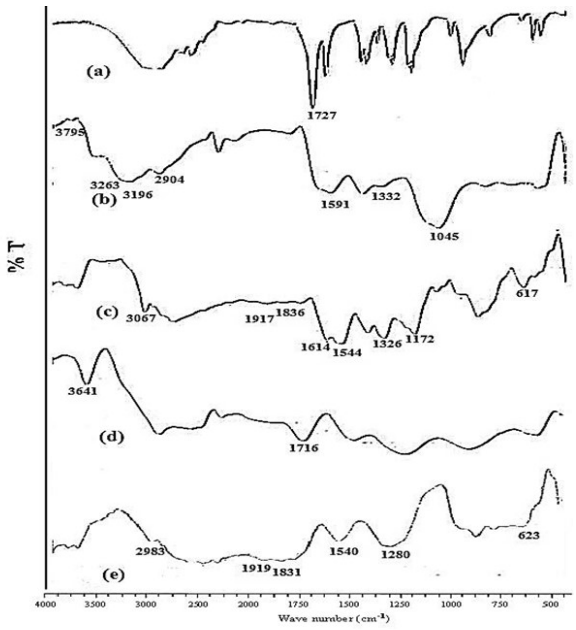

**Fig. 9**: FTIR overlay of (a) Methacrylic acid (b) *Artemisia vulgaris* (c) Lornoxicam (d & e) unloaded & drug loaded polymeric network prepared by conventional method

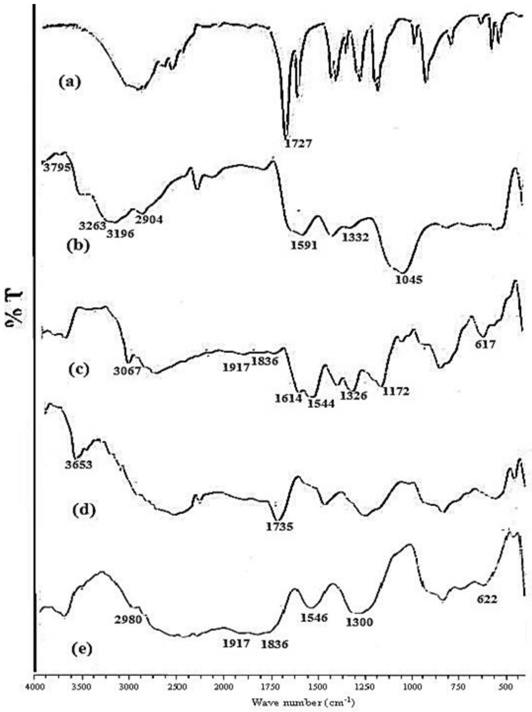

**Fig. 10**: FTIR overlay of (a) Methacrylic acid (b) *Artemisia vulgaris* (c) Lornoxicam (d & e) unloaded & drug loaded polymeric network prepared by microwave assisted method

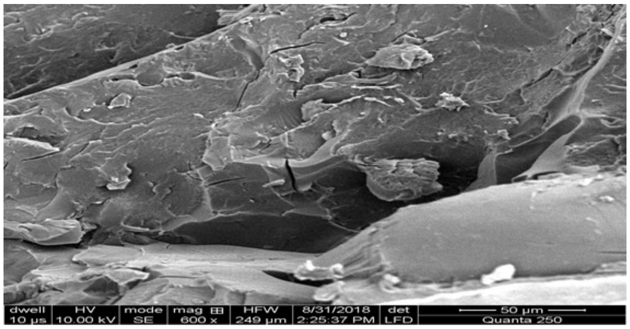

**Fig. 11**: SEM image of polymeric network prepared by conventional method with 50 µm scale

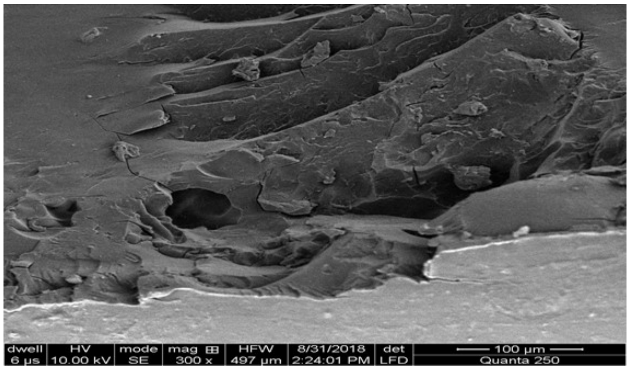

**Fig. 12**: SEM image of polymeric network prepared by conventional method with 100 µm scale

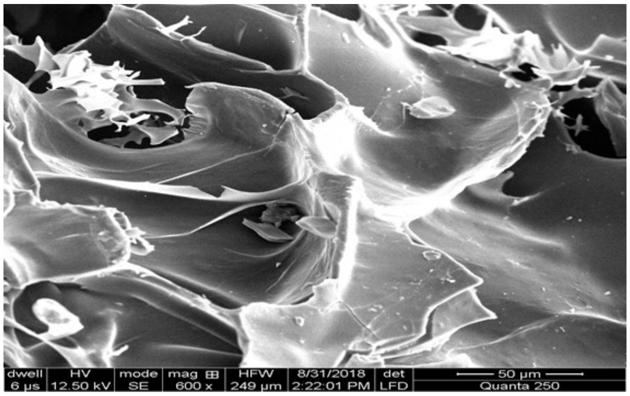

**Fig. 13**: SEM image of polymeric network prepared by microwave assisted method with 50µm scale

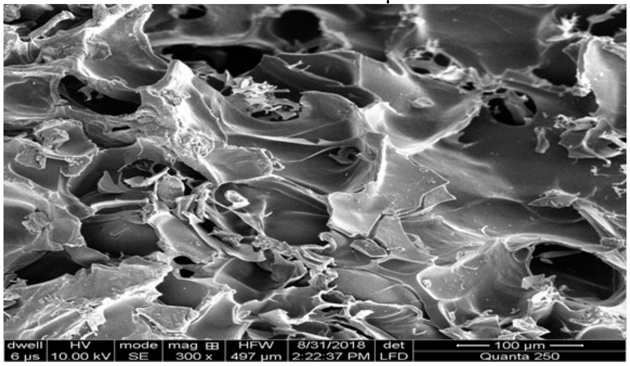

**Fig. 14**: SEM image of polymeric network prepared by microwave assisted method with 100 µm scale

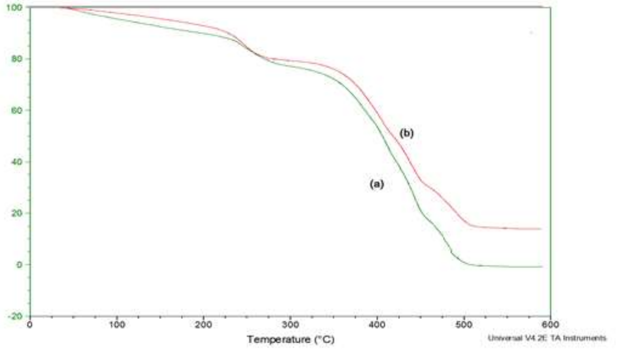

**Fig. 15**: Comparative TGA curves of polymeric networks prepared by (a) conventional heating and (b) microwave assisted method

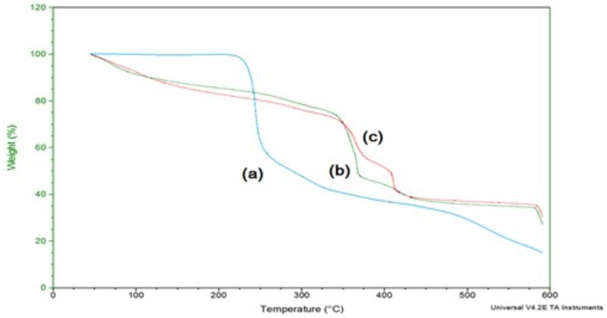

**Fig. 16**: TGA curve of (a) lornoxicam, drug loaded polymeric networks prepared by (b) conventional heating and (c) microwave assisted method

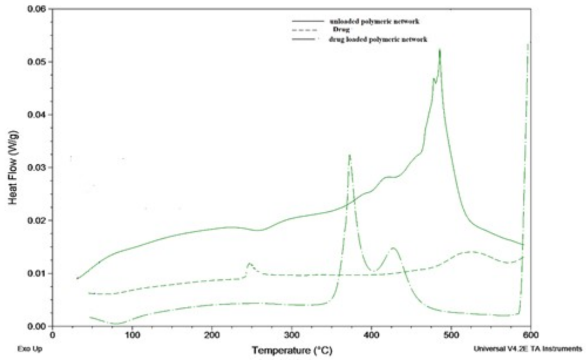

**Fig. 17**: DSC curve of drug, drug loaded and unloaded polymeric network prepared by conventional method

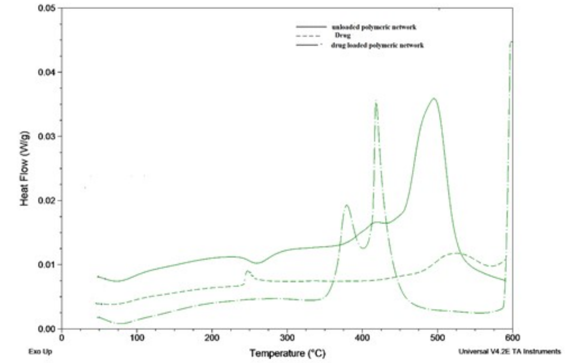

**Fig. 18**: DSC curve of drug, drug loaded and unloaded polymeric network prepared by microwave assisted method

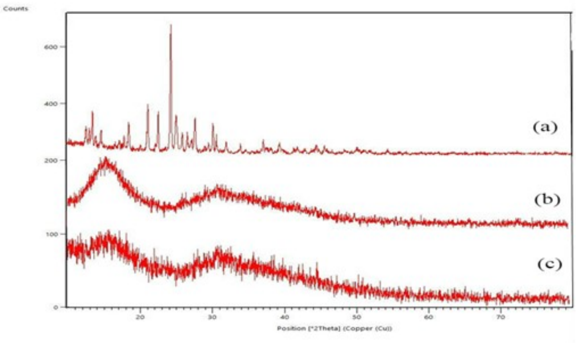

**Fig. 19**: Overlaid XRD spectra of (a) drug (b) unloaded & (c) loaded polymeric network prepared by conventional method

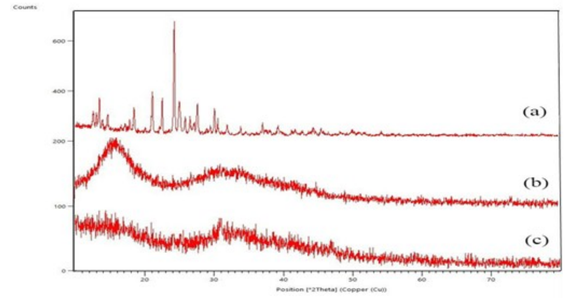

**Fig. 20**: Overlaid XRD spectra of (a) drug (b) unloaded & (c) loaded polymeric network prepared by microwave assisted method

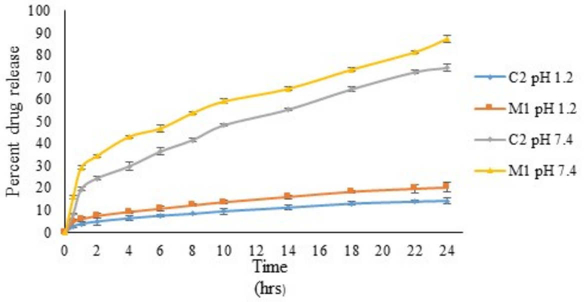

**Fig. 21**: Percentage lornoxicam release from C2 and M1 at pH 1.2 and 7.4

## DISCUSSION

### *Swelling studies of Artemisia vulgaris-MAA formulations*

Three sets of polymeric networks were synthesized to evaluate the effect of polymer, radiation dose and monomer on the swelling index. The swelling behavior of all polymeric networks was studied in buffers of pH 1.2, 4.5, 6.8 and 7.4 at different time intervals up to equilibrium swelling. Dynamic swelling ratios of polymeric networks having different concentrations of a polymer are given in Fig. 1. Swelling ratios for C1 and C2 were 3.00 and 3.12 at pH 1.2, 3.45 and 3.62 at pH 4.5, 6.76 and 7.80 at pH 6.8 and 7.21 and 8.73 at pH 7.4 respectively. Dynamic swelling ratios of polymeric networks having a different concentration of monomer are presented in Fig. 2. Swelling ratios for C3 and C4 were 3.30 and 3.46 at pH 1.2, 3.74 and 4.12 at pH 4.5, 8.09 and 11.57 at pH 6.8 and 9.42 and 12.67 at pH 7.4 respectively. Dynamic swelling ratios for polymeric networks M1 and M2 prepared using a microwave at different radiation doses were 4.65 and 4.22 at pH 1.2, 5.23 and 4.77 at pH 4.5, 19.89 and 19.10 at pH 6.8 and 21.93 and 20.33 at pH 7.4 respectively as illustrated in Fig. 3. Percent equilibrium swelling of all prepared formulations is presented in Fig. 5. All the polymeric networks showed less swelling at pH 1.2 and maximum swelling at pH 7.4. This is due to the inclusion of methacrylic acid which imparted pH-sensitive properties to all the polymeric networks. In acidic medium, the value of pH is less than the pKa of methacrylic acid, the ionization of -COOH groups do not occur and strong hydrogen bonds exist within the gel network. As the value of pH becomes greater than the pKa of methacrylic acid, the -COOH groups become ionized to -COO$^-$. This results in an increase in electrostatic repulsive forces between charged groups and causes the gel to swell. Hence, at pH 7.4 polymeric networks showed maximum swelling and also took the longest time to reach equilibrium (Sun *et al.*, 2016).

It can be seen that an increase in the polymer concentration caused an increase in the swelling. In literature most researchers have attributed increase in the swelling index with increase in polymer content to hydrophilic nature of polysaccharides (Minhas *et al.*, 2018; Tulain, Ahmad and Rashid, 2018; Kaity, Isaac and Ghosh, 2013). Also, copolymerization of vinyl monomers may increase the swelling power of natural polysaccharide due to introduction of free hydrophilic groups as stated by Singh *et al.* and Kaity *et al.* (Kaity *et al.*, 2013; Singh, Nath and Guha, 2011). However further work is needed for identification of constituents present in *Artemisia vulgaris* mucilage. It was observed that unlike polymer concentration, swelling decreased with an increase in monomer content from C4 to C2. This can be ascribed to increase in the viscosity of medium that reduced the penetration of molecules of monomer and free radicals. Also, formation of a dense network inhibited the transport of water molecules (Huang, Wang and Shang, 2017; Rashid *et al.*, 2015). Shah *et al.* observed similar trends in swelling ratios using methacrylic acid as monomer and cellulose acetate phthalate as polymer (Shah *et al.*, 2018). Polymeric networks prepared by microwave assisted method were not only synthesized in short time but also showed much higher swelling ratios. An increase in irradiation time resulted in less swelling which can be explained by the fact that increased radiation dose increases the crosslinking density and pore size is somewhat reduced (Goganian *et al.*, 2014). Zhang *et al.* prepared crosslinked starch using microwave radiations and reported similar effects of exposure time on cross linking (Zhang *et al.*, 2013).

A comparison graph between swelling ratios of polymeric networks prepared by conventional water bath method (C2) and microwave assisted method (M1) is shown in Fig. 4. It can be seen that swelling rate of M1 was much faster than C2. The percent equilibrium swelling was also higher and equilibrium time was achieved early than C2. This is due to the formation of large number of pores. A porous network allows easy and faster penetration of water molecules (Huang *et al.*, 2002; Zhao *et al.*, 2008a).

### On-Off Switching

Pulsatile swelling behavior of synthesized *Artemisia vulgaris*-MAA polymeric network was also investigated in pH 1.2 and pH 7.4 to check if it can be used as an on-off switch. It is evident from Fig. 6 that swelling process was slower than the de-swelling process. The transition between collapsed state at pH 1.2 and swollen state at pH 7.4 is attributed to the ionization of -COOH groups as discussed above. This property can be used to protect drugs like NSAIDs from the acidic environment of stomach and for targeted release in lower intestine (Haseeb *et al.*, 2017). Pulsatile swelling behavior of other pH-sensitive hydrogels has been reported in literature (Ashraf *et al.*, 2017; Bartil *et al.*, 2007; Kim and Shin, 2007).

### Determination of percent gel content and percent porosity

Percent gel content depends upon cross linking density while percent porosity is a measure of pore volume of the polymeric networks. Percent gel content and percent porosity of all synthesized formulations are given in Fig. 7 and 8 respectively. According to the results, an increase in the polymer content from 1% to 2% resulted in more porosity (41.04% to 44.87%) and decreased gel fraction (96.93% to 94.45%). While in case of monomer, percent porosity increased from 44.87% to 49.33% and percent gel content decreased from 94.45% to 88.33% upon decreasing the monomer content from 40% to 30%. This is because gel content depends on crosslinking density which effects the motion of free radicals (Ajji, Othman and Rosiak, 2005). A dense and tight structure of polymeric network will have smaller pores and limited movement of polymeric chains which in turn decreases the water uptake capacity (Yacob and Hashim, 2014). An increase in the concentration of polymer made the solution more viscous which prevented the escape of some bubbles from the gel matrix and also caused a reduction in cross linking process (Nawaz *et al.*, 2018; Shah *et al.*, 2018). On the other hand, methacrylic acid led to increased crosslinking density of the polymeric network resulting in increased gel content. Ranjha *et al.* synthesized hydrogels of isosorbide mononitrate and has reported similar results using ethyl cellulose as polymer and acrylic acid as monomer (Ranjha *et al.*, 2014). Nanda *et al.* also confirmed that gel content and porosity were inversely proportional to each other with increasing cross linking density (Nanda *et al.*, 2013).

Similar pattern was seen in case of formulations prepared by microwave radiations. An increase in radiation dose led to an increase in percent gel content from 90.90% to 93.24% and percent porosity decreased from 55.81% to 53.55%. The reason is that under the influence of microwave radiations, more free radical sites were generated due to increased interactions between polymer, monomer, initiator and cross linker (Panchan *et al.*, 2018). This led to the formation of a denser and tighter structure with decreased pore size. Norzita and Kamaruddin prepared hydrogels using electron beam as a source of radiation while Abdullah *et al.* prepared hydrogels using microwave as well as gamma radiations and obtained similar results (Yacob and Hashim, 2014; Abdullah, Azfaralariff and Lazim, 2018).

It was also noticed that the porosity of formulations prepared by microwave irradiation was higher than those prepared by water bath method. The possible explanation is that microwave radiations decreased the gelation time and more porogen bubbles were formed and trapped inside the viscous solution resulting in increased porosity (Kabiri *et al.*, 2003).

### Determination of loaded drug

Amount of drug loaded in *Artemisia vulgaris*-MAA formulations prepared by conventional water bath (C2) and microwave heating method (M1) is given table 3.

### Fourier transform infrared (FTIR) analysis

Fourier transform infrared (FTIR) analysis was done to confirm cross linking and also to determine drug-excipient compatibility. Overlays of FTIR spectra of Methacrylic acid, *Artemisia vulgaris*, lornoxicam and lornoxicam loaded and unloaded polymeric networks prepared by both methods are illustrated in figs. 9-10. *Artemisia vulgaris* showed peaks at 3795.91cm$^{-1}$ corresponding to -OH stretching vibrations. N-H stretching vibrations were observed at 31960.05 and 3263.56cm$^{-1}$. Other prominent peaks were observed at 2904.80, 1591.27, 1332.81 and 1045.42cm$^{-1}$ corresponding to C-H stretching of alkane, N-H bending, C-N stretching and C-O stretching of ether respectively. The FTIR spectra of polymeric network prepared through crosslinking was different from the pure polymer indicating the development of a gel like structure. Emergence of peaks at 1716.65cm$^{-1}$ (fig. 9d) and 1735.93cm$^{-1}$ [Fig. 10 (d)] correspond to the carbonyl group and revealed the grafting of methacrylic acid onto the polymer backbone. Similar observations were stated by Ijaz *et al.* using acrylic acid (Ijaz *et al.*, 2018). Also, the -OH stretching vibrations of *Artemisia vulgaris* at 3795.91cm$^{-1}$ shifted to 3641.90 and 3653.18cm$^{-1}$ (figs. 9d and 10d) in crosslinked polymeric networks indicating the existence of hydrogen bonding (Ranjha *et al.*, 2011).

FTIR spectrum of lornoxicam showed a characteristic peak at 3067 cm$^{-1}$ corresponding to N-H stretching vibration. An absorption peak was observed at 1614cm$^{-1}$ owing to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1544cm$^{-1}$ which were attributed to the bending vibrations of the N-H group in the secondary amide. The stretching vibrations of the C-Cl group appeared at 617cm$^{-1}$ and that of the O=S=O group appeared at 1172 and 1326cm$^{-1}$. Likewise, there was no significant shift in the characteristic stretching band and the N-H bending of lornoxicam in the spectrum after its loading into the polymeric networks. However, the lornoxicam characteristic amide bands were broadened and some bands were diminished in the FTIR spectra of loaded samples. This might indicate the inclusion of lornoxicam in the polymeric network carrier. Taking into account the observed findings together with the results of DSC and XRD studies, they all suggest an almost complete conversion of the crystalline drug into amorphous form. Similar observations were reported by Joseph *et al.* (2018) and Abd-Allah *et al.* (2016).

Moreover, it was observed that the unloaded and loaded FTIR spectra of polymeric network prepared by microwave assisted method were almost similar to the unloaded and loaded spectra of polymeric network synthesized by conventional water bath technique respectively, suggesting the successful cross linking of *Artemisia vulgaris*-MAA polymeric network using microwave radiations. This work is comparable to the research work carried out by Iqbal *et al.* who prepared hydrogels of HPMC-g-PVA-co-poly(acrylic acid) using water bath and microwave radiations and showed that crosslinking through microwave occurred relatively in a short time (Iqbal *et al.*, 2017).

### Scanning electron microscopy (SEM)

SEM analysis was performed to study and examine the morphology of polymeric networks prepared by water bath method (C2) and microwave assisted method (M1). A comparison of SEM images of polymeric networks prepared by conventional water bath method (figs. 11-12) and microwave assisted method (figs. 13-14) clearly shows that the polymeric network prepared by water bath method exhibited higher crosslinking density with smooth surface and less cavities. While the application of microwave radiations made the hydrogel more porous. The pores formed appeared to be deeper and more uniform due to instantaneous penetration of radiations (Zhao *et al.*, 2008a). These pores not only allow easy diffusion of water but also are the sites where hydrophilic groups of the polymeric network interact with external stimuli. Hence, this porous structure is responsible for higher swelling ratios (Pourjavadi *et al.,* 2007). Zhao *et al.* prepared PNIPAAM hydrogels using water bath and microwave radiations and has reported similar findings (Zhao *et al.*, 2008b).

### Thermal analysis (TGA & DSC)

Thermal stability of *Artemisia vulgaris*-MAA polymeric networks prepared using different techniques was investigated by thermogravimetric analysis. Fig. 15 shows the comparison of the thermograms of polymeric networks prepared by conventional heating and microwave irradiation. Both samples showed three stages of degradation. The first stage can be attributed to loss of moisture and inorganic impurities followed by decomposition of carboxylic groups and further (BI *et al.*, 2017). It was observed that microwave irradiated polymeric network exhibited slightly better thermal stability compared to conventionally heated polymeric network. In the first stage of degradation microwave irradiated sample showed 3-4% less weight loss than conventionally heated sample. At 359ºC total weight loss was 25.51% for microwave irradiated sample while conventionally heated sample showed 29.51% weight loss at around 357ºC. At the end of 508ºC residual weight of microwave irradiated sample was 14% while it was only around 3% in case of conventionally heated sample at the end of 492ºC. Better thermal stability of microwave irradiated polymeric network can be attributed to the less absorbed water and intensification of cross linking as a result of microwave heating. Sonker and Verma synthesized cross linked films of Poly (vinyl alcohol) using both techniques and reported similar findings (Sonker and Verma, 2018). Fig. 16 shows the TGA thermograms of the pure drug and drug loaded polymeric networks prepared by both methods. Thermal decomposition of lornoxicam occurred in two stages starting from 195ºC. Afterwards a downward trend was observed due to weight loss corresponding to degradation of lornoxicam and finished at around 600ºC (Mahmoud, Mohamed and El-Dessouky, 2014). At 258ºC upto 42.5 % weight loss was observed for pure drug. On comparing the thermograms of pure drug with drug loaded polymeric networks, it was observed that gradual weight loss was only 27% in conventionally heated sample and 29% in microwave irradiated sample at much higher temperature i-e 345ºC and 353ºC respectively. Thermal stability of drug loaded polymeric networks was also found to be improved than blank polymeric networks. Krishnat *et al.* prepared IPNs of carboxymethyl tamarind gum and chitosan for sustained delivery of aceclofenac and reported better thermal properties of drug loaded IPNs (Krishnat *et al.*, 2017).

Differential scanning calorimetry was also carried out in order to confirm the identity of drug in its pure form as well as in drug loaded formulations. Fig. 17-18 show overlaid DSC thermograms of pure drug, unloaded and drug loaded polymeric networks prepared by conventional method and microwave irradiation respectively. Lornoxicam exhibited a sharp exotherm at 247ºC corresponding to its melting point. The characteristic melting peak of lornoxicam was not detected in loaded polymeric networks suggesting that drug was either molecularly dispersed or existed in amorphous form. These findings are in agreement with the work of Madan *et al.* who synthesized proniosomal gel of lornoxicam and suggested complete amorphization of drug within the gel (Madan, Ghuge and Dua, 2016). Our XRD results were also in agreement with the findings of DSC analysis.

### *X-rays diffraction (XRD) analysis*

XRD is a useful technique and can be used as an identification tool for determination of crystalline nature of drugs (Sohail *et al.*, 2014). Overlays of XRD spectra of lornoxicam, unloaded polymeric network and drug loaded polymeric networks prepared by conventional heating and microwave irradiation are illustrated in Fig. 19 and 20 respectively. Lornoxicam showed characteristic sharp peaks at 2θ=7.8º, 10.2º, 12.96º, 13.78º, 18.85º, 21.84º, 22.87º, 24.6º, 25.35º, 26.90º, 27.95º and 30.44º that confirmed its crystalline nature (Tawfeek *et al.,* 2014). The unloaded samples of both formulations showed peaks nearly at 2θ = 10º and 2θ=31º. In drug loaded samples these peaks were less intense and the diffractograms were dense. The absence of characteristic peaks of lornoxicam in drug loaded samples indicated its amorphous dispersion in the polymeric networks. As the amorphous form is more soluble than the crystalline form, the solubility of the drug was enhanced in synthesized polymeric networks. Similar facts were stated by Sarfraz *et al.* (2018) and Sohail *et al.* (2014).

### *In-vitro drug release measurement*

Drug release profiles of polymeric networks prepared by conventional water bath method and microwave assisted method were studied in physiological media of pH 1.2 and 7.4 at 37ºC. Results presented in Fig. 21 show release of lornoxicam from *Artemisia vulgaris*-MAA polymeric networks. Drug release mainly depends on the swelling ability of the polymeric network, drug solubility in the dissolution medium and drug-polymeric network interactions (Muhammad *et al.*, 2016). Percent drug release from polymeric network prepared by conventional method (C2) ranged from 2.15% to 14.11% at pH 1.2 and 6.18% to 74.15% at pH 7.4. In case of polymeric network prepared by microwave irradiation (M1), percent drug release ranged from 3.48% to 20.14% at pH 1.2 and 10.82% to 87.26% at pH 7.4. Both formulations showed minimum drug release in acidic medium and maximum release in alkaline medium. This can be related to the restricted swelling of polymeric networks in pH 1.2 leading to limited diffusion of drug molecules whereas in pH 7.4 drug molecules were released at a faster rate owing to higher swelling ratios (Seeli and Prabaharan, 2017). It can also be attributed to the pH-dependent solubility profile of lornoxicam, which is a weak acid (pKa 4.7) and displays extremely slow dissolution in acidic medium (Joseph, 2018). However, in all cases a biphasic release pattern was observed. An initial rapid release subsequently followed by sustained release of the drug. The can be suggested due to the existence of drug on the surface and high concentration gradient between the polymeric network and the dissolution medium (Pandey *et al.*, 2013). This behavior can be beneficial in overcoming the drawbacks of delayed dissolution of lornoxicam (Hamza and Aburahma, 2010). Bashir *et al.* prepared pH-sensitive hydrogels of 5-fluorouracil and reported similar pattern of drug release (Bashir *et al.*, 2017).

A comparison of release profiles of C2 and M1 shows higher release of lornoxicam from M1 as compared to C2. This substantial difference in drug release from both polymeric networks is due to higher swelling ratios of M1 as drug release is directly related to the swelling of polymeric network. When water penetrates into the gel network, swelling occurs and drug dissolution starts inside the network followed by its gradual diffusion out of the polymeric matrix (Jalil *et al.*, 2017). Another reason can be the higher drug loading in M1 compared to C2. At lower drug concentration, most drug molecules remain bounded to carboxylic groups of monomer chains in the polymeric network whereas number of unbounded drug molecules increases when the drug concentration increases (Changez *et al.*, 2003). Also, efficient diffusion of drug occurs at higher drug loading concentration due to high concentration gradient resulting in increased rate of drug release (Malana and Zohra, 2013). Mahdavinia *et al.* synthesized porous hydrogels of polyacrylamide using calcium carbonate and investigated the influence of different variables on the release of potassium nitrate from these hydrogels. Their results indicated that the release of potassium nitrate increased with increased percent loading and was also related to water sorption kinetics of hydrogels (Mahdavinia *et al.*, 2009).

### *Evaluation of drug release kinetics*

Model independent ($f_1$,$f_2$) and model dependent approaches (Korsmeyer-Peppas, Higuchi, Hixon-Crowell, Zero-order and First-order) were applied to evaluate the drug release kinetics of polymeric networks prepared by both methods using DD solver. Values of fit factors are given in Table 4. Values of $R^2$ and the release exponent 'n' are given in Table 5. A selection criteria for most appropriate model was based on goodness of fit which was indicated by values of regression co-efficient ($R^2$) near to 1.

Values of difference factor ($f_1$) and similarity factor ($f_2$) show dissimilarity between the release profiles of both polymeric networks. From the values of $R^2$ given in Table 5, it is obvious that the drug release kinetics of both polymeric networks gave close fit to Korsmeyer-Peppas model ($R^2$>0.99) followed by Higuchi model. Korsmeyer-Peppas model is used for describing drug release pattern from polymeric systems and is applicable when the mechanism of release is unknown or encompasses more than one type of mechanisms. It considers that often drug release deviates from Fick's law and follows an anomalous behavior (Vaghani *et al.,* 2012). Release kinetics in swell-able systems is governed by rate of liquid diffusion as well as relaxation rate of polymeric chains. When rate of liquid diffusion is slower than the polymer chain relaxation rate, mechanism of release is Fickian. When relaxation process is slower than liquid diffusion rate, case II transport occurs. However, when both processes occur at same magnitude release becomes non-Fickian or anomalous (Korsmeyer and Peppas, 1983). The values of release exponent 'n' determined from equation 14 were in the range of 0.541-0.673 suggesting non-Fickian or anomalous mechanism of drug release i-e involvement of diffusion as well as relaxation of polymer chains in the release mechanism (Khalid *et al.*, 2018). Jana *et al.* prepared IPN microparticles of aceclofenac and reported that the drug release followed Korsmeyer-Peppas model and anomalous mechanism of drug release (Jana *et al.*, 2013). In another study Kaity *et al.* grafted acrylamide onto locust bean gum using microwave radiations and further prepared matrix tablets for controlled delivery of buflomedil hydrochloride. They also showed that the drug release from prepared matrix tablets followed anomalous diffusion (Kaity *et al.*, 2013).

## CONCLUSION

In this study, Artemisia vulgaris mucilage was used as natural polymer to synthesize polymeric network drug carrier. Natural polymers are biodegradable and are easily available at low cost. Also microwave radiations were successfully used to synthesize crosslinked polymeric networks in short duration. Furthermore, polymeric network prepared by microwave assisted method exhibited better swelling, porosity, thermal stability and drug release properties as compared to the one prepared by conventional water bath method. Hence, microwave irradiation method can be used as an effective alternative of conventional heating method. Prepared polymeric networks also showed pH sensitive properties and can be promising carriers for controlled delivery of lornoxicam for achieving patient compliance.

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