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In vitro release dynamics of thiram fungicide from starch and poly(methacrylic acid)-based hydrogels

Baljit Singh *, D.K. Sharma, Atul Gupta

Department of Chemistry, Himachal Pradesh University, Shimla 171005, India

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Abstract

In order to make the judicious use of pesticide/fungicide and to maintain the environment and ecosystem we have developed the starch and poly(methacrylic acid)-based agrochemical delivery system for their controlled and sustained release. The delivery device was prepared by using *N*,*N*′-methylenebisacrylamide (*N*,*N*′-MBAAm) as crosslinker and was characterized with FTIR, TGA and with swelling studies as a function of time and crosslinker concentration. This article discusses the swelling kinetics of polymer matrix and release dynamics of thiram (fungicide) from hydrogels for the evaluation of the diffusion mechanism and diffusion coefficients. The values of the diffusion exponent '*n*' for both cases, that is the swelling of hydrogels and for the release of thiram from the hydrogels have been observed between 0.7 and 0.9 when the concentration of the crosslinker in the polymers were varied from 6.49×10^{-3} to 32.43×10^{-3} moles/L. It is inferred from the values of the '*n*' that Non-Fickian diffusion mechanism has occurred in both the cases.

Keywords: Fungicide; Hydrogels; Swelling kinetics; Release dynamics

1. Introduction

Volatilization, photo-degradation, leaching and surface migration decrease the efficiency of agrochemicals, which is compensated by increasing frequency and dose of their application. This creates environmental, ecological and economic problems. An ideal strategy for effective and safe use of agrochemicals would be one which limits the amount available at any time to be adequate for pest control but not for the above mentioned efficiency lowering natural phenomenons. This can be achieved by controlled and sustained release of these chemicals from their formulations.

Polymers-based formulations provide controlled release of chemical agents. Various controlled release formulations based on natural polymers such as alginate [1,2], alginate–bentonite [3], ethylcellulose [4], lignin [5,6], and starch [7–11] have been reported in the literature. These formulations have provided slow release of active ingredient. Pepperman and Kuan [12] have observed decrease in rate of release of metribuzin (a herbicide) from its formulation based on alginate as compared to the conventional formulation. In another example, the release rate of isoproturon (herbicide) has also been found to decrease from the alginate-based granules as compared to the technical product [13]. The use of controlled release formulations have also reduced the vertical mobility of herbicide into the soil thus recommended the use of such formulations in reducing leaching and ground water contamination [14]. Further, the utility of controlled release formulations can be improved by combining different herbicides and a fertilizer source in a single formulation [15]. Recently, hydrogel-based pesticide release devices have become very popular. These devices consist of a pesticide in a polymer in the form of a microcapsule or granule [16]. The polymer-encapsulated compounds are superior to non-encapsulated commercial formulations in extending activity [17], reducing evaporative and degradation losses [18], reducing leaching [19], and decreasing dermal toxicity [20]. Water [21], soil moisture [22], soil microorganisms and soil enzymes such as amylases [23] release the active compounds from polymer matrices in controlled and sustained manner. Hydrogels are three-dimensional polymeric networks those swell quickly by imbibing a large amount of water or de-swell in response to changes in their external environment. The

* Corresponding author. Tel.: +91 1772830944; fax: +91 1772633014.
E-mail address: baljitsinghhpu@yahoo.com (B. Singh).

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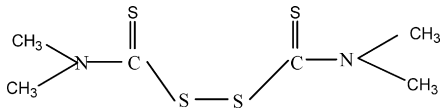
volume phase transitions as a response to different stimuli make these materials interesting objects of scientific observations and useful materials for use in advanced technologies. These changes can be induced by changing the surrounding pH, temperature, ionic strength and electro stimulus [24–29]. Hydrogels exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media and makes them potential candidates for agrochemicals release devices [16].

Thiram (tetramethylthiuramdisulphide) is one of the representative dithiocarbamate pesticides and has been used as a fungicide to control soil fungi that causes root rot diseases of plants [30] and has also been used to protect harvested crops, cereals, seeds, fruits, vegetables, and turf crops from deterioration in storage or transport [31,32]. It has been reported to have adverse effects on hepatic system [33], the reproductive system [34–36], and on the developmental processes [37]. Because of the wide range of uses of thiram and its toxic effects, there is concern about its potential effects not only on general population from dietary exposure to residues left on food crops, but also potential occupational health risks to workers who handle and often come in contact with this chemical. Skin lesions including hand eczema or dermatitis have been often recognized among exposed workers [38–40].



Keeping in view the importance of thiram fungicide and its adverse effect on environment, ecosystem and human health, controlled and sustained delivery devices are required for its release. Therefore, the present study is an attempt, to synthesize starch and poly(MAAc)-based hydrogels, by using *N*,*N*′-methylenebisacrylamide (*N*,*N*′-MBAAm) as crosslinker and ammonium persulphate (APS) as initiator, to develop delivery devices. The polymeric networks [starch-*cl*-poly(MAAc)], thus formed have been characterized by FTIR, TGA and swelling responses as a function of time and crosslinker concentration. The swelling kinetics of hydrogels and release dynamics of thiram from hydrogels have also been discussed, for the evaluation of the release mechanism and diffusion coefficients.

2. Experimental

2.1. Materials and method

Methacrylic acid (MAAc) and acetonitrile were obtained from Merck-Schuchardt, Germany. Ammonium persulphate, starch and *N*,*N*′,-methylenebisacrylamide were obtained from S.D. Fine Mumbai, India. Tetramethylthiuram disulphide (thiram) was obtained from Fluka, Switzerland and was used as received.

2.2. Synthesis of starch-cl-poly(MAAc)

Polymer synthesis was carried out with 1 g of starch, 4.38×10^{-3} moles/L of APS, 1.18 moles/L of MAAc and known concentration of crosslinker in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for 2 h in distilled water and for 2 h in ethanol to remove the soluble fraction and then were dried in an oven at 40 °C. To study the effect of crosslinker variation on swelling kinetics and thereafter on the release dynamics of thiram from fungicide loaded hydrogels, different polymeric networks [starch-*cl*-poly(MAAc)] were synthesized by varying [*N*,*N*′-MBAAm] from 6.49×10^{-3} to 32.40×10^{-3} moles/L. The polymeric networks thus formed were cylindrical in shape and their thickness was measured with 25 mm × 1 mm screw gauge and presented in Table 1.

2.3. Characterization

Starch and starch-*cl*-poly(MAAc) polymer were characterized by the following techniques.

2.3.1. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of starch and starch-*cl*-poly(MAAc) were recorded in KBr pellets on Nicolet 5700 FTIR to study the modified nature of starch.

2.3.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis of starch and starch-*cl*-poly(MAAc) was carried out on a Perkin-Elmer (Pyris Diamond) Thermal Analyzer in air at a heating rate of 20 °C/min to examine the thermal properties of the polymers.

2.4. Swelling studies

Swelling studies of the polymeric networks were carried out in aqueous medium by gravimetric method. Known weight of polymers were taken and immersed in excess of solvent for fixed time interval (6 h) at room temperature and then polymers were removed, wiped with tissue paper to remove excess of solvent and weighed immediately. The percent swelling (P_s) of the

Table 1
Thickness and entrapment efficiencies (%) of starch-*cl*-poly(MAAc) hydrogels prepared with different concentration of [*N*,*N*′-MBAAm]

Hydrogels prepared with different [*N*,*N*′-MBAAm] (×10³ moles/L)	Initial concentration of thiram (μg/mL)	Thickness (mm)	Entrapment efficiency (%)
6.49	382.25	7.845 ± 0.026	75.93 ± 2.06
12.97	382.25	7.845 ± 0.005	75.04 ± 2.22
19.46	382.25	7.575 ± 0.034	77.27 ± 1.17
25.95	382.25	7.425 ± 0.110	68.81 ± 2.13
32.43	382.25	7.755 ± 0.027	52.65 ± 1.19

polymeric networks was calculated as:

$$P_s = \left[\frac{W_s - W_d}{W_d}\right] \times 100$$

where W_s is weight of swollen polymers and W_d is the weight of dried polymers. Swelling kinetics of the polymer networks prepared with different crosslinker concentration was studied.

2.5. Preparation of calibration curves for pure thiram

In this procedure the absorbance of a number of standard solutions of the reference compound at concentrations encompassing the samples concentrations were measured spectrophotometrically using Carry 100 Bio UV–Visible spectrophotometer by modifying Verma et al. method [41] as follows.

Aliquots (0.05–1.5 mL) of standard solution of thiram (10^{-3} M) in acetonitrile were taken in 100 mL separating funnels and diluted to 2 mL with acetonitrile. To each solution was added 5 mL of water and tetraacetonitritocopper(I) perchlorate (1 mL, 0.004 M in acetonitrile). Each mixture solution was equilibrated two times with 4 mL of chloroform for 10 min each. The yellow chloroform layer was separated, dried over anhydrous sodium sulphate (2 g) and final volume made to 10 mL with chloroform. The absorbance of the yellow chloroform extract was measured at 421 nm (λ_{max} of yellow coloured copper-dithiocarbamate complex) against a reagent blank. Calibration curve was constructed by plotting absorbance values against concentration of thiram taken. The Beer's law is obeyed up to 48 μg/mL of thiram. Using the straight line equation $y = mx + c$, the slope and intercept values were 0.03874 and −0.03183 respectively.

2.6. Fungicide loading to polymer matrix

The loading of the fungicide (thiram) in to starch-*cl*-poly(MAAc) polymers was carried out by swelling equilibrium method. The polymers were allowed to swell in the fungicide solution (in 10 mL water) of known concentration for 72 h at room temperature (23 ± 1 °C) and then dried to obtain the release device.

2.7. Entrapment efficiency (%)

After 72 h the thiram content left in the solution was again determined by spectrophotometric method mentioned in Section 2.5. The entrapment efficiency (%) was then calculated as:

$$\text{Entrapment efficiency} = \left\{\frac{C_i - C_f}{C_i}\right\} \times 100$$

where C_i is initial concentration of thiram given to the polymer in the solution and C_f is final concentration of thiram left in the solution. The entrapment efficiency (%) of the polymers prepared with the different crosslinker concentration is presented in Table 1.

2.8. Fungicide release from polymer matrix

In vitro release of the fungicide has been carried out by placing dried and loaded sample in definite volume of releasing medium (10 mL water) at room temperature (23 ± 1 °C). The amount of thiram released was measured spectrophotometrically as yellow chloroform solution after 6 h at 421 nm and fungicide release dynamics was studied.

3. Results and discussion

Polymeric networks were synthesized by chemically induced polymerization through free radical mechanism. APS has generated the reactive sites, both on the starch and monomer, leading to the propagation of the reaction. In the presence of crosslinker *N*,*N*′-MBAAm (CH_2=CHCONHCH$_2$ NHCOCH=CH_2), because of its poly-functionality, a new macro-radical get formed that has four reactive sites and these sites can be linked both with the radical on the starch and the poly(MAAc) and will form crosslinked polymers [i.e. starch-*cl*-poly(MAAc)].

3.1. Characterization

3.1.1. Fourier transform infrared spectroscopy

To study the modification of the starch, FTIR spectra of starch and crosslinked polymers were recorded in KBr pellets and are presented in Fig. 1a and b respectively. The strong and broad absorption band observed at 3600–3200 cm^{-1} due to –OH stretching in starch get diminished to 3426.3 cm^{-1} in starch-*cl*-poly(MAAc). In addition absorption band at 1718.1 cm^{-1} due to C=O stretching of carboxylic acid association in starch-

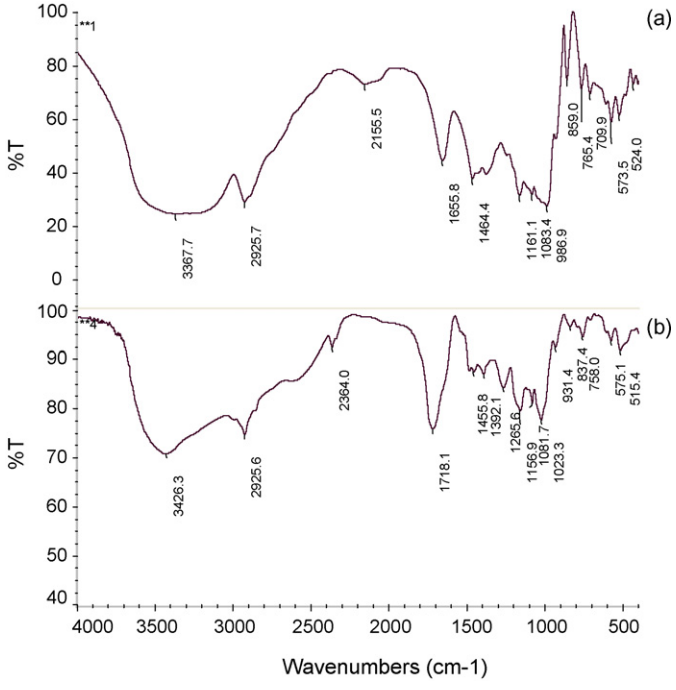


Fig. 1. FTIR of (a) starch and (b) starch-*cl*-MAAc.

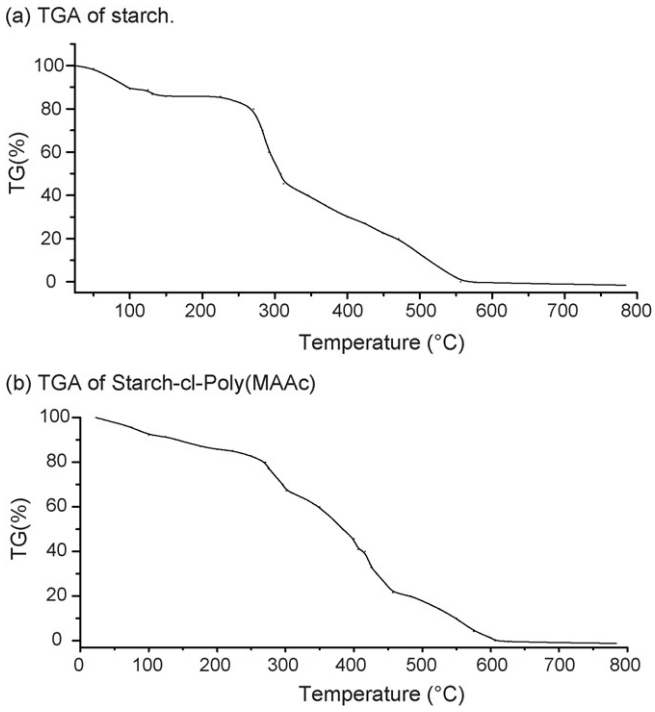


Fig. 2. TGA of (a) starch and (b) starch-*cl*-poly(MAAc).

cl-poly(MAAc) has been observed apart from usual peaks in starch.

3.1.2. Thermogravimetric analysis

From the TGA of starch and starch-*cl*-poly(MAAc) Fig. 2a and b respectively, it was observed that the mechanism of decomposition in both the cases are different. Two stages and four stages decomposition mechanisms have been observed respectively for the starch and starch-*cl*-poly(MAAc). The initial decomposition temperature (IDT) was observed at 252 and 223 °C and final decomposition temperature (FDT) was observed at 556.25 and 606 °C respectively for starch and starch-*cl*-poly(MAAc). Decomposition of starch-*cl*-poly(MAAc) started earlier as compare to starch but its rate of decomposition with respect to temperature was slower than starch and also its final decomposition temperature was higher than starch. It is thus comprehensible that the modification has induced the thermal stability in the crosslinked networks. Such thermal behavior of these networks can be explained by fact that polymers can undergo cyclization reactions at higher temperature. This observation is further supported by the decomposition temperature corresponding to the 10% weight loss (Table 2). Further, it is observed that maximum loss in crosslinked polymer occurred after first stage of decomposition where temperature range was usually corresponded to the de-polymerization process. These all results indicated that the modification has occurred in starch.

3.2. Mathematical modeling of swelling of hydrogels and fungicide release from hydrogels

Mathematical modeling of drug release from swellable polymeric systems has been applied for the release of pesticide from the polymer matrix. Although there are a number of reports dealing with mathematical modeling of drug release from swellable polymeric systems, no single model successfully predicts all the experimental observations [42–46]. Fickian, Non-Fickian and Case II diffusion mechanism for swelling of hydrogels and for the drugs release from the hydrogels can be calculated from Eq. (1).

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fractional release of drug in time t, 'k' is the constant characteristic of the drug–polymer system, and 'n' is the diffusion exponent characteristic of the release mechanism. For Normal Fickian diffusion the value of $n = 0.5$, Case II diffusion $n = 1.0$ and Non-Fickian $n = 0.5$–1.0 [47–50].

Initial diffusion coefficient, average diffusion coefficient and late diffusion coefficient can be calculated from Eqs. (2)–(4) [49,50]

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\ell^2}\right)^{0.5} \tag{2}$$

$$D_A = \frac{0.049\ell^2}{t^{1/2}} \tag{3}$$

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right)\exp\left[\frac{(-\pi^2 Dt)}{\ell^2}\right] \tag{4}$$

where (M_t/M_∞) is the fractional release and M_t and M_∞ is drug released at time 't' and at equilibrium respectively, D is the diffusion coefficient and ℓ is the thickness of the sample. The values of 'n', 'k' and D have been evaluated for the swelling kinetics and release dynamics of fungicide from the polymer matrix from Figs. 3 and 4 respectively and result thus obtained have been presented in Tables 3 and 4 respectively.

3.3. Swelling kinetics

To observe the effect of crosslinker concentration on swelling kinetics, the polymers were prepared with different [*N*,*N*′-MBAAm] keeping the monomer concentration constant.

Table 2
Thermogravimetric analysis of starch and starch-*cl*-poly(MAAc)

Sample	IDT (°C)	FDT (°C)	DT (°C) at every 10% weight loss									
			10	20	30	40	50	60	70	80	90	100
Starch	252	556	97	270	283	291	308	345	400	470	512	556
Starch-*cl*-poly(MAAc)	223	606	142	271	296	350	383	416	433	483	550	606

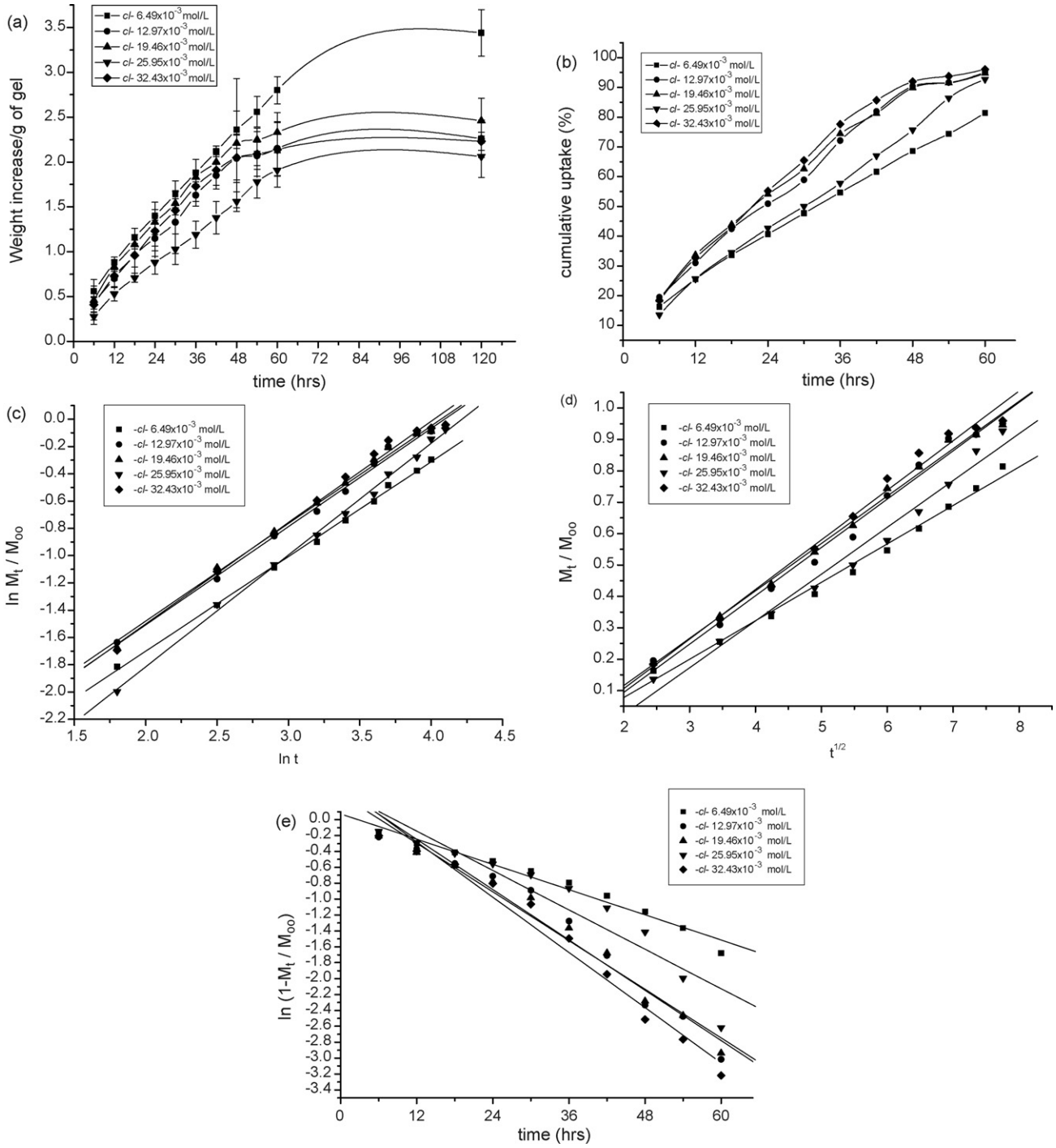


Fig. 3. (a) Swelling kinetics for the hydrogel samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (b) Percentage cumulative uptake of water by hydrogel samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (c) Plot of $\ln M_t/M_\infty$ versus $\ln t$ for the evaluation of '*n*' and '*k*' for the swelling kinetics of hydrogel samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (d) Plot of M_t/M_∞ versus $t^{1/2}$ for the evaluation of initial diffusion coefficient (D_i) for the swelling kinetics of hydrogel samples of Starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (e) Plot of $\ln(1 - M_t/M_\infty)$ versus time for the evaluation of late diffusion coefficient (D_L) for the swelling kinetics of hydrogel samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm].

Swelling of hydrogels decreases with increase in [*N*,*N*′-MBAAm] from 6.49×10^{-3} to 32.4×10^{-3} moles/L (Fig. 3a) because the crosslinking density increases with increase of crosslinker concentration in the polymers and pore size of the crosslinked network decreases, which has decreased the swelling. The 50% of the total increase in the weight of the polymers occurred in 29.92, 21.62, 20.79, 27.04 and 20.07 h respectively for the polymers prepared with different [*N*,*N*′-MBAAm], i.e. 6.49×10^{-3}, 12.97×10^{-3}, 19.40×10^{-3}, 25.95×10^{-3} and 32.43×10^{-3} moles/L (Fig. 3b).

From the slope and intercept of the plot (Fig. 3c) of $\ln M_t/M_\infty$ versus $\ln t$, the diffusion exponent '*n*' and gel characteristic

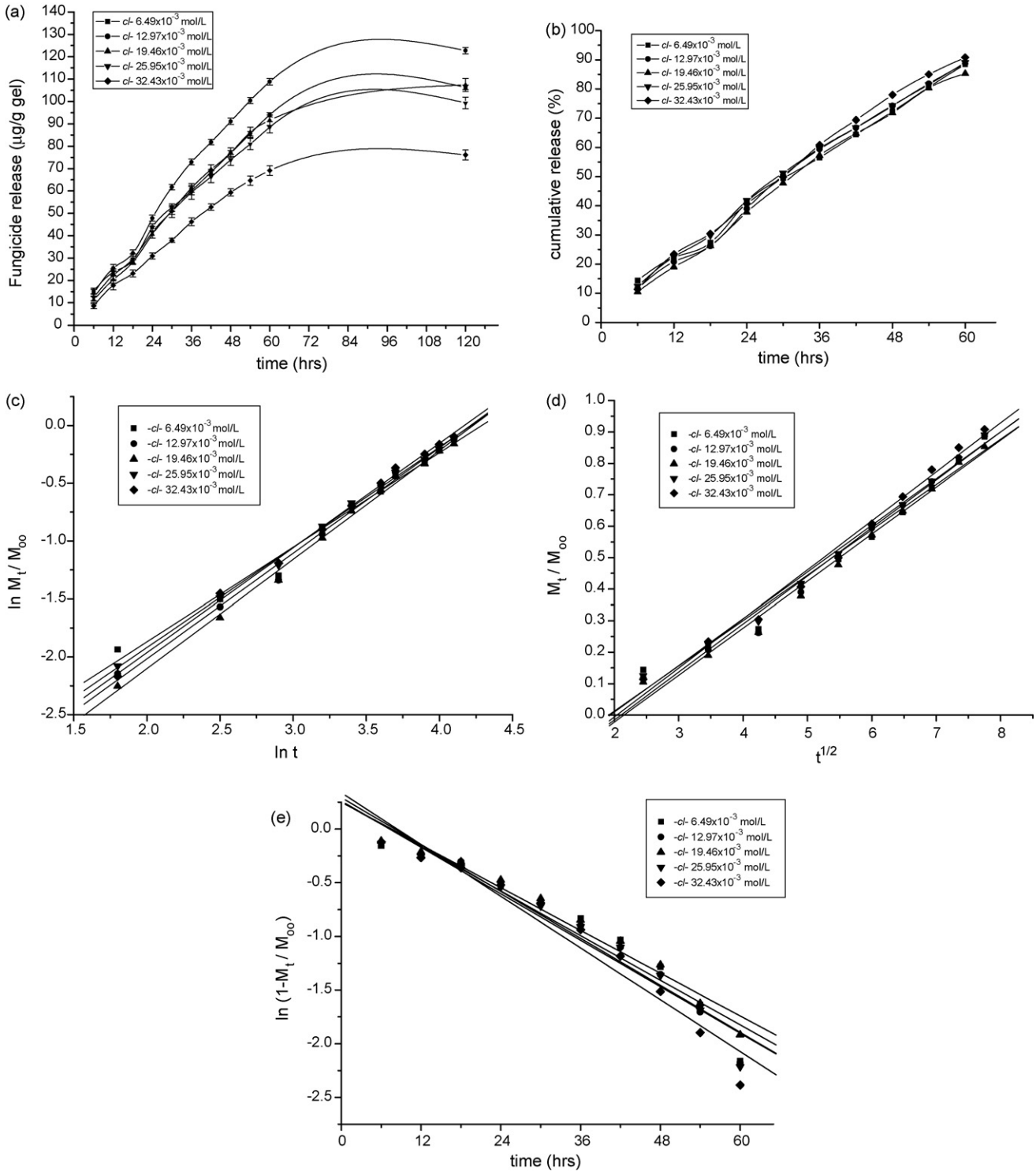


Fig. 4. (a) Release dynamics of thiram from fungicide loaded samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (b) Percentage cumulative release of thiram from fungicide loaded samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (c) Plot of $\ln M_t/M_\infty$ versus $\ln t$ for the evaluation of '*n*' and '*k*' for the release dynamics of thiram from fungicide loaded samples of Starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (d) Plot of M_t/M_∞ versus $t^{1/2}$ for the evaluation of initial diffusion coefficient (D_i) for the release dynamics of thiram from fungicide loaded samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]. (e) Plot of $\ln(1 - M_t/M_\infty)$ versus time for the evaluation of late diffusion coefficient (D_L) for the release dynamics of thiram from fungicide loaded samples of Starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm].

constant '*k*' has been obtained and results are presented in Table 3. It was observed from table that the values of the '*n*' is remained between the 0.5 and 1 and hence corresponding to Non-Fickian diffusion mechanism for the diffusion of water from the polymer matrix prepared with different crosslinker concentration. Non-Fickian or Anomalous diffusion occurs when the diffusion water molecules to the polymer matrix and relaxation rates of polymer chains are comparable. Diffusion

Table 3
Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the swelling kinetics of samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]

Hydrogels prepared with different [*N*,*N*′-MBAAm] ($\times 10^{-3}$ moles/L)	Diffusion exponent 'n'	Gel characteristic constant, 'k' ($\times 10^{2}$)	Diffusion coefficients (cm^2/h)		
			Initial, D_i ($\times 10^{3}$)	Average, D_A ($\times 10^{3}$)	Late time, D_L ($\times 10^{3}$)
6.49	0.70	4.55	14.64	5.52	2.04
12.97	0.72	5.25	22.95	6.49	4.06
19.46	0.72	5.45	20.57	6.17	3.67
25.95	0.82	3.16	19.24	5.20	2.85
32.43	0.74	5.05	23.6	6.59	4.36

Table 4
Results of diffusion exponent 'n', gel characteristic constant 'k' and various diffusion coefficients for the release of thiram from fungicide loaded samples of starch-*cl*-poly(MAAc) prepared with different [*N*,*N*′-MBAAm]

Hydrogels prepared with different [*N*,*N*′-MBAAm] ($\times 10^{3}$ moles/L)	Diffusion exponent 'n'	Gel characteristic constant, 'k' ($\times 10^{2}$)	Diffusion coefficients (cm^2/h)		
			Initial, D_i ($\times 10^{3}$)	Average, D_A ($\times 10^{3}$)	Late time, D_L ($\times 10^{3}$)
6.49	0.82	3.01	20.06	5.58	2.67
12.97	0.91	2.15	22.65	5.61	2.81
19.46	0.94	1.86	20.03	5.11	2.38
25.95	0.87	2.59	19.24	5.10	2.49
32.43	0.91	2.30	23.01	5.63	3.02

coefficient has been evaluated from Fig. 3d and e and results are presented in Table 3. The values of initial diffusion coefficient have been observed more than the average and late diffusion coefficient. This observation indicated that in the initial stages the swelling of the polymers and the rate of diffusion of water molecules into polymer are higher as compared to the later stages.

3.4. Release dynamics thiram fungicide from polymer matrix

The release of chemicals entrapped in a hydrogels occurs only after water penetrates the network to swell the polymer and dissolve the chemicals, followed by diffusion along the aqueous pathways to the surface of the device. The release of chemicals is closely related to the swelling characteristics of the hydrogels, which in turn, is a, key function of chemical architecture of the hydrogels. In the present studies, the release of thiram from the hydrogels occurred in very controlled and sustained manner, which is the primary requisite for the use of agrochemicals to control the environment and health hazards (Fig. 4a). It is evident from the figure that after attaining certain concentration, release of thiram from the hydrogels occurred in very controlled manner, where the concentration of thiram has been maintained constant after 60 h until 120 h. It is further observed from the figure that as the crosslinker concentration increases in the polymer matrix, the release of thiram decreases. The 50% of the total release of thiram from of the loaded hydrogels occurred in 29.27, 28.94, 30.36, 28.09 and 27.46 h respectively for the polymers prepared with different [*N*,*N*′-MBAAm] (i.e. 6.49×10^{-3}, 12.97×10^{-3}, 19.40×10^{-3}, 25.95×10^{-3} and 32.43×10^{-3} moles/L) (Fig. 4b).

From the slope and intercept of the plot (Fig. 4c) of $\ln M_t/M_\infty$ versus $\ln t$, the diffusion exponent 'n' and gel characteristic constant 'k' has been obtained and presented in Table 4. It has been observed from table that the values of the 'n' are corresponding to Non-Fickian or Anomalous diffusion mechanism for the release of thiram from the polymer matrix prepared with different crosslinker concentrations. Non-Fickian or Anomalous diffusion occurs when the diffusion and relaxation rates are comparable. Thiram release depends on two simultaneous rate processes, water migration into the device and thiram diffusion through continuously swelling hydrogels is highly complicated. From the values of diffusion coefficient reported in Table 4, obtained from Fig. 4d and e, it has been observed that the initial diffusion coefficient is more than the average and late diffusion coefficient. In the initial stages rate of diffusion of thiram from the hydrogels has been observed more as compared to the late stages. This observation is corresponding to the trends obtained in the diffusion coefficients of swelling kinetics.

4. Conclusion

It is concluded from the forgone discussion that the release of thiram from the hydrogels increases with time and after certain time the release occurred in very controlled and sustained manner. It is also concluded that the increase in crosslinker concentration in the polymer matrix has decreased the release of fungicide from the releasing device; hence, the hydrogels prepared with higher concentration of crosslinker provide fungicide release for longer duration. In the present study, the optimum concentration of crosslinker 32.43×10^{-3} moles/L has been obtained for the synthesis of the polymers, which can be used for the release of fungicide from hydrogel for longer duration.

Further, from the values of the diffusion exponent '*n*' it is concluded that the Non-Fickian diffusion mechanism has occurred for the diffusion of water molecules into polymer matrix prepared with different crosslinker concentration and also for the release of thiram from these polymeric matrix.

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