Int. J. Chem. Sci.: 14(2), 2016, 874-890
ISSN 0972-768X
www.sadgurupublications.com

FORMULATION AND EVALUATION OF CONTROLLED RELEASE CEFIXIME-CMC BIOPOLYMER USING ION CROSS LINKING TECHNIQUE

YOUSIF K. ABDUL AMIR, MOHAMMED A. K. ALSOUZ* and ALI J. SALIM

Chemistry Department, College of science, Al-Mustansiriya University, BAGHDAD, IRAQ

ABSTRACT

The main concept in the design controlled-release drug delivery systems is the kinetics of drug release, rather than the kinetics of drug absorption controls the availability of the drug. The controlled release microspheres of cefixime using sodium carboxy methyl cellulose and $FeCl_3/FeCl_2$ as cross linking agent. The micro-beads were prepared using ionotropic gelatin technique. The prepared micro-beads were evaluated by *in vitro* drug release and Fourier transform infra red spectroscopy (FTIR). The evaluation of drug controlled release was performed at different pH (1.2 & 7.2) and different temperatures (27, 37, 45^oC). The results were revealed that the drug releasing was increased with rising of temperatures and faster at pH equal to 7.2.

FTIR Spectroscopy was revealed that there is no chemical interaction between the drug and excipients. Korsmeyer-Peppas and Higuchi, zero and first order kinetic models was studied and discussed**.** Correlation coefficient (r^2) values of the kinetic release process suggest that the drug release obey Korsmeyer-Peppas kinetic model.

Key words: Cefixime, Sodium carboxymethyl cellulose, Kinetics, Drug release.

INTRODUCTION

Controlled drug delivery systems were broadly classified into temporal and targeted drug delivery systems[1,2]. Temporal drug delivery systems were designed to release therapeutic levels of drugs from a matrix of desired period time. The advantage of such system was the therapeutic concentration of a drug maintained in the body for long time without repeatable times of administration. Furthermore, it is more economical due to lower drug waste, reproducible, and increase patient compliance[3]. The attempts to develop a novel

*Author for correspondence; E-mail: alsouz.m@gmail.com

delivery systems can further fine-control the drug release pattern by a synthesis of some polymers as a matrix systems as well as by developing smart polymer systems can be delivered the multiple drugs under a controlled manner or under the effect of an external stimulus[4-6].

The polymers are macromolecules, which have very large chains that contain a variety of functional groups. The polymers can be blended with other low- and high molecular weight materials and can be tailored for any applications. There are becoming increasingly important in the field of drug delivery systems. The developments in the polymer science, which have led to synthesis several novel drug-delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug-delivery applications[7].

The polymers were used as a main tool to control the drug release system from their formulations also used as stabilizer, taste-masking and protective agents in oral drug delivery systems. The polymer was bound the particles of the solid form and change the flow rate properties of a liquid form. The extensive applications of polymers in drug delivery system have been realized because the polymers have unique properties, which have not been attained by any other materials.

Carboxymethyl cellulose (CMC) was an important industrial polymer with a wide range applications in flocculation, drag reduction, detergents, textiles, paper, food, drugs, and oil well drilling operation. CMC is a derivative of cellulose molecule and formed by its reaction with sodium hydroxide and chloro-acetic acid, it has a number of sodium carboxymethyl groups ($–CH_2COONa$), introduced into the cellulose molecule, which promotes water solubility. Among all the polysaccharides, the CMC is easily available and it is also very cheap[8]. The structural formula of carboxymethyl cellulose was shown in Fig. 1[9].

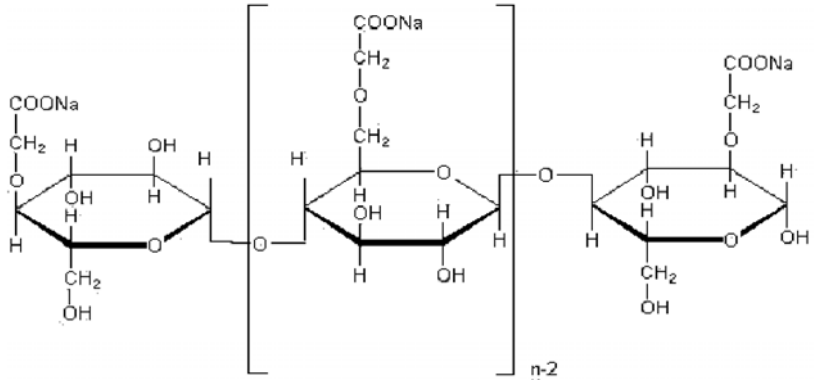

Fig. 1: The chemical structure of sodium carboxymethyl cellulose[9]

The interactions of carboxylic groups of the CMC with multivalent metal ions can be used to form so called ion-tropic gels, which are predominantly stabilized by the electrostatic interactions. In addition, the interactions between the –OH groups of the polymer and the metal ions contribute to the stability and the water insolubility of their polymeric aggregates. The CMC can be cross-linked with ferric/aluminum salt to get biodegradable hydro-gel beads[10,11].

Cefixime "Suprax" is a semi synthetic of cephalosporin antibiotic drug[12]. The structural formula of Cefixime was shown Fig. 2, which is available for oral administration with 400 mg film coated tablets and as powder for oral suspension when reconstituted provides either 100 mg/5 mL or 200 mg/5 mL of cefixime trihydrate. Cefixime is effective on infections of the middle ear (otitis media), tonsillitis, throat infections (pharyngitis), laryngitis, bronchitis, and pneumonia caused by susceptible bacteria. It is also used for treating urinary tract infections and gonorrhea as well as acute bacterial bronchitis in patients with chronic obstructive pulmonary disease (COPD)[13].

The main objective of this study aimed to formulate drug controlled release of "Cefixime–CMC" biopolymer using $FeCl_3/FeCl_2$ ionic cross linked technique to observe the swelling study and *in vitro* drug control release characteristics.

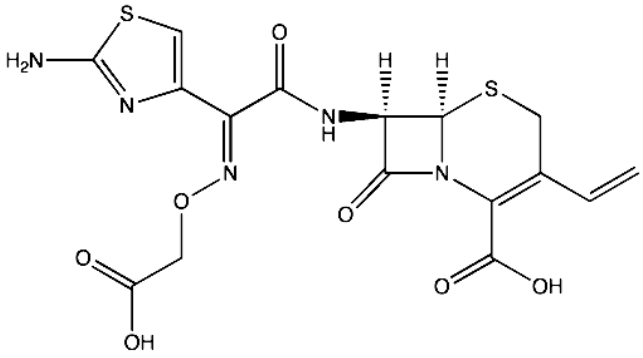

Fig. 2: The structural formula for cefixime[13]

EXPERIMENTAL

Materials and methods

Material

The sodium carboxymethyl cellulose (Na-CMC) was purchased from Sigma Aldrich and used as received without any variations, Cefixime from Arab company for antibiotics

industries (ACAI). Ferric chloride, ferrous chloride and monobasic sodium phosphate, dibasic sodium phosphate were purchased from (BDH, England) and all are Analar grade.

Instrumentation

Water bath shaker type lab companion BS-11, digital scale KERN-ABBS, pH meter type trans BP 300, UV-Visible (Cary – 1000, Austria) spectrophotometer, Fourier transform infrared spectroscopy (FTIR) (Shimadzu, 8400S, Japan) were employed in this study.

Methods

Preparation of buffer solutions

The two different buffer solutions were prepared. Firstly, The buffer solution at pH equal to 1.2 was prepared by mixing 50 mL of 0.2 M KCl and 85 mL 0.2 M HCl into 200 mL volumetric flask then the volume was completed with deionized-distilled water while the buffer solution at pH equal to 7.2 was prepared similarly by mixing 28 mL of 0.2 M monobasic sodium phosphate and 72 mL 0.2 M dibasic sodium phosphate into 200 mL volumetric flask and the volume was completed with deionized-distilled water[14].

Preparation of the cefixime calibration curve

Solutions of different concentrations (5-30 mg/L) of Cefixime were prepared by serial dilutions from the standard stock solution (100 mg/L). Absorbance values of these solutions were measured at the selected λ_{max} (285 nm) and plotted versus the concentrations as shown in Fig. 3.

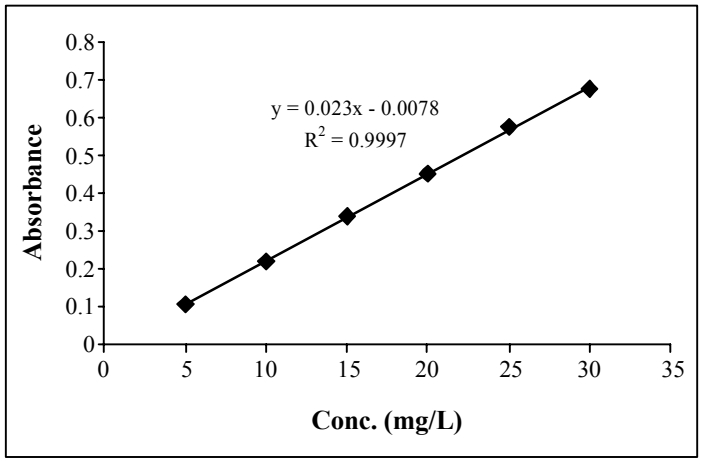

Fig. 3: Calibration curve of cefixime by UV-Vis absorbance at 285 nm

Preparation of biopolymer bead

The beads were prepared by ionic gelatin method using $FeCl_3/FeCl_2$ as cross-linking agent. The loading of drug on polymer was performed by the swelling equilibrium method; 2% w/v of polymer was dissolved in deionized-distilled water using gentle heat and magnetic stirring, certain amount of Cefixime was dissolved in an aqueous solution of polymer and mixed gently by using magnetic stirrer. The mixture was added drop wise into (0.02/0.01 M) $FeCl_3/FeCl_2$ solution until the beads appeared. The beads filtered by using millipore stainless steel sieve (pore size: 0.25 mm). The beads were washed with distilled water at least (3) times to remove the un-reacted ions then dried on (oven) at 40ºC for 10 hrs to obtain the dried beads form.

Antibiotic release kinetic experiments

The drug controlled release systems were performed by using the loaded drug polymer beads. The beads were immersed in 500 mL of buffer solution in 1 liter volumetric flask at a given pH conditions (pH 7.2 and pH 1.2) at temperature intervals (27, 37, 45°C). The system was continuously stirred at a certain speed (about 80 rpm) using a water bath shaker. Each 30 min intervals time, 3 mL of solution was taken from the flask and put into 5 mL volumetric flask, then the volume was completed to the mark with the same fresh buffer solution. The collected samples were analyzed to assess the cefixime concentration using UV-Vis spectrophotometer at λ_{max} 285 nm. The concentration of each drug released was determined after 24 hr, which gives $M\infty$.

RESULTS AND DISCUSSION

FTIR Characterization

The FT-IR spectrum of the SCMC (meaning) was illustrated in Fig. 4. The absorption peaks at 3313 and 3184 cm^{-1} were assigned to the stretching vibration of 2º and 1º OH group, respectively. The peak at 2916 cm^{-1} was appeared to the stretching vibration of aliphatic CH while the band at 1602 cm^{-1} was represented the asymmetrical stretching vibration of COO^{-} groups. Similar peaks at 1442 and 1317 cm^{-1} were assigned to symmetrical stretching vibration of COO^{-} groups and the band appeared at 1066 cm^{-1} is attributed to the C-O-C stretching vibration[15].

The FT-IR spectrum of Cefixime was illustrated in Fig. 5. The absorption band at 3295 cm^{-1} was a normal range of primary amines absorption while the CH of the aromatic as well as aliphatic groups are observed at 3211, 3140, 2978 and 2945 cm^{-1}, respectively. The C=O absorption peak of the carboxylic acid have given rise to an over lapping

absorption of two carboxylic acids functional groups and appeared at 1776 cm^{-1}. C=O of the amide both cyclic imides and amide were seen at 1664 cm^{-1}. These observations were in concurrence with the structure of the drug molecule. The FTIR spectrum of SCMC blended with Cefixime was represented in Fig. 6, the broad bands of hydroxyl and amine or amide groups represented the overlap between functional groups of Cefixime and SCMC, which conclude that this formulation is not a final product but it is an intermediate mixture of the drug and polymer, these results agree with recent studies[16].

In vitro drug release study

The behavior release of antibiotic drug molecules from hydrogel was depended on several factors, such as the composition of hydrogel, the structure, chemical nature of the solute, the gelling polymers and the experimental conditions of the release medium (pH and temperature).

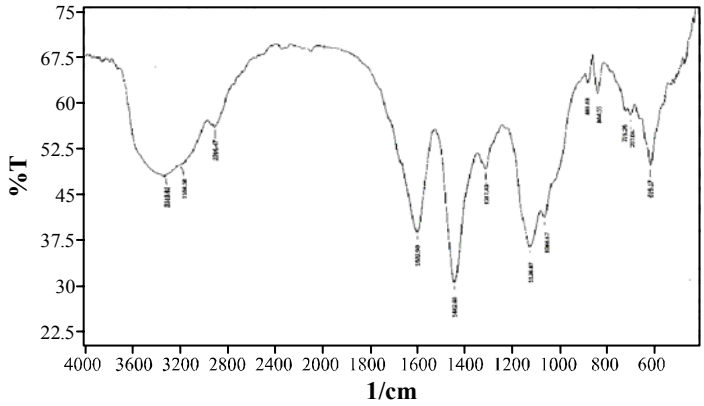

Fig. 4: FT-IR Spectrum of SCMC beads

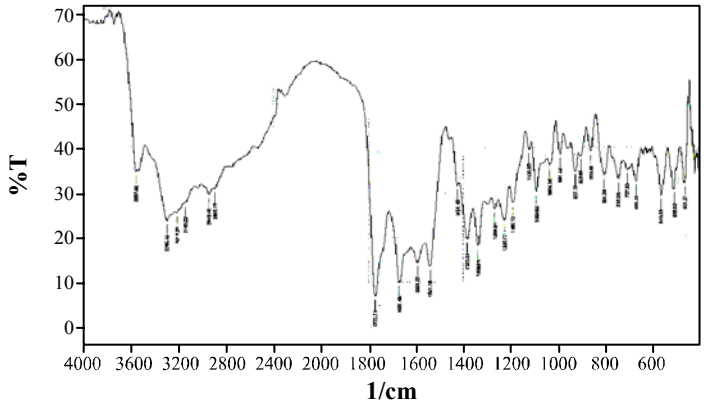

Fig. 5: FT-IR Spectrum of cefixime

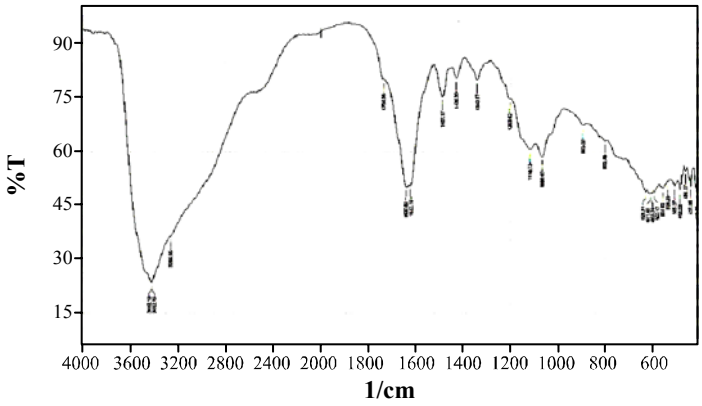

Fig. 6: FT-IR Spectrum of SCMC loaded with cefixime

Influence of pH on cefixime release from SCMC beads

The *in vitro* controlled release study of Cefixime on SCMC beads was performed at different pH buffer solution (1.2 and 7.2) and different intervals of temperatures (27ºC, 37ºC and 45ºC). It was clearly shown that the amount of antibiotic released from polymer beads increased with changing the pH from 1.2 to 7.2. At pH 7.2 the free carboxyl groups are negatively charged, which leads to repelling effect, this causes an increase in free space within the polymeric matrix, which favors the release of Cefixime[17] chains. While at pH 1.2 these groups are present as non-ionized and linked together through hydrogen bonds, which hinder the release of Cefixime. The Figs. 7, 8 & 9 were shown the differences between the release of Cefixime from SCMC beads at two pH buffers (pH 1.2 and pH 7.2) in different temperature intervals

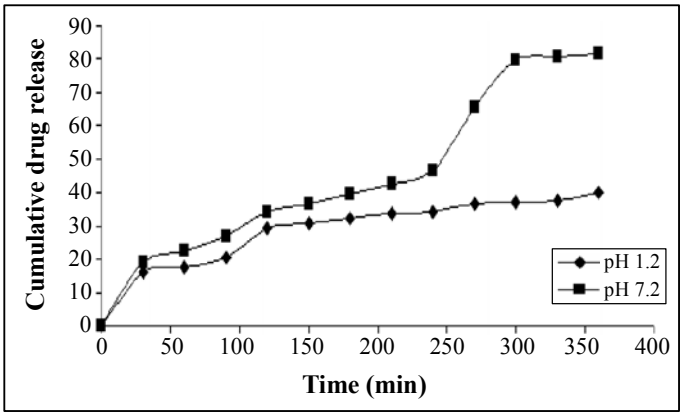

Fig. 7: *In vitro* cefixime release from SCMC beads at different pH, shaking speed 80 at 27ºC

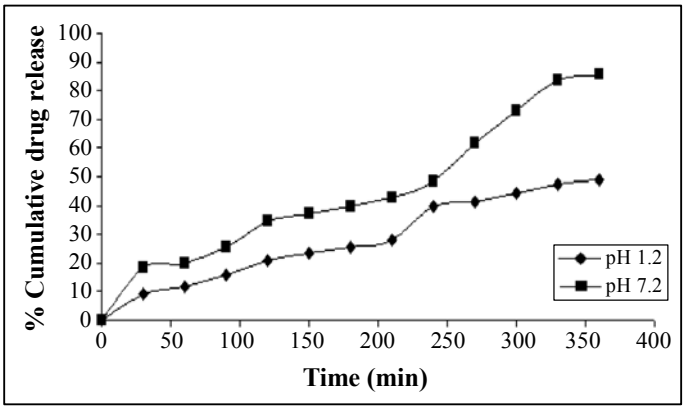

Fig. 8: *In vitro* cefixime release from SCMC beads at different pH, shaking speed 80 at 37ºC

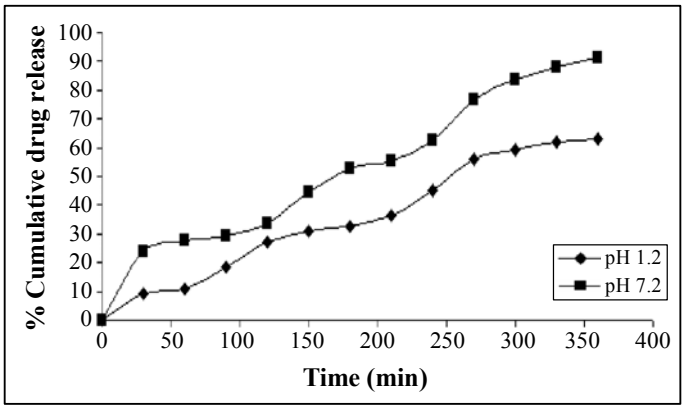

Fig. 9: *In vitro* cefixime release profile from SCMC beads at different pH, shaking speed 80 rpm at 45ºC

The influence of temperature on Cefixime release from SCMC beads

The cefixime release from SCMC beads polymer was studied at different temperatures (27, 37 & 45ºC) in two different buffer solutions (pH = 1.2 & pH = 7.2). In general the amount of cefixime drug released increase with increasing temperature. The Fig. 10 was appeared that the cefixime was completely released at 27ºC when it reached equilibrium after 300 min from starting whereas at 37ºC and 45ºC the equilibrium exceed 350 min. The Fig. 11 shows that there were not remarkable differences between equilibrium profiles at pH = 7.2. All were taken about 330 min. Moreover, the temperature increases results in an enhancement of Cefixime solubility in present water. This behavior may be convenient in the bacterial infection treatment[18].

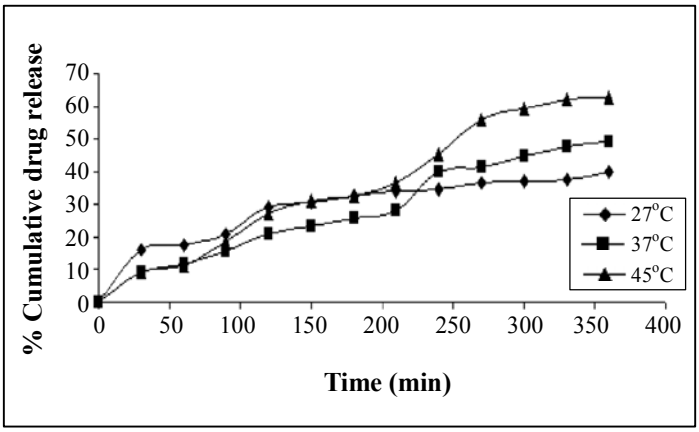

Fig. 10: Release kinetics of cefixime from SCMC beads at pH 1.2, different temperatures, shaking speed 80 rpm

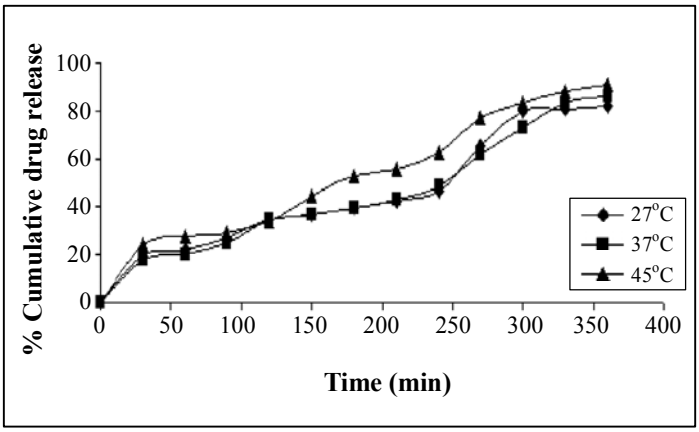

Fig. 11: Release kinetics of Cefixime from SCMC beads at pH 7.2, different temperatures, and shaking speed 80 rpm

Drug release kinetics

There are a number of kinetic models, which describe the overall release of drug from the dosage forms. Because qualitative and quantitative changes in a formulation may alter drug release *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable. In this regard, the use of *in vitro* drug dissolution data predict *in vivo* bio-performance can be considered as the rational development of controlled release formulations[19-21].

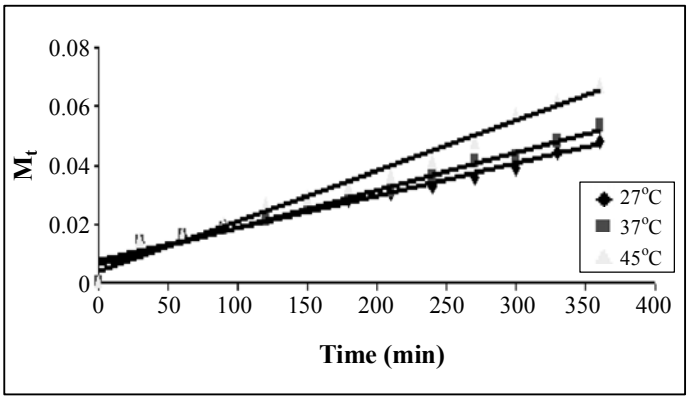

Fig. 12: Plot of M_t vs. time of release of cefixime from SCMC beads at pH 1.2, different temperatures, and shaking 80 rpm

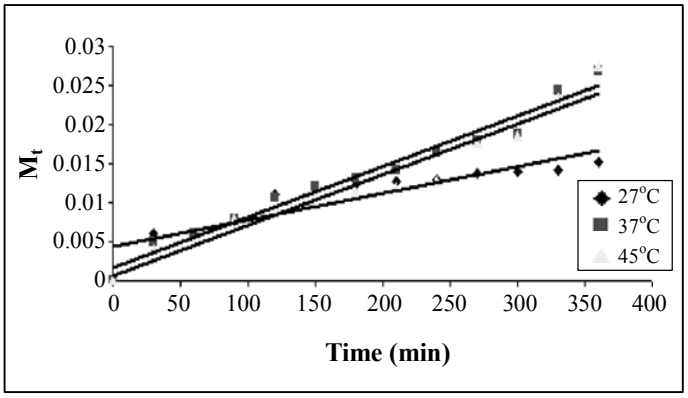

Fig. 13: Plot of M_t vs. time of release of Cefixime from SCMC beads at pH 7.2, different temperatures, shaking 80 rpm

The mechanism of drug release from the formulations can be examined by implementing, the zero-order, first order, second order, krosmeyer-peppas (k-p) and Higuchi kinetic models (Fig. 12 and 13).

Zero-order

Where M_t is the amount of drug dissolved in time *t,* M_0 is the initial amount of drug in the solution (most times, $M_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time[22,23].

$$M_t = M_0 + K_0 t \quad ...(1)$$

First-order

Where, M_0 is the initial amount of drug, k is the first order rate constant, and t is the time[24]. The data obtained are plotted as log cumulative percentage of drug remaining *vs.* time which would yield a straight line with a slope of -K/2.303.

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices[25,26] (Fig. 14, 15).

$$\text{Log } M_\infty - \log M_t = - Kt/2.303 \quad \ldots(2)$$

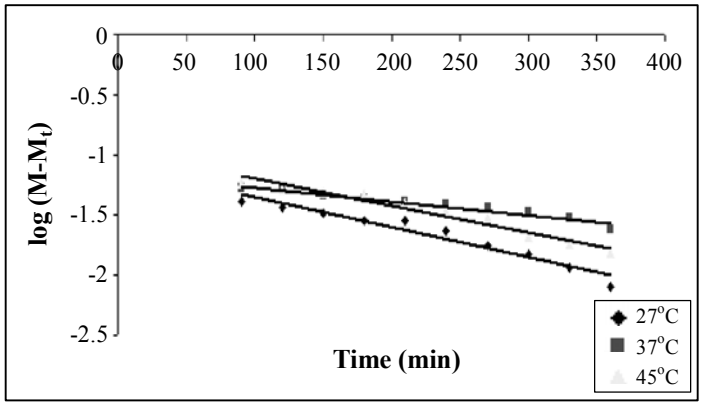

Fig. 14: Plot of log (M_∞-M_t) vs. time of of release of Cefixime from SCMC beads at pH 1.2, different temperatures, and shaking 80 rpm

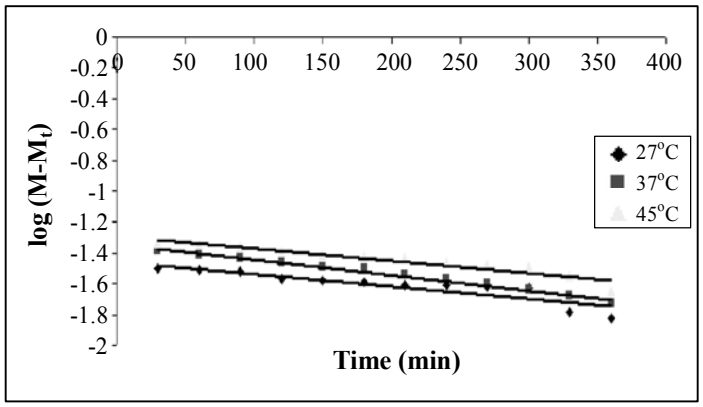

Fig. 15: Plot of log (M_∞- M_t) vs. time of of release of Cefixime from SCMC beads at pH 7.2, different temperatures, and shaking 80 rpm

Higuchi

Where, K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time. This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs[27,28] (Fig. 16 and 17).

$$M_t = M_0 + KHt^{1/2} \quad \ldots(3)$$

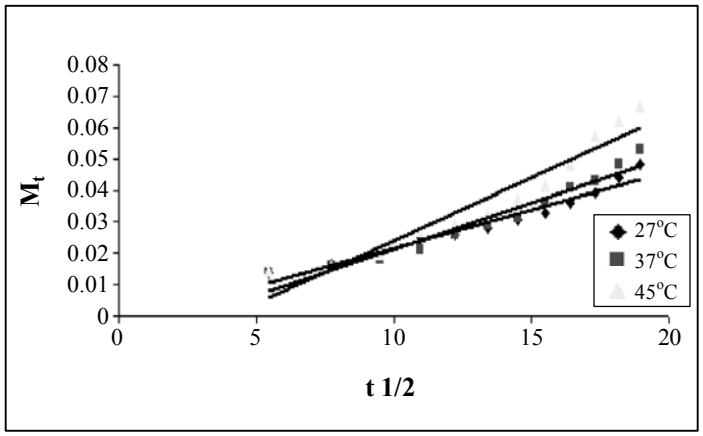

Fig. 16: Plot of M_t vs. t ½ release of Cefixime from SCMC beads at pH 1.2, different temperatures, and shaking speed 80 rpm

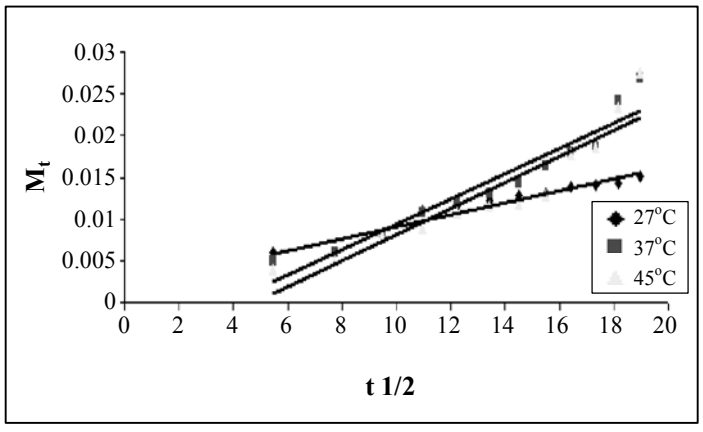

Fig. 17: Plot of M_t vs. $t^{1/2}$ release of Cefixime from SCMC beads at pH 7.2, different temperatures, and shaking speed 80 rpm

Krosmeyer-Peppas (k-p)

Where M_t/M_∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug as described in Table 2. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxation) transport, and $n > 0.89$ to super case II transport[29,30] (Fig. 18 and 19).

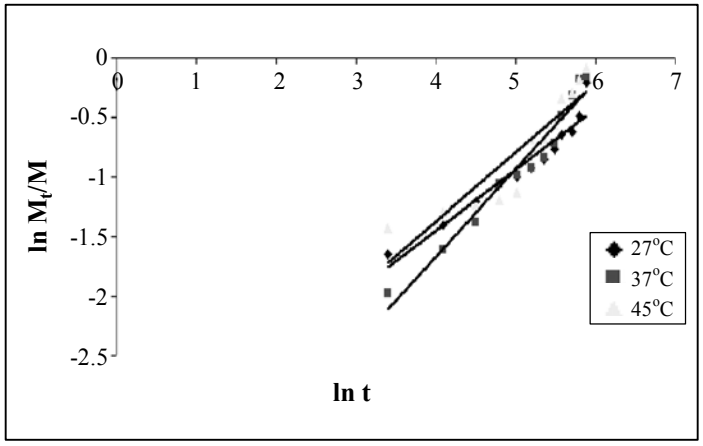

Fig. 18: Plot of In M_t/M_∞ vs. In t for release of Cefixime from SCMC beads at pH 1.2, different temperatures, and shaking speed 80 rpm

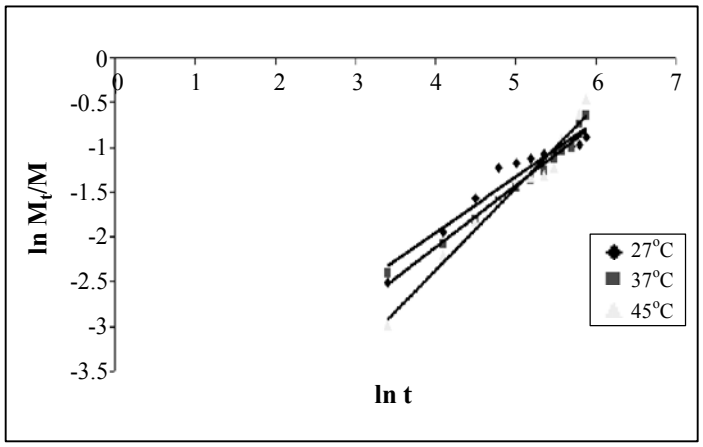

Fig. 19: Plot of InM_t/M_∞ vs. In t for release of Cefixime from SCMC beads at pH 7.2, different temperatures, and shaking speed 80 rpm

To find out the exponent of *n* the portion of the release curve, where $M_t/M_\infty < 0.6$ should only be used. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

$$M_t / M_\infty = k\, t^n \quad \ldots(4)$$

The kinetic release was studied using different release models. The correlation coefficient (r^2) was used as an indicator of the best fitting for each of the models considered. The correlation coefficient (r^2) for zero order kinetics, first order kinetics, Higuchi and Korse Meyer-Peppas model was shown in (Table 1 and 2). The results revealed that Higuchi and Kros Meyer-Peppas model are significtive by their higher correlation coefficient (r^2).

Table 1: Kinetic parameters for Cefixime release from SCMC beads at pH 1.2 and different temperatures

Temp. (^oC)	Zero-order		First-order		Higuchi		Krosmeyer-Peppas		
	R^2	K_0 (mg/h^{-1})	R^2	K1	R^2	(mg.h^{-1})	R^2	n	K_0
27	0.9808	$2*10^{-4}$	0.9216	$4.6*10^{-4}$	0.957	$2.4*10^{-4}$	0.929	0.513	0.544
37	0.9758	$1*10^{-4}$	0.954	$3*10^{-4}$	0.940	$2.9*10^{-4}$	0.958	0.73	0.664
45	0.9508	$2*10^{-4}$	0.9409	$3.4*10^{-4}$	0.925	$4*10^{-3}$	0.957	0.578	0.565

Table 2: Kinetic parameters for Cefixime release from SCMC beads at pH 7.2 and different temperatures.

Temp. (^oC)	Zero-order		First- order		Higu chi		Krosmeyer-Peppas		
	R^2	K_0 (mg/h^{-1})	R^2	K1 (h^{-1})	R^2	K (mg.h^{-1})	R^2	n	K_0
27	0.829	$1*10^{-4}$	0.816	$1.8*10^{-4}$	0.938	$7*10^{-4}$	0.9357	0.618	0.645
37	0.969	$5*10^{-3}$	0.983	$2.3*10^{-4}$	0.919	$1.5*10^{-4}$	0.968	0.690	0.687
45	0.944	$4*10^{-3}$	0.895	$1.8*10^{-4}$	0.864	$1.6*10^{-3}$	0.9722	0.918	0.781

CONCLUSION

In this research paper, sodium carboxymethyl cellulose (Na-CMC) has been modified by ionic gellation method using $FeCl_3/FeCl_2$ as cross linking agent. The FT-IR technique was revealed that the drug physically holded on the micro bead. The controlled drug release study of antibiotic at different temperature and pH revealed that the release of

drug was faster at 27^{o}C and the complete equilibrium was attained at 300 min. The drug release kinetic studies showed that the Krosmeyer-Peppas model well fitted with the experimental data for all temperatures at pH 7.2.

ACKNOWLEDGEMENT

We are grateful to the Ministry of Higher Education and Scientific Research for financial support of this work.

REFERENCES

1. R. Langer, Drug Delivery and Targeting, Nature, **392 (Supp)**, 5 (1998).
2. M. E. Nimni, Polypeptide Growth Factors: Targeted Delivery Systems, Biomater., **18**, 1201 (1997).
3. J. R. Robinson and V. H. L. Lee, Controlled Drug Delivery Fundamentals and Applications, 2nd Ed., New York, NY: Marcel Dekker, (1987) pp. 524.
4. Y. Qiu and K. Park, Environment-Sensitive Hydrogels for Drug Delivery, Adv. Drug Deliv., **53**, 321 (2001).
5. P. K. Prashant, B. P. Vivek, N. D. Deepashree and P. P. Pranav, Hydrogels as A Drug Delivery System and Applications: A Review, Int. Pharm. Pharmaceut. Sci., **4(1)**, 1 (2012).
6. A. R. Mullaicharam, A Review on Chronopharmaceutical Drug Delivery Sestem, Res. J. Pharmaceut. Biol. Chem., **4(3)**, 200 (2013).
7. J. Krushnakumar, V. Subhash and R. Kailash, Polymers in Pharmaceutical Drug Delivery System, Int. J. Pharm. Sci., **14(2)**, 57-66 (2012). Omanathanu Pillai, Ramesh, Polymers in Drug Delivery, Curr. Opinion in Chem. Biol., **5(4)**, 447 (2001).
8. P. Ramakrishna, K. Madhusudana Rao, K. V. Sekharnath, P. Kumarbabu, S. Veeraprathap, K. Chowdoji Rao and M. C. S. Subha, Synthesis and Characterization of Interpenetrating Polymer Network Microspheres of Acryl Amide Grafted Carboxymethylcellulose and Sodium Alginate for Controlled Release of Triprolidine Hydrochloride Monohydrate, J. Appl. Pharmaceut. Sci., March, **3(03)**, 101 (2013).
9. T. G. Mahewicz and T. J. Kirk, Othmer Concise of Chemical Technol., 4 Ed., Wiley, New York (1999) p. 368.

10. R. V. Kulkarni, C. M. Setty and N. V. Kalyane, Carboxymethylcellulose-Aluminum Hydrogel Microbeads for Prolonged Release of Simvastatin, Acta Pharmaceut. Sci., **52**, 137 (2010).

11. M. D. Dhanaraju, V. D. Sundar, S. Nandha Kumar and K. Bhaskar, Development and Evaluation of Sustained Delivery of Diclofenac Sodium from Hydrophilic Polymeric Beads, J. Young Pharmacists, Pharmaceut., **1 Suppl 4**, 301 (2009).

12. P. TripathiI, G. Priyanka and G. Mahesh, Charectarization and Validation of Cefixime Trihydrate Tablets with FTIR and RP-HPLC Techeniques, Indian J. Appl. Res., **5(4)**, 691 (2015).

13. National Committee for Clinical Laboratory Standards, Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests (M2-A3), December (1984).

14. D. E. Rodriguez-Felix, C. J. Perez-Martinez, M. M. Castillo-Ortga, M. Perez-Tello and J. Romero-Garcia, pH and Temperature-Sensitive Semi-Interpenetrating Network Hydrogels Composed of Poly (Acryl Amid) and (γ-glutamic Acid) as Amoxicillin Controlled-Release System, Polym. Bull., **68**, 197 (2012).

15. K. Mudhusudana, B. Malikarjuna, K. S. V. Krishna, M. N. Prabhakar, K. Chowdoji and M. C. S. Subha, Preparation and Characterization of pH Sensitive Poly (Vinyl Alcohol)/Sodium Carboxy Methyl Cellulose IPN Microspheres for *In Vitro* Release Studies of an Anti-Cancer Drug, Polym. Bull., **68(7)**, 1905 (2012).

16. Raghavendra, N. G. Rao, Pentewar Ram, Thube Ketan and V. B. Suryakar, Formulation and *In Vitro* Evaluation of Gastric Oral Floating Tablets of Cefixime for Controlled Release, Res. J. Pharmaceut. Biol. Chem. Sci., **1(3)**, 141 (2010).

17. K. M. Rao, B. Mallikarjuna, K. S. V. Krishna Rao, M. N. probhakar, K. Chowdoji Rao and M. C. S. Subha, Preparation and Characterization of pH Sensitive PVA/SCMC IPN Microspheres for *In Vitro* Release Studies of Anti-Cancer. Polym, Bull., **68**, 1905 (2011).

18. D. E. Rodriguez-Felix, C. J. Perez-Martinez, M. M. Castillo-Ortga, M. Perez-Tello and J. Romero-Garcia, pH and Temperature-Sensitive Semi-Interpenetrating Network Hydrogels Composed of Poly (Acryl Amid) and (γ-Glutamic Acid) as Amoxicillin Controlled-Release System, polym. Bull., **86**, 197 (2012).

19. S. S. Ozturk, B. O. Palsson, B. Donohoe and J. B. Dressman, Kinetics of Release from Enteric-Coated Tablets, Pharm. Res., **5(9)**, 64 (1988).

20. J. B. Dressman and D. Fleisher, Mixing-Tank Model for Predicting Dissolution Rate Control of Oral Absorption, J. Pharm. Sci., **75**, 109 (1986).

21. J. B. Dressman, D. Fleisher and G. L. Amidon, Physicochemical Model for Dose-Dependent Drug Absorption, J. Pharm. Sci., **73**, 1274 (1984).

22. B. Narashimhan, S. K. Mallapragada and N. A. Peppas, Release Kinetics, Data Interpretation, in, Encyclopedia of Controlled Drug Delivery, Eds., John Wiley and Sons, Inc, New York (1999) p. 921.

23. T. P. Hadjiioannou, G. D. Christian and M. A. Koupparis, Quantitative Calculations in Pharmaceutical Practice and Research, Eds., VCH Publishers Inc., New York, 345 (1993).

24. D. W. Bourne, Pharmacokinetics, in, Modern Pharmaceutics, 4th Ed., G. S. Banker, C. T. Rhodes, Eds., Marcel Dekker Inc, New York (2002).

25. B. Narashimhan, S. K. Mallapragada and N. A. Peppas, Release Kinetics, Data Interpretation, in, Encyclopedia of Controlled Drug Delivery, E. Mathiowitz Ed., John Wiley and Sons, Inc, New York (1999).

26. A. Silvina, M. Bravo, C. Lamas and J. Claudio, *In Vitro* Studies of Diclofenac Sodium Controlled-Release from Biopolymeric Hydrophilic Matrices, J. Pharm. Sci., **5(3)**, 213 (2002).

27. T. Higuchi, Mechanism of Rate of Sustained-Action Medication. Theoretical Analysis of Rate of Solid Drugs Dispersed In Matrices, J. Pharm. Sci., **52**, 1145 (1963).

28. H. M. Shoaib, J. Tazeen, A. H. Merchant and I. R. Yousuf, Evaluation of Drug Release Kinetics from Ibuprofen Matrix Tablets using HPMC, Pak. J. Pharm. Sci., **19**, 24 (2006).

29. P. L. Ritger and N. A. Peppas, A Simple Equation for Description of Solute Release II Fickian and Anomalous from Swellable Devices, J. Control Rel., **5**, 37 (1987).

30. J. Siepmann and N. A. Peppas, Mathematical Modeling of Bioerodible, Polymeric Drug Delivery Systems Adv. Drug Deliv., **48**, 139 (2001).

Revised : 19.01.2016 *Accepted : 21.01.2016*