MAJOR PROJECT

SYNTHESIS AND CHARACTERIZATION OF NOVEL XANTHAN GUM-BASED pH-SENSITIVE HYDROGEL FOR METFORMIN HYDROCHLORIDE RELEASE

A PROJECT WORK

SUBMITTED IN THE PARTIAL FULFILLMENT OF THE

REQUIREMENT FOR THE AWARD OF THE DEGREE OF

MASTER OF SCIENCE (M.Sc.)

In

CHEMISTRY

Submitted by

TUSHAR
[2K21/MSCCHE/47]

YASH SARASWAT
[2K21/MSCCHE/50]

Under the supervision of

Prof. S.G. WARKAR

Department of Applied Chemistry
Delhi Technological University
Delhi-110042

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering Bawana Road, Delhi-110042)

CANDIDATE DECLARATION

We Tushar (2K21/MSCCHE/47) and Yash Saraswat (2K21/MSCCHE/47) students of M.Sc. (Chemistry) hereby declare that the project Dissertation titled **"Synthesis and characterization of novel Xanthan Gum-based pH-sensitive hydrogel for metformin hydrochloride release"** which is submitted by us to the Department of Applied Chemistry, Delhi Technological University, Delhi in the partial fulfillment of the requirement for the award of the degree of Master of Science, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma, Associateship. Fellowship or other similar title or recognition.

PLACE- DELHI

DATE- 23/05/2023

Tushar (2K21/MSCCHE/47)

Yash Saraswat (2K21/MSCCHE/50)

Department of Applied Chemistry
DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering) Bawana Road, Delhi-110042

CERTIFICATE

I/We hereby certify that the Project Dissertation titled "Synthesis and characterization of novel Xanthan Gum-based pH-sensitive hydrogel for metformin hydrochloride release" which is submitted by Tushar (2K21/MSCCHE/59) & Yash Saraswat (2K21/MSCCHE/47), Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the Master of Science, is a record of the project work carried out by the students under my supervision. To the best of my/our knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

PLACE- DELHI

DATE- 23/05/2023

PROF. S.G. WARKAR

(SUPERVISOR)

ACKNOWLEDGEMENT

The success and outcome of this project required a lot of guidance and assistance from many people and We are extremely fortunate to have got this all along the completion of this project work.

We wish to express our gratitude towards my project supervisor, Prof. S.G. WARKAR, Department of Applied Chemistry, Delhi Technological University, who provided us with a golden opportunity to work under their able guidance. Their scholastic guidance and sagacious suggestions helped me to complete the project on time.

We wish to thank Prof. Anil Kumar, Head of the Department of Applied Chemistry, at Delhi Technological University for his constant motivation.

We are thankful for and fortunate enough to get constant encouragement, support, and guidance from all teaching staff of the Department of Applied Chemistry, which helped me in completing my project work. We are also thankful to Ph.D. scholar Priyanka Meena for her constant support and motivation.

Finally, yet importantly, We would like to express our heartfelt thanks to our beloved family and friends who have endured our long working hours and whose motivation kept us going.

Tushar & Yash Saraswat

ABSTRACT

In the current study, the synthesis of hydrogel based on carboxymethyl tamarind kernel gum (CMTKG), poly sodium acrylate (PSA), xanthan gum (XG), and its loading with Metformin hydrochloride (Metformin HCl) was successfully carried out and characterized using various techniques. Further, the optimization of hydrogel was done by varying the amount of CMTKG, MBA, or KPS, and their influence on the swelling ratio was examined. The fabricated hydrogels were characterized by Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy (ATR-FTIR), Powder X-ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM), whereas thermal stability was confirmed by Thermogravimetry Analysis (TGA). The hydrogels' swelling ratio and drug release studies were assessed in pH 1.2 and 7.4 buffer solutions and showed better results in alkaline pH. The drug release profile of Metformin-loaded CMTKG/PSA/XG hydrogel obeyed the Korsmeyer-Peppas model and follow non-fickian diffusion in pH 7.4 and fickian diffusion mechanism at pH 1.2. This pH-dependent behavior of the Metformin HCl- loaded CMTKG/PSA/XG hydrogel could be applicable for site-specific release of Metformin HCl.

Keywords CMTKG, Biopolymer, Metformin HCl, pH-sensitive hydrogel, Kinetic Modeling

Content

List of Table, Scheme & Figure Captions

Table

Scheme

Figures

1. Introduction and Literature Survey

Earlier in the 1960s, Wichterle and Lim developed hydrogels for biomedical applications by cross-linking hydrophilic poly(2-hydroxyethyl methacrylate) polymers into a network to produce a contact lens[1]. Several studies and attempts have been made in the past and present to enhance and broaden the prospects associated with hydrogels. Hydrogel innovation, constantly evolving, has dramatically changed the biomedical and pharmaceutical sectors [2]. In terms of the definition, hydrogels are three-dimensional structured polymeric networks that have a high absorption capacity for biological or aqueous fluids. Hydrophilic groups like -OH, $-CONH_2$, $-SO_3H$, etc., are found in polymers that form hydrogel structures, and these groups are considered responsible for the polymers' propensity to absorb water [3]. These polymeric networks share a unique feature with living tissues, which is related to their smooth and porous consistency, low adhesion strength with water or biological fluids, and excessive water content [4]. A hydrogel's water content governs its specific physicochemical characteristics. Because of the vital cross-links in the hydrogel structure, they exhibit a swelling tendency despite having a high attraction for water that prevents them from dissolving in the aqueous environment [5].

The term "stimuli-sensitive hydrogels" refers to hydrogels that respond to various physical and chemical stimuli including light, temperature, pH, etc.[6]. The most promising stimulant to enhance the hydrogel's swelling properties among all of them is pH. The pH-responsive hydrogels are either anionic or cationic. Anionic hydrogels are ionized at a pH greater than the pKa of the hydrogel and thus swollen. Cationic hydrogels are ionized at a pH lower than the polymer network's pKa [7]. pH-responsive anionic hydrogels are used in gastrointestinal drug delivery systems to safeguard drugs from gastric breakdown and inactivation at low pH and to release drugs in target sites [8].

Polysaccharides are one of the most commonly used organic biopolymers, as they have significant applications in many physiological and biomedical processes. Researchers prefer biopolymers as pharmaceutical formulations because of their biodegradable, low toxic, and biocompatible behavior [9]. Xanthan gum is one of the most significant biopolymers made by bacterial fermentation. Xanthan gum's core qualities of being biodegradable and biocompatible make it possible for it to be used in biomedical applications[12]. Due to its solid matrix and resilience to any pH fluctuation, xanthan gum is stable in acidic and alkaline situations [13].

Another biopolymer that shows its potential in drug delivery applications is CMTKG which is a derivative of tamarind kernel gum (TKG). TKG is a biopolymer acquired from the Tamarindus Indica L. tree's seeds., and it has a good ability for water retention [14].As TKG and its derivatives are non-toxic and susceptible to bacterial decomposition, they have been employed as promising

biopolymers for hydrogel formation [15]. Numerous TKG-based modified products are used in industries, paper, food, plywood, and medicine [16]. The TKG derivative CMTKG is one such example; comparatively, it has outstanding properties to TKG[17]. Its molar ratios of galactose, xylose, and glucose are 1:2:3 in total [15]. The addition of a carboxylic group gives CMTKG an anionic property because of carboxylate ions, enabling the development of interpolymer complexes with cationic polymers. The carboxymethylation of tamarind kernel gum results in increased stability, solubility, and biodegradability of the biopolymer [18]. For enhancing the structural properties, stability, swelling ratio, and drug release, poly sodium acrylate has been used as a synthetic polymer with highly absorbent properties[19]. Poly sodium acrylate is a polyacrylic acid sodium salt having the molecular formula $[-CH_2-CH(COONa)^-]_n$. It can soak up 200 to 300 times its weight in water. [20]. Poly sodium acrylate is an anionic polyelectrolyte with negatively charged carboxylic groups in the functional group, enabling them to respond to different pH [21]. The positive anionic charge of the many sequences of acrylate compounds that constitute poly sodium acrylate sodium attracts the conjunction of water-based molecules, creating Na polyacrylate, a highly absorbent substance [22].

A disease called diabetes mellitus has the potential to increase mortality and morbidity. It is also regarded as a dangerous illness in many nations around the World. This could shorten the life span and make people more vulnerable to diseases [23]. One of the most widely prescribed drugs for treating type 2 diabetes mellitus is metformin HCl. It functions as an antihyperglycemic drug used to treat diabetes mellitus that is insulin-resistant [24]. Within 24 hours, about 30% to 50% of metformin is eliminated in the urine, and about 30% in sludge. The release kinetics of metformin has incomplete absorption [25]. Therefore, Metformin HCl-loaded hydrogel has been developed to improve adherence and reduce adverse effects.

Poly sodium acrylate and xanthan gum are being employed with carboxymethyl tamarind kernel gum (CMTKG) for the first time, to the extent that we are aware of. This work involves synthesis, swelling, drug release, and kinetic modeling of Metformin-loaded CMTKG, PSA, and XG-based hydrogels

Table 2. Literature on bio-polymer based hydrogel used in controlled drug delivery systems

Hydrogel	Application	Reference
Chitosan/PEG	Cefixime release	https://doi.org/10.1016/j.ijbiomac.2015.06.044
Chitosan/Guar Gum	Paracetamol release	https://doi.org/10.1016/j.ijbiomac.2017.12.008
MAA/PEO-PVP	Metaprolol release	https://doi.org/10.1080/00914030802461899
Chitosan/PVP	Diclofenac Sodium release	https://doi.org/10.1016/j.ijbiomac.2020.06.133
Xanthan Gum/Starch/PAA	Paracetamol and Aspirin release	https://doi.org/10.1007/s10570-020-03082-0
ASP/ALPAA	Ibuprofen release	https://doi.org/10.3390/gels7020068
Sodium Alginate/PVA	Chloramphenicol release	https://doi.org/10.1002/mawe.201900163
NaAlg/NaCMC	Metformin HCl release	https://doi.org/10.1016/j.ijbiomac.2015.03.019
Chitosan/GeIMA	Aspirin release	https://doi.org/10.3389%2Ffchem.2022.874985
Sodium Alginate/PVA	Diclofenac Sodium release	https://doi.org/10.1016/j.ijbiomac.2010.03.004

2. MATERIALS AND METHODS

2.1 Materials

Hindustan Gum and Chemicals Ltd., Bhiwani, Haryana, kindly provided CMTKG, which has 0.20° of substitution. Sodium hydroxide (Fischer Scientific, Mumbai), Xanthan gum (s d fine chem. Ltd.), Potassium per sulfate (KPS, Fischer Scientific, Mumbai), Acrylic acid (AA, CDH,New Delhi), and N, N'-methylene bis(acrylamide) (MBA, Merck, Germany), were consumed as provided. For the preparation of the solutions, distilled water was employed.

2.2. Synthesis of CMTKG/PSA/XG Hydrogel and Metformin HCl- loaded CMTKG/PSA/XG Hydrogels

The hydrogels based on PSA, CMTKG, and XG were fabricated by free radical polymerization with KPS as the initiator and MBA as the cross-linker, as presented in Fig.1. This reaction procedure was conducted by combining NaOH and Acrylic acid while keeping the pH neutral. The desired amount of CMTKG and XG was then diluted with distilled water and poured into the following mixture, and then stirred. Then, a predetermined quantity of MBA and KPS was introduced and magnetically stirred. After that resultant solution was poured into the test tubes and placed in a hot water bath at 60°C. The hydrogels were recovered from the test tube and sliced. The hydrogel slices were then left to dry in the oven at 50 °C till completely dried [28]. The various combination of Metformin HCl-loaded CMTKG/PSA/XG Hydrogels has been formulated using the same procedure with minute changes. Metformin HCL was introduced with KPS and MBA addition, and the rest of the procedure was the same. The proportion of the reactants used in the synthesis of hydrogels is presented in Table 1 [29]

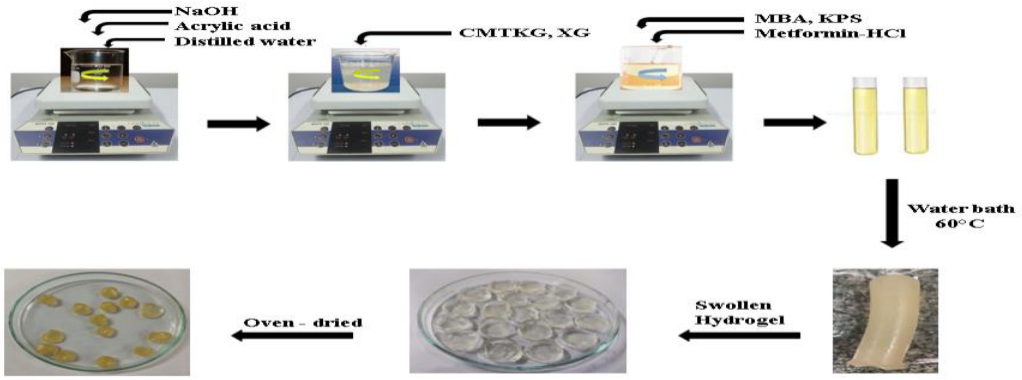


Fig 1: Demonstration of the formation of Metformin HCl-loaded Hydrogels

Table 1: The proportion of reactants used in hydrogel formation.

Sample code	CMTKG (g)	Acrylic Acid (ml)	NaOH (g)	MBA (mg)	KPS (mg)	XG (mg)	Metformin HCl (mg)	Swelling Ratio (%)	
								pH 7.4	pH 1.2
S-1	0.1	5	2	20	35	20	50	801	689
S-2	0.2	5	2	20	35	20	50	809	716
S-3	0.3	5	2	20	35	20	50	899	767
S-4	0.4	5	2	20	35	20	50	937	790
S-5	**0.5**	**5**	**2**	**20**	**35**	**20**	**50**	**1033**	**838**
S-6	**0.5**	5	2	25	35	20	50	773	725
S-7	**0.5**	5	2	30	35	20	50	650	600
S-8	**0.5**	5	2	35	35	20	50	640	564
S-9	**0.5**	5	2	40	35	20	50	549	528
S-10	**0.5**	5	2	20	20	20	50	723	620
S-11	**0.5**	5	2	20	25	20	50	808	684
S-12	**0.5**	5	2	20	30	20	50	824	699
S-13	**0.5**	5	2	20	40	20	50	826	809
S-14	**0.5**	5	2	20	35	20	00	1002	827

3. EXPERIMENTAL SECTIONS

3.1. Swelling Studies

By using gravimetric analysis, the swelling studies of synthesized hydrogels were analyzed. Weighed precisely, thoroughly dried hydrogel samples were submerged in pH 1.2 and pH 7.4 solutions. After a preset amount of time, the swollen hydrogels were removed and weighed after the surface water had been wiped off with filter paper [30]. The swelling ratio was determined by applying the equation formula:

$$\text{Swelling Ratio (\%)} = (W_s - W_d)/W_d$$

where W_d is the dry hydrogel's initial weight and Ws is the swollen hydrogel's weight [31].

3.2 Metformin HCl Loading (%) and encapsulation efficiency (%)

The drug loading and encapsulation efficiency were found out for formulation S-5 as it shows the highest swelling of 1033% in pH 7.4. A 0.1g hydrogel disc was submerged in pH 7.4 buffer solutions for 24 hours at 37°C. At a particular time, the 3ml solution was withdrawn, a fresh buffer was added to maintain the volume, and a UV-vis spectrophotometer was used to detect the absorbance of the solution at λ_{max} 233 nm. A calibration curve was used to measure the amount of the drug [32]. The formula used to calculate the drug loading (%).;

$$\text{Drug Loading (\%)} = \frac{Amount\ of\ drug\ in\ hydrogel\ disc}{weight\ of\ hydrogel\ disc} * 100$$

The formula used to calculate encapsulation efficiency;

$$\text{Drug encapsulation efficiency (\%)} = \frac{Amount\ of\ drug\ in\ hydrogel\ disc}{Theoretical\ drug\ amount\ in\ hydrogel\ disc} * 100$$

3.3 In vitro release of Metformin HCl

The in vitro investigation of Metformin HCl was performed in HCl buffer and phosphate buffer saline for formulation S-5 as it shows the highest swelling. The release investigation was evaluated in an orbital incubator by placing 0.1 g of the hydrogel disc loaded with Metformin HCl in 100 mL of pH 1.2 and 7.4 solutions at 37°C and 150 rpm shaker. After each 3 mL sample was taken out at regular intervals, an equivalent fresh buffer solution was added. A UV spectrophotometer (Model: Cary 300 UV-Vis) was used to measure the absorbance of the solution at λ_{max} 233 nm. By constructing a calibration curve, the amount of drug release was ascertained [33].

3.4 Kinetic Modeling of Metformin HCl

Numerous mathematical simulations have been utilized to interpret drug release mechanisms, including the Zero Order, First Order, Korsmeyer-Peppas, Higuchi, and Hixson-Crowell models.The model's coefficient of determination (R^2) values was compared for each model following the fitting of the release data to it. To be called the best fit, the model's R^2 value must be near 1.[34]

4. Characterization

4.1 Powder X-Ray Diffraction (PXRD)

Using a Bruker D8 diffractometer at 2θ range of 5 to 70°C with Cu K-α radiation, the diffraction patterns of Metformin HCl, CMTKG/PSA/XG hydrogel, and Metformin HCl loaded-CMTKG/PSA/XG hydrogel were captured.

PXRD is employed to assess the substance crystallinity and analyze the drug dispersion into the polymeric network. The X-ray diffraction patterns of Metformin HCl, CMTKG/PSA/XG hydrogel, and Metformin HCl-loaded CMTKG/PSA/XG hydrogel are illustrated in Fig. 4.

The sharp peak of Metformin HCl at 2θ values of 17.64, 23.2, 24.36, 29.4, 32.56, and 45.68 reflects the crystalline nature of Metformin HCl[37]. In x-ray patterns of Metformin HCl-loaded CMTKG/PSA/XG hydrogel, no peak associated with the drug is noticed, which denotes drug is evenly distributed throughout the hydrogel [30].

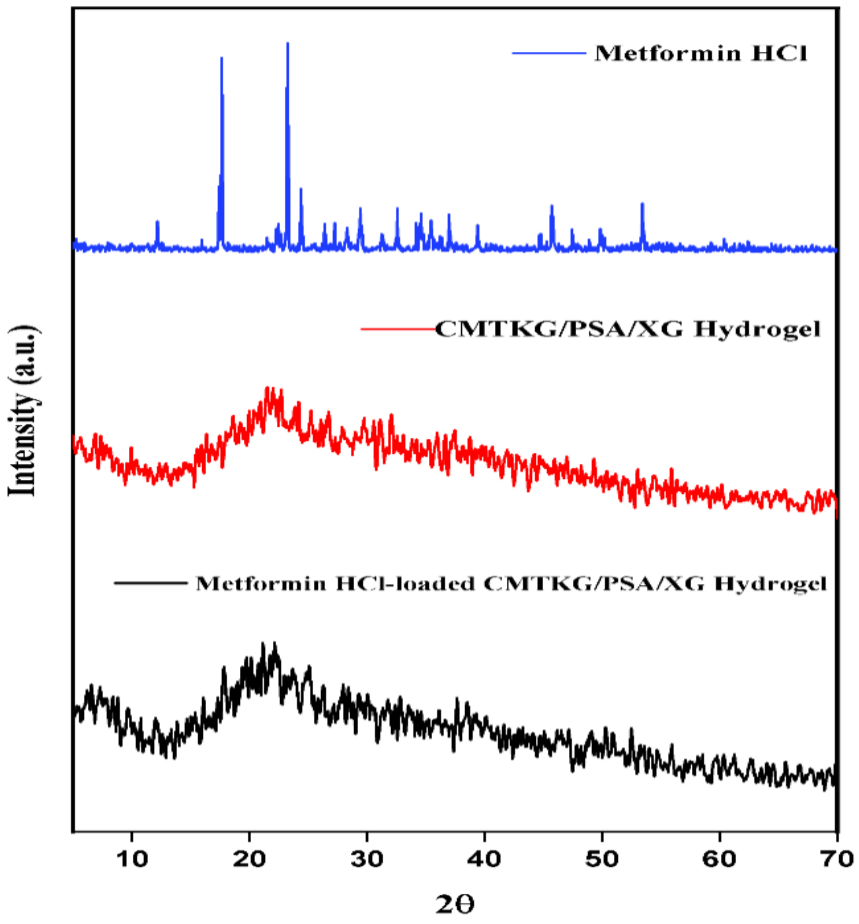


Fig 2: PXRD pattern of Metformin HCl, CMTKG/PSA/XG, and Metformin HCl -loaded CMTKG/PSA/XG Hydrogel.

4.2 ATR-FTIR Spectroscopy

The ATR-FTIR spectrum of CMTKG/PSA/XG hydrogel, Metformin HCl-loaded CMTKG/PSA/XG hydrogel, and MBA were recorded using an ATR-FTIR spectrophotometer (Model: Nicolet iS50 FTIR).

ATR-FTIR spectra of synthesized CMTKG/PSA/XG hydrogel, Metformin HCl-loaded CMTKG/PSA/XG, and MBA have been shown in Fig. 5. For CMTKG/PSA/XG hydrogel and Metformin HCl-loaded CMTKG/PSA/XG hydrogel, the -OH stretching peak has been seen at 3322cm^{-1} and 3324cm^{-1}. The COO^-symmetric stretching vibrations are recorded at 1394cm^{-1} and 1398cm^{-1}. In contrast, the COO^- asymmetric vibration bands correspond to peaks at 1567cm^{-1} and 1569cm$^{-1,}$ respectively [29]. The asymmetric stretching peak of the C-H bond was noticed at 2937cm^{-1} and 2942cm^{-1}. For the glycosidic linkage corresponding to the C-O-C bond, the peakis noticed at 1041cm^{-1} and 1043cm^{-1} [36].

In the spectrum of MBA, the peak associated with C-N is observed at 1307cm^{-1}, which shifted to 1317cm^{-1} in the CMTKG/PSA/XG hydrogel and at 1319cm^{-1} in Metformin HCl-loaded CMTKG/PSA/XG hydrogel, signifies a reduction in conjugation due to cross-linking. Hence, cross-linked CMTKG/PSA/XG hydrogel has been successfully formulated [38]. In Metformin HCl-loaded CMTKG/PSA/XG, the characteristics -C=N band of Metformin HCl is observed at 1631cm^{-1}, which signifies that the drug is entrapped into the hydrogel. No new band other than the drug was recorded in the drug-loaded hydrogel, which denotes the hydrogel and drug's physical contact (hydrogen bonding) [39].

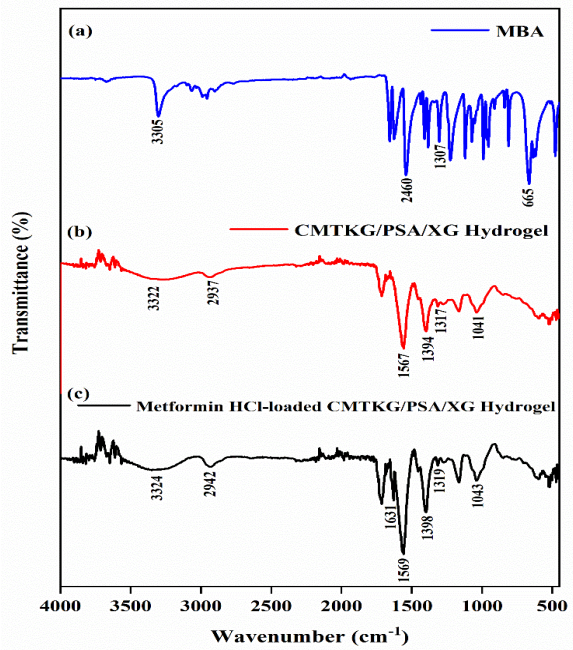


Fig 3: ATR-FTIR spectrum of the(a) MBA, (b) CMTKG/PSA/XG, (c) Metformin HCl-loaded CMTKG/PSA/XG hydrogel.

4.3 Thermogravimetric Analysis (TGA)

With a PerkinElmer TGA 4000 using a nitrogen environment at a steady heating rate of 10°C/min from 30°C to 850°C, the thermogravimetric analysis of CMTKG/PSA/XG hydrogel and Metformin HCl loaded- CMTKG/PSA/XG hydrogel was recorded.

TGA was done to understand the hydrogel and drug interaction and their stability pattern. TGA curve of synthesized CMTKG/PSA/XG hydrogel and Metformin-HCl loaded CMTKG/PSA/XG hydrogel has been displayed in Fig. 6. Weight loss in both the hydrogels was found in the four steps. Initially, by the vapourization of a molecule of water from the hydrogel matrix, weight loss of 7.4% and 5.7% from 30-215°C was seen in the CMTKG/PSA/XG hydrogel and Metformin HCl-loaded CMTKG/PSA/XG hydrogel. Then secondly, weight loss of 20.6% and 19.7% from 215-422°C was found due to the polymer backbone's breakdown, because of the loss of carboxymethyl and hydroxyl group of the hydrogel. In the third step, weight loss of 22.8% and 22.1.% from 422-514°C was seen due to the loss of cross-link in the hydrogel. Lastly, because of the complete breakdown of the hydrogel, weight loss of 20.7% and 19.8% from 514-850°C was observed.

The TGA graphs of CMTKG/PSA/XG hydrogel are relatively similar to that of Metformin HCl-loaded CMTKG/PSA/XG hydrogel means that there was only physical interaction (hydrogen bonding) between Metformin-HCl and the polymer network. Hence, stability is not much affected [29].

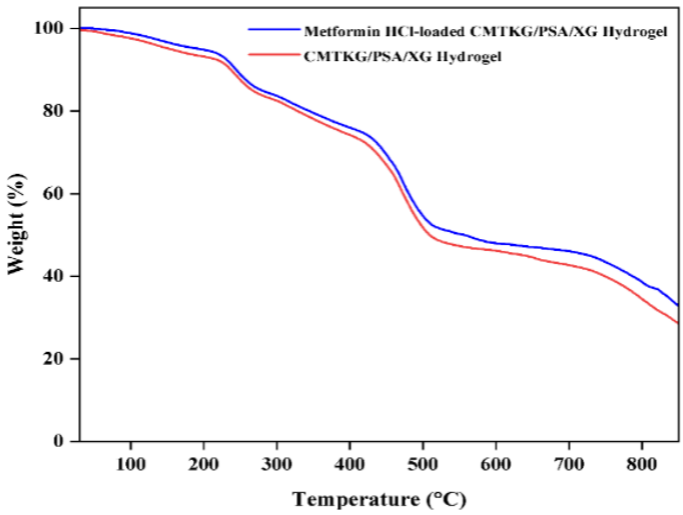


Fig 4: TGA curve of the CMTKG/PSA/XG, Metformin HCl- loaded CMTKG/PSA/XG hydrogel.

4.4 Scanning Electron Microscopy (SEM)

Using SEM (Model: JEOL Japan Mode: JSM 6610LV), the surface composition of CMTKG/PSA/XG hydrogel and Metformin HCl-loaded CMTKG/PSA/XG hydrogel was examined.

SEM images of CMTKG/PSA/XG hydrogel and Metformin HCl-loaded CMTKG/PSA/XG hydrogel were shown in Figures 7(a) and (b). The CMTKG/PSA/XG hydrogel has a very irregular and porous surface, which permits the hydrogel to effectively load drug molecules. While in a SEM microgram of Metformin HCl-loaded CMTKG/PSA/XG hydrogel, a regular surface, and fewer pores are viewed, as metformin HCl occupies the pore [40].

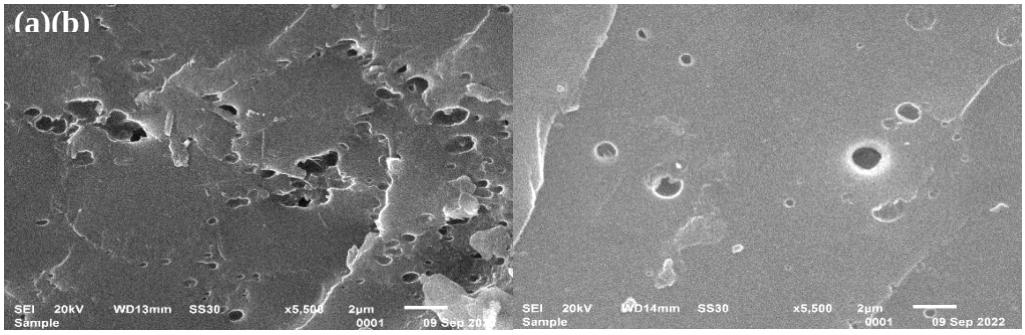
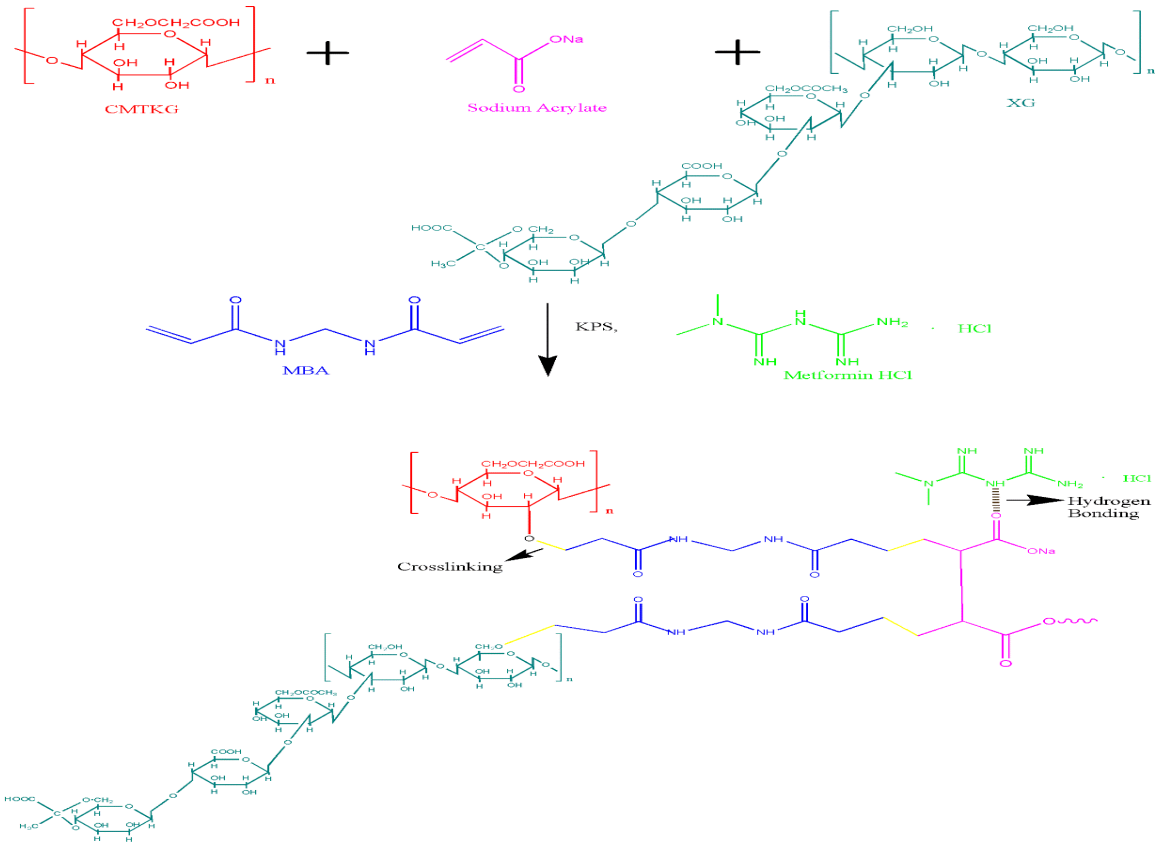


Fig 5: SEM micrograms of (a) CMTKG/PSA/XG hydrogel, (b) Metformin HCl- loaded CMTKG/PSA/XG hydrogel.

5. Results and Discussions

5.1 Overview of CMTKG/PSA/XG hydrogel and Metformin HCl-loaded CMTKG/PSA/XGhydrogel synthesis.

As shown in Table 1, various hydrogels are produced employing various compositions of CMTKG, KPS, and MBA. Scheme 1 demonstrates the overall proposed methodology. At 60°C,the initiator KPS initially decomposes to create the persulfate radicals. These persulfate radicals breakdown the vinylic bond of the sodium acrylate to produce radicals on sodium acrylate. The sodium acrylate radical then attacks another sodium acrylate monomer, and the chain propagation step continues, which leads to polysodium acrylate (PSA) formation. Further, the MBA radical forms cross-linking via the -OH group of CMTKG, -OH group of XG, and a vinylic group of PSA to form the network. The hydrogen bonding occurs between Metformin-HCland PSA. This resulted in forming a three-dimensional network of Metformin HCl-loaded CMTKG/PSA/XG hydrogel.



Scheme 1: Reaction mechanism of Metformin HCl-loaded CMTKG/PSA/XG hydrogeL

5.2 Swelling studies

Swelling studies were done at pH 1.2 and pH 7.4 for all hydrogels. Figure 3 depicts the influence of biopolymer, initiator, and cross-linker concentration on the hydrogel's swelling ratio.

5.2.1 Influence of Biopolymer

The different CMTKG amounts significantly impacted the ability to absorb water. This phenomenon might be explained as the CMTKG rose from 0.1g to 0.5g, and the COO^- groups along the polymer network rose tremendously. The repulsion of similarly charged COO^- groups enhances the chain relaxation and free space in the network increase leading to high swelling. Additionally, it should be mentioned that attempts were made to synthesize hydrogel with even elevated concentrations of biopolymer. However, in those instances, the solution tended to become quite dense and was, therefore, very tricky to swirl [35].

The synthesized hydrogel with sample code S-5 exhibits a higher swelling ratio among all the formulations as seen in Fig. 2. In the S-5 sample, the swelling ratio was higher for alkaline pH ranges than for acidic pH ranges. The deprotonated COO^- ion of the polymeric chain initiates the rise of swelling at pH 7.4. The COO^- ion experiences anion-anion repulsion; as a result, polymeric chains relax, and greater space for water absorption occurs [36]. But at pH 1.2, hydrogen bonding between PSA, CMTKG, and XG exists, which tends to shrink the hydrogel network and reduces its capacity to absorb water [31].

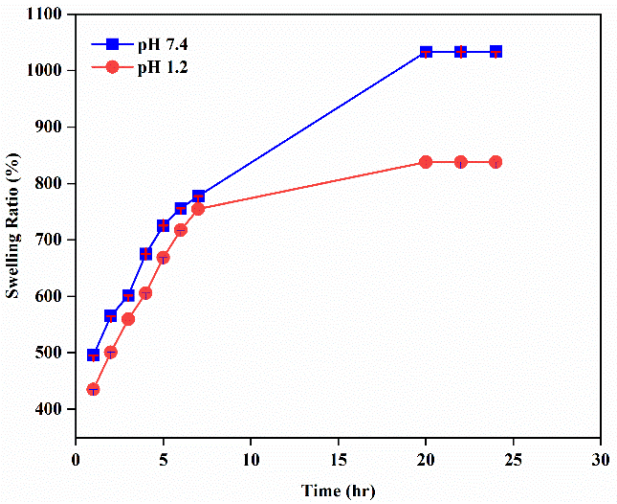


Fig 6: Swelling analysis of Metformin HCl-loaded CMTKG/PSA/XG hydrogel (S-5) in pH 7.4. and 1.2 buffer solution

5.2.2 Influence of cross-linker

As per Flory's network theory, cross-linking density is crucial in hydrogel swelling. As seen in Fig. 3, a slight alteration in the number of crosslinkers induces significant variations in the swelling percentage (c). The hydrogel swelling ratio declined when the MBA concentration was elevated from 20 to 40 mg. A greater cross-linker concentration minimizes free space inside the hydrogels, reducing swelling. As a consequence, the resulting stiff structure cannot expand, and swelling reduces. A jelly like sample was generated when the quantity of MBA was less than 20 mg because of the absence of a sufficient cross-linked network[35].

5.2.3 Influence of Initiator

By producing numerous active sites on the polymer chains, the initiator impacts the swelling ratio of hydrogels. While maintaining the cross-linker at 20mg, the concentration of the initiator, KPS, was changed, and the swelling results were examined. As the initiator amount was raised, the swelling initially grew and then decreased. High fluid absorbance was reported at 35mg ofthe initiator's concentration. The swelling was found to drop rapidly below 35 mg. This is an outcome of a high amount of unreacted soluble monomer, resulting in a loose hydrogel network, which minimizes swelling. Since the increased collisions between monomer free radicals caused by the reaction's rapid velocity, a drop in swelling were once more seen above 35mg of an initiator. This is an outcome of the solubility of oligomeric components, which did not promote swelling [35].

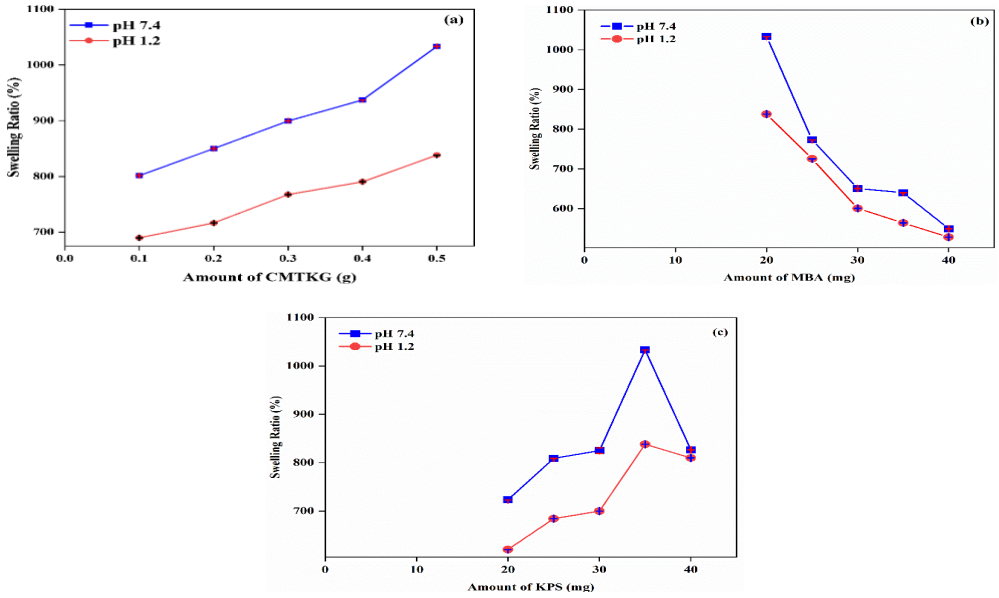


Fig 7: Influence of (a) CMTKG, (b) MBA, and (c) KPS on swelling ratio.

5.3 Loading of Drug and Encapsulation Efficiency

The drug loading and encapsulation efficiency (%) was calculated for the Metformin HCl- loaded CMTKG/PSA/XG hydrogel (S-5), which shows the highest swelling ratio. Loading of drug and encapsulation efficiency (%) was 16.23% and 62.96%, respectively.

5.4 In vitro Release Study of Metformin HCl

To determine the amount of the drug released from the synthesized hydrogels, in vitro release analysis was carried out for Metformin HCl- loaded CMTKG/PSA/XG hydrogel (S-5) in pH 1.2 and pH 7.4 buffer solutions for 24 hours at 37°C as given in Fig. 8.

A high percentage of the drug is released at pH 7.4 compared to pH 1.2 because of the larger concentration of deprotonated COO^- groups. This COO^- group of the XG and CMTKG exhibits electrostatic repulsion, which widens network gaps. Due to this, the swelling ratio increases, increasing the drug's loading and release. The maximum release of Metformin HCl was noticed to be 72.2% in 24 hours at pH 7.4. At pH 1.2, the carboxylate ion, however, becomes protonated and forms a hydrogen bond, which causes the hydrogel network to contract. As a result, the swelling ratio drops, which lowers the percentage of drug release and loading of the drug. 15.8% Metformin HCl release was noticed in 24 hours in pH 1.2. Thus, it may be concluded that the CMTKG/PSA/XG hydrogel works as an ideal system for the oral delivery of Metformin HCl in alkaline pH [28].

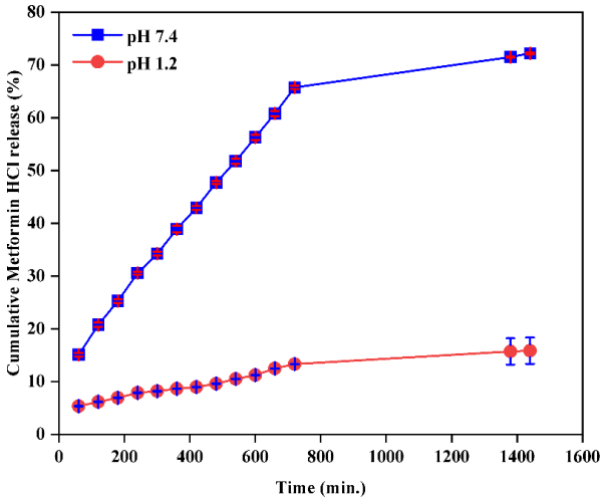


Fig.8 Drug release profile for Metformin HCl-loaded CMTKG/PSA/XG hydrogel in pH 7.4 and 1.4

5.5 Kinetic Modelling of Metformin HCl

The drug release mechanism for the Metformin HCl-loaded CMTKG/PSA/XG hydrogel (S-5)was studied using a variety of models, including the Zero-order, Hixson-Crowell, Korsmeyer-Peppas, Higuchi, and First-order model as can be seen in Table 2. Based on the "R^2" value's proximity to 1, an appropriate model was selected. The release exponent "n" value determines the type of diffusion. The R^2-value was greater for the Korsmeyer-Peppas model among all. The R^2-value for the Korsmeyer-Peppas model at pH 7.4 is determined to be 0.9941, and the n-value is 0.5389, indicating non-Fickian diffusion. While the R^2 value in pH 1.2 wasdetermined to be 0.9876, and the n value was 0.2830, indicating Fickian diffusion. Hence,the non- fickian diffusion mechanism was followed in pH 7.4 and the fickian mechanism in thecase of pH 1.2, as illustrated in Fig.9(a) and (b), respectively [29].

Model	Mechanism	Equation	pH 7.4		pH 1.2		Ref.
			n	R^2	n	R^2	
Zero Order	Rate is independent of drug concentration	$W_t = W_\infty + W_0 t$	-	0.8249	-	0.9296	[32]
Higuchi	Fickian diffusion followed	$F = W_t/W_\infty = k_H t^{1/2}$ k_H = kinetic constant	-	0.9358	-	0.9725	[19]
First Order	The amount of the drug and its release rate is directly proportional.	$\text{Log } W_t = \text{Log } W_\infty + \frac{kt}{2.303}$ k = rate constant	-	0.6963	-	0.8527	[33]
Hixson-Crowell	Erosion	$(W_0)^{1/3} - (W_t)^{1/3} = k_{HC} t$ k_{HC} = Hixson Crowell constant	-	0.7454	-	0.8829	[33]
Korsmeyer–Peppas	1. Fickian Diffusion ($n < 0.5$) 2. Non-Fickian Diffusion ($0.89 \geq n \geq 0.5$) 3. Case II transport ($n > 0.89$)	$F = W_t/W_\infty = kt^n$ k = kinetic constant n = diffusion exponent	0.5389	0.9941	0.2830	0.9876	[33]

Table 3. Kinetic modeling data of Metformin HCl using various models

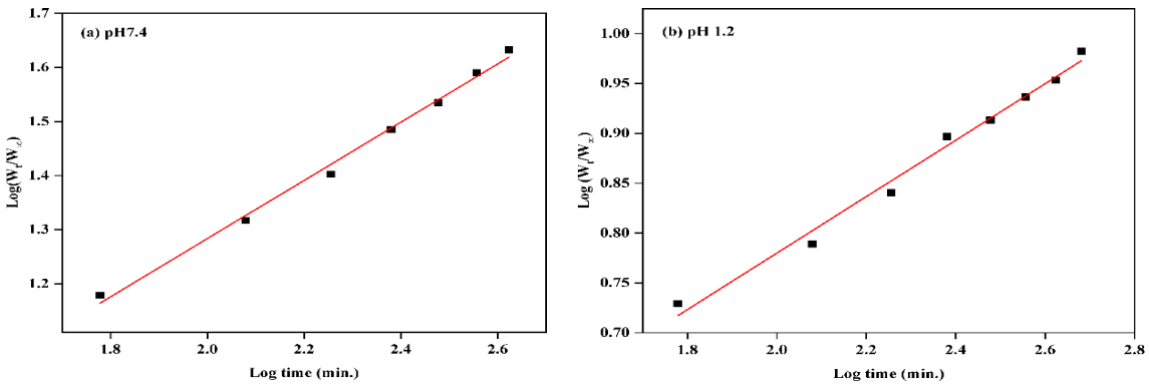


Fig.9(a) Release kinetic of Metformin HCl in accordance to the Korsmeyer–Peppas model in pH-7.4, **(b)** 1.2.

5.6 Conclusion

In this work, pH-sensitive Metformin HCl-loaded ~~C~~MTKG/PSA/XG hydrogel was fabricated using a free radical mechanism. The fabricated hydrogel was characterized using ATR-FTIR, PXRD, SEM, and TGA. In addition, the influence of the amount of CMTKG, MBA, and KPS on the swelling ratio of developed hydrogel was also studied. It was seen that as the amount of CMTKG rises, high swelling was observed at alkaline pH due to interionic repulsions between COO^- anions resulting in relaxation of the polymeric chains. With the increase in the amount of crosslinker MBA, the swelling ratio decreased as crosslinking minimizes the free volume of the polymeric network. Furthermore, when the initiator's amount was raised, the swelling initially increases and then decreased because of a high amount of unreacted monomer, resulting in a loose hydrogel network which minimizes swelling.

The swelling and *in vitro* drug release analysis were conducted at pH 1.2 and 7.4, and observed to be higher at pH 7.4. The in-vitro release kinetics of Metformin HCl concludes that the release data fits well in the Korsmeyer-Peppas model in both pH 1.2 and 7.4 and follows the Fickian mechanism of diffusion release at pH 1.2 indicating only diffusion whereas non-Fickian-diffusion is noticed at pH 7.4 which implies that both polymers chain relaxation as well as diffusion occurs. The developed hydrogels showed good metformin HCl release ability at pH 7.4 and temperature of 37^{o}C. Hence, the results showed that the CMTKG/PSA/XG hydrogel could be employed for pH-dependent and controlled drug release of Metformin HCl.

6. REFERNCES

(1) Majcher, M. J.; Hoare, T. *Applications of Hydrogels*; 2019. https://doi.org/10.1007/978-3-319-95990-0_17.

(2) Caló, E.; Khutoryanskiy, V. V. Biomedical Applications of Hydrogels: A Review of Patents and Commercial Products. *Eur. Polym. J.* **2015**, *65*, 252–267. https://doi.org/10.1016/j.eurpolymj.2014.11.024.

(3) Madduma-Bandarage, U. S. K.; Madihally, S. V. Synthetic Hydrogels: Synthesis, Novel Trends, and Applications. *J. Appl. Polym. Sci.* **2021**, *138* (19), 1–23. https://doi.org/10.1002/app.50376.

(4) Rizwan, M.; Rubina Gilani, S.; Iqbal Durani, A.; Naseem, S. Materials Diversity of Hydrogel: Synthesis, Polymerization Process and Soil Conditioning Properties in Agricultural Field. *J. Adv. Res.* **2021**, *33* (xxxx), 15–40. https://doi.org/10.1016/j.jare.2021.03.007.

(5) Ahmed, E. M. Hydrogel: Preparation, Characterization, and Applications: A Review. *J. Adv. Res.* **2015**, *6* (2), 105–121. https://doi.org/10.1016/j.jare.2013.07.006.

(6) Rizwan, M.; Yahya, R.; Hassan, A.; Yar, M.; Azzahari, A.; Selvanathan, V.; Sonsudin, F.; Abouloula, C. PH Sensitive Hydrogels in Drug Delivery: Brief History, Properties, Swelling, and Release Mechanism, Material Selection and Applications. *Polymers (Basel).* **2017**, *9* (12), 137. https://doi.org/10.3390/polym9040137.

(7) Sharpe, L. A.; Daily, A. M.; Horava, S. D.; Peppas, N. A. Therapeutic Applications of Hydrogels in Oral Drug Delivery. *Expert Opin. Drug Deliv.* **2014**, *11* (6), 901–915. https://doi.org/10.1517/17425247.2014.902047.

(8) Liu, L.; Yao, W.; Rao, Y.; Lu, X.; Gao, J. PH-Responsive Carriers for Oral Drug Delivery: Challenges and Opportunities of Current Platforms. *Drug Deliv.* **2017**, *24* (1), 569–581. https://doi.org/10.1080/10717544.2017.1279238.

(9) Singh, A. V. Biopolymers in Drug Delivery: A Review. *Pharmacologyonline* **2011**, *1*, 666–674.

(10) Katzbauer, B. Properties and Applications of Xanthan Gum. *Polym. Degrad. Stab.* **1998**, *59* (1–3),

81–84. https://doi.org/10.1016/S0141-3910(97)00180-8.

(11) Kumar, A.; Rao, K. M.; Han, S. S. Application of Xanthan Gum as Polysaccharide in Tissue Engineering: A Review. *Carbohydr. Polym.* **2018**, *180*, 128–144. https://doi.org/10.1016/j.carbpol.2017.10.009.

(12) Petri, D. F. S. Xanthan Gum: A Versatile Biopolymer for Biomedical and Technological Applications. *J. Appl. Polym. Sci.* **2015**, *132* (23), n/a-n/a. https://doi.org/10.1002/app.42035.

(13) Singhvi, G.; Hans, N.; Shiva, N.; Kumar Dubey, S. *Xanthan Gum in Drug Delivery Applications*; Elsevier Inc., 2019. https://doi.org/10.1016/B978-0-12-817055-7.00005-4.

(14) Malviya, R.; Sundram, S.; Fuloria, S.; Subramaniyan, V.; Sathasivam, K. V.; Azad, A. K.; Sekar, M.; Kumar, D. H.; Chakravarthi, S.; Porwal, O.; Meenakshi, D. U.; Fuloria, N. K. Evaluation and Characterization of Tamarind Gum Polysaccharide: The Biopolymer. *Polymers (Basel).* **2021**, *13* (18), 1–18. https://doi.org/10.3390/polym13183023.

(15) Khushbu; Warkar, S. G. Potential Applications and Various Aspects of Polyfunctional Macromolecule- Carboxymethyl Tamarind Kernel Gum. *Eur. Polym. J.* **2020**, *140* (September), 110042. https://doi.org/10.1016/j.eurpolymj.2020.110042.

(16) Goyal, P.; Kumar, V.; Sharma, P. Carboxymethylation of Tamarind Kernel Powder. *Carbohydr. Polym.* **2007**, *69* (2), 251–255. https://doi.org/10.1016/j.carbpol.2006.10.001.

(17) Khushbu; Warkar, S. G. Carboxymethyl Tamarind Kernel Gum Based Controlled Drug Delivery Excipients: A Review. *J. Eng. Res.* **2022**, *10*, 27–40. https://doi.org/10.36909/jer.ICAPIE.15061.

(18) Kaur, G.; Jain, S.; Tiwary, A. K. Chitosan-Carboxymethyl Tamarind Kernel Powder Interpolymer Complexation: Investigations for Colon Drug Delivery. *Sci. Pharm.* **2010**, *78* (1), 57–78. https://doi.org/10.3797/scipharm.0908-10.

(19) Sun, X.; Shi, J.; Zhang, Z.; Cao, S. Dual-Responsive Semi-Interpenetrating Network Beads Based on Calcium Alginate/Poly(N-Isopropylacrylamide)/Poly(Sodium Acrylate) for Sustained Drug Release. *J. Appl. Polym. Sci.* **2011**, *122* (2), 729–737. https://doi.org/10.1002/app.33872.

(20) Al-nasra, M. Optimizing the Use of Sodium Polyacrylate in Plain Concrete. *Int. J. Eng. Res. Appl.*

2013, *3* (3), 1058–1062.

(21) Ogawa, I.; Yamano, H.; Miyagawa, K. Rate of Swelling of Sodium Polyacrylate. *J. Appl. Polym. Sci.* **1993**, *47* (2), 217–222. https://doi.org/10.1002/app.1993.070470204.

(22) Manzur, T.; Iffat, S.; Noor, M. A. Efficiency of Sodium Polyacrylate to Improve Durability of Concrete under Adverse Curing Condition. *Adv. Mater. Sci. Eng.* **2015**, *2015*. https://doi.org/10.1155/2015/685785.

(23) Deshpande, A. D.; Harris-Hayes, M.; Schootman, M. Epidemiology of Diabetes and Diabetes-Related Complications. *Phys. Ther.* **2008**, *88* (11), 1254–1264. https://doi.org/10.2522/ptj.20080020.

(24) Cheng, A. Y. Y.; Fantus, I. G. Oral Antihyperglycemic Therapy for Type 2 Diabetes Mellitus. *C. Can. Med. Assoc. J.* **2005**, *172* (2), 213–226. https://doi.org/10.1503/cmaj.1031414.

(25) Barleany, D. R.; Ananta, C. V.; Maulina, F.; Rochmat, A.; Alwan, H.; Erizal. Controlled Release of Metformin Hydrogen Chloride from Stimuli-Responsive Hydrogel Based on Poly(N-Isopropylacrylamide)/Chitosan/Polyvinyl Alcohol Composite. *Int. J. Technol.* **2020**, *11* (3), 511–521. https://doi.org/10.14716/ijtech.v11i3.2330.

(26) Adepu, S.; Ramakrishna, S. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules*. September 29, 2021, p 5905. https://doi.org/10.3390/molecules26195905.

(27) Wen, H.; Jung, H.; Li, X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. *AAPS J.* **2015**, *17* (6), 1327–1340. https://doi.org/10.1208/s12248-015-9814-9.

(28) Wei, Q. B.; Fu, F.; Zhang, Y. Q.; Wang, Q.; Ren, Y. X. PH-Responsive CMC/PAM/PVP Semi-IPN Hydrogels for Theophylline Drug Release. *J. Polym. Res.* **2014**, *21* (6). https://doi.org/10.1007/s10965-014-0453-0.

(29) Khushbu; Warkar, S. G.; Thombare, N. Controlled Release and Release Kinetics Studies of Boron through the Functional Formulation of Carboxymethyl Tamarind Kernel Gum-Based Superabsorbent Hydrogel. *Polym. Bull.* **2022**, *79* (4), 2287–2303. https://doi.org/10.1007/s00289-021-03634-9.

(30) Suhail, M.; Khan, A.; Rosenholm, J. M.; Minhas, M. U.; Wu, P. C. Fabrication and Characterization of Diclofenac Sodium Loaded Hydrogels of Sodium Alginate as Sustained Release Carrier. *Gels* **2021**, *7* (1), 1–16. https://doi.org/10.3390/gels7010010.

(31) Tan, L. S.; Tan, H. L.; Deekonda, K.; Wong, Y. Y.; Muniyandy, S.; Hashim, K.; Pushpamalar, J. Fabrication of Radiation Cross-Linked Diclofenac Sodium Loaded Carboxymethyl Sago Pulp/Chitosan Hydrogel for Enteric and Sustained Drug Delivery. *Carbohydr. Polym. Technol. Appl.* **2021**, *2*, 100084. https://doi.org/10.1016/j.carpta.2021.100084.

(32) Niu, B.; Jia, J.; Wang, H.; Chen, S.; Cao, W.; Yan, J.; Gong, X.; Lian, X.; Li, W.; Fan, Y. Y. In Vitro and in Vivo Release of Diclofenac Sodium-Loaded Sodium Alginate/Carboxymethyl Chitosan-ZnO Hydrogel Beads. *Int. J. Biol. Macromol.* **2019**, *141*, 1191–1198. https://doi.org/10.1016/j.ijbiomac.2019.09.059.

(33) Jana, S.; Sharma, R.; Maiti, S.; Sen, K. K. Interpenetrating Hydrogels of O-Carboxymethyl Tamarind Gum and Alginate for Monitoring Delivery of Acyclovir. *Int. J. Biol. Macromol.* **2016**, *92*, 1034–1039. https://doi.org/10.1016/j.ijbiomac.2016.08.017.

(34) Varahala Setti, M. L.; Ratna, J. V. Preparation and Evaluation of Controlled Release Tablets of Carvedilol. *Asian J. Pharm.* **2009**, *3* (3), 252–256. https://doi.org/10.4103/0973-8398.56307.

(35) Khushbu; Warkar, S. G.; Kumar, A. Synthesis and Assessment of Carboxymethyl Tamarind Kernel Gum Based Novel Superabsorbent Hydrogels for Agricultural Applications. *Polymer (Guildf).* **2019**, *182*, 121823. https://doi.org/10.1016/j.polymer.2019.121823.

(36) Mali, K. K.; Dhawale, S. C.; Dias, R. J. Synthesis and Characterization of Hydrogel Films of Carboxymethyl Tamarind Gum Using Citric Acid. *Int. J. Biol. Macromol.* **2017**, *105*, 463–470. https://doi.org/10.1016/j.ijbiomac.2017.07.058.

(37) Jagdale, S. C.; Patil, S. A.; Kuchekar, B. S.; Chabukswar, A. R. Preparation and Characterization of Metformin Hydrochloride-Compritol 888 ATO Solid Dispersion. *J. Young Pharm.* **2011**, *3* (3), 197–204. https://doi.org/10.4103/0975-1483.83758.

(38) Malik, R.; Warkar, S. G.; Saxena, R. Carboxy-Methyl Tamarind Kernel Gum Based Bio-Hydrogel for Sustainable Agronomy. *Mater. Today Commun.* **2023**, *35* (October 2022), 105473. https://doi.org/10.1016/j.mtcomm.2023.105473.

(39) Roy, H.; Brahma, C.; Nandi, S.; Parida, K. Formulation and Design of Sustained Release Matrix Tablets of Metformin Hydrochloride: Influence of Hypromellose and Polyacrylate Polymers. *Int. J. Appl. Basic Med. Res.* **2013**, *3* (1), 55. https://doi.org/10.4103/2229-516x.112242.

(40) Shoukat, H.; Pervaiz, F.; Noreen, S.; Nawaz, M.; Qaiser, R.; Anwar, M. Fabrication and Evaluation Studies of Novel Polyvinylpyrrolidone and 2-Acrylamido-2-Methylpropane Sulphonic Acid-Based Crosslinked Matrices for Controlled Release of Acyclovir. *Polym. Bull.* **2020**, *77* (4), 1869–1891. https://doi.org/10.1007/s00289-019-02837-5.

(41) Goonoo, N.; Bhaw-Luximon, A.; Ujoodha, R.; Jhugroo, A.; Hulse, G. K.; Jhurry, D. Naltrexone: A Review of Existing Sustained Drug Delivery Systems and Emerging Nano-Based Systems. *J. Control. Release* **2014**, *183* (1), 154–166. https://doi.org/10.1016/j.jconrel.2014.03.046.

(42) Das, D.; Das, R.; Mandal, J.; Ghosh, A.; Pal, S. Dextrin Crosslinked with Poly(Lactic Acid): A Novel Hydrogel for Controlled Drug Release Application. *J. Appl. Polym. Sci.* **2014**, *131* (7), 1–12. https://doi.org/10.1002/app.40039.

7. List of conferences attended

1. Presented our research work at the International Conference on ***"Chemical and Allied Science and their Applications''*** *held* at **Delhi Technological University** on 20th January 2023.

2. Presented our research work and secured 1st position in Digital Poster Presentation at International Conference on "***Recent Trends in Chemical Sciences-2023***" held at **Miranda House, University of Delhi** on 14&15 February 2023.

3. Presented our research work and poster presentation at International Conference on ***"Recent Trends in Chemical Sciences and sustainable energy"*** held at the **National Institute of Technology (NIT), Delhi** on 24&25 January 2023.

4. Presented our research work at the International Conference on ***"Smart materials- Perspectives and Prospective (SMPP-2023)"***, organized by the **Department of Chemistry, University of Delhi** on March 29, 2023.

NITD/AS/RTCSSE/2023/131

Azadi Ka Amrit Mahotsav

1st International Conference on
"Recent Trends in Chemical Sciences & Sustainable Energy"
(RTCSSE-2023)

CERTIFICATE OF PARTICIPATION

This is to certify that Prof./Dr./Mr./Ms. ***Yash Saraswat, Tushar, Prof. S. G. Warkar*** of Delhi Technological University, Delhi, India presented a oral/**poster** paper titled ***Synthesis of Polysaccharide based Hydrogels for Drug Delivery*** in the 1st International Conference on "Recent Trends in Chemical Sciences & Sustainable Energy" RTCSSE- 2023 held at National Institute of Technology Delhi during 24th - 25th March, 2023.

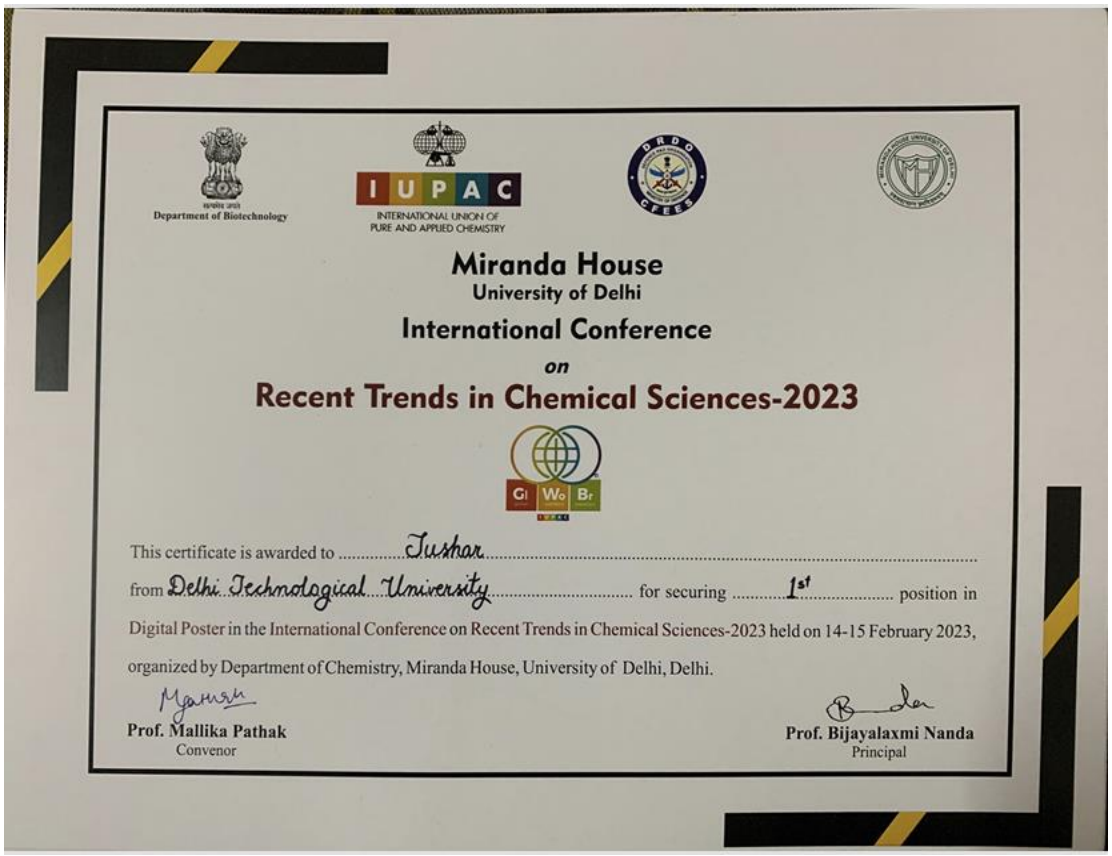
Organized by

Department of Applied Sciences
National Institute of Technology Delhi

Department of Chemistry
Swami Shraddhanand College, University of Delhi

Dr. Pratibha
Secretary, RTCSSE- 2023

Dr. Amit Pratap Singh
Convener, RTCSSE- 2023



Department of Biotechnology

IUPAC
INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

DRDO CFEES

Miranda House
University of Delhi

International Conference

on

Recent Trends in Chemical Sciences-2023

Gi Wo Br

This certificate is awarded to Tushar

from Delhi Technological University for securing 1st position in Digital Poster in the International Conference on Recent Trends in Chemical Sciences-2023 held on 14-15 February 2023, organized by Department of Chemistry, Miranda House, University of Delhi, Delhi.

Prof. Mallika Pathak
Convenor

Prof. Bijayalaxmi Nanda
Principal

Department of Biotechnology

IUPAC
INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

DRDO CFEES

Miranda House
University of Delhi

International Conference

on

Recent Trends in Chemical Sciences-2023

Gi Wo Br

This certificate is awarded to Yash

from Delhi Technological University for securing First position in Digital Poster in the International Conference on Recent Trends in Chemical Sciences-2023 held on 14-15 February 2023, organized by Department of Chemistry, Miranda House, University of Delhi, Delhi.

Prof. Mallika Pathak
Convenor

Prof. Bijayalaxmi Nanda
Principal