Impact of various monomers on release of losartan potassium from guar gum based polymeric network

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Abstract: Present study was carried out to analyze the impact of three different monomers on release of losartan potassium from graft polymeric network prepared through free radical polymerization. N, N-methylene bis acrylamide was used as crosslinker and potassium persulfate as initiator. Losartan potassium as used as model drug because, it has very small plasma half-life and wide range of applications as an effective and efficient ARB (Angiotensin II Receptor Blockers) causing lower incidence of side effects. Influence of three different monomers on swelling and in vitro drug release of the delivery system was evaluated at pH 1.2 and 7.4. The polymeric networks were characterized by Fourier transform infrared spectroscopy, Thermogravimetric analysis and Scanning electron microscopy. Polymeric network prepared with acrylic acid and methacrylic acid showed pH responsive behavior and while acrylamide based nexus exhibited pH independent style in swelling and drug release. However, among all the formulations, maximum swelling ratio (25.86) and optimal prolonged drug release (82.92%) was observed for GG-co-AA (M2) polymeric network at intestinal pH 7.4. The results indicated that GG-co-AA polymeric network could be an impending pH-sensitive drug delivery system for Losartan potassium. (M2) designated as formulation code with varying acrylic acid contents.

Keywords: Monomer, network, crosslinking, graft polymeric network, polymerization, biomaterials.

INTRODUCTION

Crosslinked 3-dimensional hydrogel captured a lot of attraction as superabsorbent in drug carrier and wound dressing. Superabsorbent properties can be altered via chemical alteration. These polymeric nexus are smart enough to respond the external stimuli like pH, temperature, ionic strength, electric field, presence of enzyme etc and often termed as “smart” or “intelligent” material. pH sensitivity is attributed to weakly acidic and basic pendent groups (Oliva et al., 2021). Water uptake was attributed to functional group ionization, pH and ionic strength of surrounding media. Such systems are also termed as “switch-on and -off systems” (Bustamante-Torres et al., 2021). They have found widespread applications in drug delivery, pharmaceutical, biomedical and tissue engineering. However, polymeric nexus also found its application in regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells and barrier materials to regulate biological adhesions (Capella-Monsoñís et al., 2019). Hydrogel contains natural and synthetic polymers which formulate dense crosslinked meshwork between -COOH, -OH, and –NH₂ of polymer and monomer by employing suitable epoxy crosslinker like N,N methylene bisacrylamide (Ijaz et al., 2022).

Guar gum (GG) is a natural nonionic polysaccharide extracted from the seeds of Cyanaposis tetragonolobus composed of d-mannose residues (Man) attached via (1→4)-β-glycosidic linkages to (1-6) galactose. Due to its biodegradable, biocompatible, bio-safety, nontoxic, low cost, high viscosity, water solubility, release retarding attributed it has been well studied as a carrier for colon-specific drug delivery (Mishra et al., 2018). It’s a fascinating functional attribute of controlling drug release in the colon, making it an attractive polymer for a pharmaceutical scientist (Li and Mooney, 2016).

Chemical crosslinking of GG via polyacrylamide (AAm), polyacrylic acid (AA) and methacrylic acid (MAA) results in polyelectrolyte hydrogels with molded mechanical attributed like pH sensitivity, higher swelling and controlled release characteristics. Literature survey supports the fact that vinyl monomer enhance the water absorbency and swelling degree of superabsorbent matrix. Furthermore, vinyl monomer imparts greater stability to nexus as compared to individual substrate (Ijaz et al., 2022, Mishra et al., 2018). Acrylamide have been used widely as grafting agent. It is vinyl monomer and act as polymeric add on which is attributed to its hydrophilic nature. It is polar, water soluble and least expensive vinyl monomer (Sumaira et al., 2021). Hydrogels are 3D cross linked polymeric structures, eligible to absorb a massive amount of water due to the existence of hydrophilic
groups such as -OH, -CONH-, -CONH₂, -COOH and -SO₃H. The water-absorbing capacity of hydrogels modifies its significant features like porosity, mechanical strength surface morphology, and biocompatibility. This property of hydrogel makes it resembling with that of living tissue (Mahinroosta et al., 2018). These hydrophilic groups are responsible for high absorbing capacity of water almost 90%. This property depends on nature of aqueous environment and polymer composition (Das and Pal, 2015).

Losartan potassium (LP) is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5h. Administration of LP in a controlled release dosage form with an extended release over 8 h, would be more desirable. The intentionally delaying the drug absorption for a specified time period (lag time) was controlled by polymeric network plug which will be taken at bed time with a programmed initiation of drug release in early morning (Saravi et al., 2021). Chemical structure of LP is shown in fig. 1.

In current research work, guar gum (GG)-based superabsorbent nexus were prepared by polymerizing AA, MAA and AAm on to GG in the presence of epoxy compound (MBA). Hydrogels can be prepared by a connection or series of connections linking two or more monomers by crosslinking, in that sense it can be called a Nexus. The impact of monomer on drug release was studied in order to elucidate the optimum reactant ratio for an efficient yield of the polymeric graft with significant water absorbency.

![Structure of Losartan Potassium](image1)

**Fig. 1:** Chemical Structure of Losartan Potassium

**MATERIALS AND METHODS**

**Materials**

Acrylic acid and methacrylic acid were purchased from Sigma Aldrich® (Germany), Guar gum (Uni-chem), Acrylamide (USA laboratories), Potassium chloride (Sigma-Aldrich®, Germany), Ethanol (Merck, Germany), Potassium dihydrogen phosphate (Merck, Germany), Sodium hydroxide, Potassium persulfate (KPS) and N,N-methylene bisacrylamide (MBA) were purchased from Fluka, Switzerland. Losartan potassium was received as a gift sample from Murfy Pharmaceuticals (Pvt.) Ltd., Pakistan.

**Formulation of guar gum based graft polymeric network**

Three series of Guar gum (GG) based polymeric network formulations were prepared using three different monomers (acrylic acid, acrylamide, methacrylic acid) by free radical polymerization method. A presumptive diagram of formulated graft is shown in fig. 2.

**Preparation of guar gum based polymeric networks**

Guar gum based polymeric networks were prepared by using varying concentrations of acrylic acid as monomer. Guar gum polymer solution was prepared by dissolving it in distilled water in a beaker with continuous stirring for at 60°C using hot plate. Initiator was added slowly in polymer solution with continuous stirring until homogenous blend was achieved. Solution of cross-linker and monomer was drop casted into the reaction mixture prepared in the first step with continuous stirring for 10 minutes at room temperature. Final weight of this solution of polymeric network preparation was made up to 100g with distilled water and stirred for 2 minutes. The prepared solution was transferred to test tube, and placed at 55°C for 1h, then 65°C for another hour and finally at 80°C for 8hours, in water bath. A transparent polymeric network was formed in the test tube which was then removed from water bath, cooled to room temperature and ejected from test tube by tapping. Then polymeric network was cut into discs of 0.5 cm thickness. These discs were washed with excess of ethanol: water solution (30:70 v/v%) (For extracting impurities and unreacted monomer from discs) until initial pH of mixture obtained. Polymeric network discs were dried in oven at 50°C until constant weight and then stored in desiccator for further studies (Azam et al., 2021). Synthesis of hydrogel is shown in fig. 3.

![Chemical synthesis of GG-co-AA](image2)

a) Chemical synthesis of GG-co-AA.
measurements were executed in 100°C temperature range was from 20°C to 900°C. The standard uncertainty in each measurement was ±0.5% (Patel et al., 2017).

**Differential Scanning Calorimetry (DSC)**

The differential scanning calorimetry (DSC) thermograms were recorded using SDT Q-600 (TA, New Castle, DE) thermal analyzer. Thermal properties of dried and ground samples of the drug Losartan potassium and GG-co-AA (unloaded and loaded) polymeric networks were analyzed by sealing them in crimped aluminum pans at 10°C/min heating rate at under dry N₂ gas (25 ml/min) over a temperature range from 20°C to 900°C. The TGA thermal analyzer. The thermal stability of the drug loaded polymeric network formulation (Shabir et al., 2017).

**Scanning electron microscopy (SEM) of Guar gum based polymeric networks**

Dried unloaded GG-co-AA, GG-co-AAm and GG-co-MAA polymeric network samples were scanned using an electron microscope to visualize their surface morphology. For better morphological characterization and observation of the pores, the swollen polymeric networks were first freeze-dried using a freeze dryer (Christ Alpha 1-2, Germany) at -52°C for 6 hrs. Cross-sections of freeze-dried polymeric network samples were cut to expose the internal structures. Samples were then fixed on an aluminum stub and coated with gold to a thickness of ~300 Å under an argon atmosphere using a gold sputter module in a high vacuum operator and examined with a scanning electron microscope SEM (JEOL JSM 5400, Tokyo, Japan) (Li and Mooney, 2016).

**Swelling ratio (q) determination**

Swelling ratio measurements were executed in 100mL buffer solutions of pH 1.2 and 7.4. Dried discs of each formulation were firstly weighed and then immersed in respective solutions, at scheduled time intervals, weighed after bloating with filter paper. After that, discs were again soaked in respective solutions (Bayat and Baghani, 2021). The swelling ratio of each formulation was determined using following equation:

\[ Q = \frac{M_t}{M_0} \]  

(Eq. 1)

\( M_i \) is the mass of swollen disc at time \( t \) and \( M_0 \) is the mass of desiccated disc (Kausar et al., 2021).

**Equilibrium swelling determination**

Percent equilibrium swelling (% ES) or equilibrium water content (EWC) of each polymeric network was calculated by following equation:

\[ \% \text{ES} = \frac{M_{eq} - M_0}{M_{eq}} \times 100 \]  

(Eq. 2)

\( M_{eq} \) is the mass of swelled polymeric network disc after equilibrium is reached and \( M_0 \) is the mass of desiccated disc (Kausar et al., 2021).
Impact of various monomers on release of losartan potassium from guar gum based polymeric network

Fig. 3: Synthesis of Hydrogel

Fig. 4: FTIR spectra of drug, substrate and Formulated Hydrogel
Fig. 5: TGA thermogram of Losartan potassium and GG-co-AA (drug loaded and unloaded) hydrogel

Fig. 6: DSC thermogram of Losartan potassium and GG-co-AA (drug loaded and unloaded) hydrogels

Fig. 7: Scanning electron micrograph (SEM) of lyophilized GG-co-AA hydrogel at magnifications of 160 X, 300 X and 600 X at 300 μ, 100 μ and 50 μ scale bar respectively
Impact of various monomers on release of losartan potassium from guar gum based polymeric network

Drug loading in Guar gum based polymeric networks
For the purpose of drug loading by Absorption method in formulated polymeric networks (GG-co-AA, GG-co-AAm, GG-co-MAA), solution of Losartan potassium (1% w/v) was prepared in buffer of pH 7.4. Weighed and dried discs of each formulation were separately soaked in drug solution (100 mL) for 48 hrs. Swollen polymeric network discs were then washed with ethanol solution (50 %) and then dried in oven for 3-4 days at 40°C (Bajpai et al., 2015).

Determination of drug loading
Amount of drug incorporated into the polymeric network discs was determined by the following equation:

\[ \text{Amount of drug loaded in disc (mg)} = W_D - W_d \]  

(Eq. 3)

\( W_D \) and \( W_d \) are the weights of desiccated polymeric network discs after and before soaking in the solution of drug respectively (Tulain et al., 2018).

Percentage drug release measurement
Drug release from cross-linked polymeric networks of GG-co-AA, GG-co-AAm and GG-co-MAA was analyzed by using the USP paddle apparatus (II) at 37°C±0.5°C and 50 rpm. Loaded discs were immersed in 900 mL of dissolution media, i.e. acidic buffer of pH 1.2 and phosphate buffer of pH 7.4 separately for 24 hrs. Each time 5 mL aliquot was taken out, filtered, diluted and analyzed on UV-Visible spectrophotometer and solution was replaced with 5 mL of fresh buffer. The absorbance of Losartan potassium released was determined at \( \lambda_{\text{max}} \) 208 nm in phosphate buffer and at \( \lambda_{\text{max}} \) 213 nm at 0.5, 1, 2, 4, 6, 8, 10, 14, 18, 22 and 24 hrs intervals. Percentage of Losartan potassium released at each time interval was determined by plotting standard calibration curve (Patel et al., 2019). All studies were carried out in triplicate.

Evaluation of release kinetics
In vitro analysis of drug release pattern and mechanism of drug release from prepared polymeric network

Fig. 8: Scanning electron micrograph (SEM) of lyophilized GG-co-AAm hydrogel at magnifications of 160 X, 300 X and 600 X at 200 μ, 100 μ and 50 μ scale bar respectively

Fig. 9: Scanning electron micrograph (SEM) of lyophilized GG-co-MAA hydrogel at magnifications of 160 X, 300 X and 600 X at 200μ, 100μ and 50μ scale bar respectively
formulations was conducted in buffers of pH 1.2 and pH 7.4 by applying various drug release kinetic models to in vitro release data using “DD solver software”. Data obtained was fitted in all kinetic models, i.e., zero-order, first-order, Korsmeyer-Peppas, Higuchi and Hixson-Crowell models. The method that best fits the release data was estimated by the correlation coefficient-(R²) (Tulain et al., 2018).

STATISTICAL ANALYSIS

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

RESULTS

Results are shown in table 2 and fig. 4-21

DISCUSSION

Instrumental Analysis

FTIR analysis

FTIR characterization of unloaded graft polymeric network of guar gum with acrylic acid

The FTIR spectra of guar gum, Acrylic acid and GG-co-AA polymeric network were shown in fig. 4. FTIR spectra of pure guar gum showed characteristic bands at 3493cm⁻¹ and 2909cm⁻¹ for -O-H stretching vibration along with -C-H stretching. The bands at 1524cm⁻¹ and 1152 cm⁻¹ corresponded to -C-H and -O-H bending vibrations [24]. While the main peaks of AA were of -OH stretch at 3308cm⁻¹, -CH stretch at 2903cm⁻¹ and -C = O stretch at 1759cm⁻¹ [11]. Whereas, a new band at 1599 cm⁻¹ was observed for guar gum grafted acrylic acid indicating formation of ester group and the presence of carboxylic anion as reported by Shruthi et al., in 2016 (Shruthi et al., 2016).

FTIR characterization of unloaded and loaded grafted polymer of guar gum with acrylic acid and drug polymer compatibility study of guar gum based polymeric networks

The FTIR spectra of GG-co-AA (unloaded), Losartan potassium and GG-co-AA (loaded) polymeric network were shown in fig. 4. The FTIR spectrum of Losartan potassium pure drug appeared at 3073cm⁻¹, 3582cm⁻¹, 1098cm⁻¹, 1649cm⁻¹, 1342cm⁻¹, 1582cm⁻¹ and 2940cm⁻¹ denoting stretching vibration of C-H, N-H, O-H, C=N, C-N, N=N and aromatic ring, respectively. The FTIR spectrum of GG-co-AA (loaded) polymeric network formulation showed approximately same peaks which suggested that there was no significant drug-polymer and drug-monomer interaction which indicated the stable nature of the drug in all GG-co-AA (loaded) formulations as reported by kumar et al., in 2015 (Kumar et al., 2015).

Fig. 10: Interaction of Swelling Ratio of Formulation M1-M8 in pH 1.2 and 7.4

Fig. 11: Interaction of Equilibrium Swelling Ratio of Formulation M1-M8 in pH 1.2 and 7.4

FTIR characterization of unloaded grafted polymer of guar gum with acrylamide

The FTIR spectra of guar gum, Acrylamide and GG-co-AAm polymeric network were shown in fig. 4. In the case of acrylamide, a broad absorption band at 3327cm⁻¹ was for the -NH stretching frequency of the NH₂ group. Two bands around 1427cm⁻¹ and 2810cm⁻¹ were for the C-N and C-H stretching vibrations. The acrylamide and guar gum grafting was established by a sharp peak at 1670cm⁻¹ which signified the carbonyl group of amide moiety of the grafted acrylamide chain and was not detected in guar gum spectrum. The -NH stretching of the graft polymeric network at 3186cm⁻¹ was coincided with a broad peak lying between 3858cm⁻¹ and 2940 cm⁻¹ of hydroxyl group of guar gum (Rai et al., 2020).

FTIR characterization of unloaded and loaded graft polymeric network of guar gum with acrylamide and drug polymer compatibility study of guar gum based polymeric networks

The FTIR spectra of GG-co-AAm (unloaded), Losartan potassium and GG-co-AAm (loaded) polymeric network were shown in fig. 4. The FTIR spectrum of pure drug...
was compared with spectrum of GG-co-AAm (loaded) polymeric network. Similar peaks i.e. 662 cm$^{-1}$, 1015 cm$^{-1}$, 1325 cm$^{-1}$, 1429 cm$^{-1}$, 1666 cm$^{-1}$, 2938 cm$^{-1}$ and 3181 cm$^{-1}$ was reported in optimized formulation. It was established that all characteristic peaks of losartan potassium were present in the GG-co-AAm (loaded) spectrum, demonstrating compatibility of the drug losartan potassium with the GG and monomer (Patil et al., 2014, Rodrigues Sousa et al., 2021)(Patil et al., 2014, Rodrigues Sousa et al., 2021)(Patil et al., 2014, Rodrigues Sousa et al., 2021).

FTIR spectrum of pure MAA showed an absorption band at 1649 cm$^{-1}$ due to the C=O stretching vibration of carboxylic acid. Two bands around 1333 cm$^{-1}$ and 1468 cm$^{-1}$ were due to bending vibration of CH$_3$ and O-H bending vibration of carboxylic acid, respectively. The absorption bands at 2718 cm$^{-1}$, 2637 cm$^{-1}$ and 2506 cm$^{-1}$ were due to -OH stretching vibration of carboxylic acid as described by Lee et al. (Lee et al., 2020).

**Fig. 12:** Swelling Ratio of Formulation M1-M8 in pH 1.2 and 7.4

**Fig. 13:** Equilibrium Swelling Ratio of Formulation M1-M8 in pH 1.2 and 7.4

**Fig. 14:** Drug Loading in Formulation M1-M8

**FTIR characterization of unloaded graft polymeric network of guar gum with methacrylic acid**
The FTIR spectra of guar gum, methacrylic acid and GG-co-MAA polymeric network were shown in fig. 4. The FTIR characterization of unloaded and loaded graft polymeric network of guar gum with methacrylic acid and drug polymer compatibility study of guar gum based polymeric networks

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The FTIR spectra of GG-co-MAA (unloaded), Losartan potassium and GG-co-MAA (loaded) polymeric network were shown in fig. 4. For GG-co-MAA (loaded), all peaks which have been obtained for the pure drug were available at approximately same wavelength i.e. for OH (3279 cm⁻¹), CH stretching aliphatic (2966 cm⁻¹), C=O (1721 cm⁻¹) and C-O-C Ether linkage (1275 cm⁻¹). The FTIR spectrum of the formulation showed that there was no significant evidence for interaction between drug and the polymer and other components of formulation in accordance with the results discussed by Bukhari et al., in 2015 (Bukhari et al., 2015).

Thermal analysis
Thermal Gravimetric Analysis (TGA)
The thermal transition behaviors of the Losartan potassium and GG-co-AA (drug loaded and unloaded) polymeric network were shown in fig. 5. From the fig. it can be observed that decomposition of loaded GG-co-AA followed two stages. Firstly, it was detected at 325-360°C with weight loss of 15% owing to dehydration. Secondly at 360 to 650°C with weight loss of 60%, then weight remained constant. The figure elucidated that formulated GG-co-AA (loaded) polymeric network was more thermostable than GG-co-AA (unloaded) polymeric network as GG-co-AA (unloaded) polymeric network showed % weight loss of 2.5%, 10%, 14% and 17% at 50°C, 100°C, 150°C and 200°C temperature respectively, while GG-co-AA (loaded) polymeric network showed relatively less % weight loss i.e. 2.2%, 5%, 10% and 13% at 50°C, 100°C, 150°C and 200°C respectively. At 650°C, loaded formulation showed only 72% weight loss while unloaded formulation was completely degraded i.e. 100%. These results demonstrated that thermal stability of loaded polymeric network formulation was greater than unloaded formulation which may be attributed to the fact that addition of losartan potassium enhanced the thermal stability of the polymeric network as reported by Shruthi et al., in 2016 (Shruthi et al., 2016).
Differential Scanning Calorimetry
Differential Scanning Calorimetry (DSC) thermogram of Losartan potassium and GG-co-AA (drug loaded and unloaded) polymeric network was shown in fig. 6. DSC thermogram elucidated that Losartan potassium remained stable up to 330 °C, GG-co-AA up to 425 °C and GG-co-AA (loaded) polymeric network up to 370 °C. LP showed exothermic transition peaks at temperatures of 335 °C and 475 °C, which was due to the melting and decomposition of losartan. GG-co-AA polymeric network exhibited low intensity exothermic transition peaks at temperatures of 430 °C and 555 °C while GG-co-AA (loaded) polymeric network exhibited sharp exothermic transition peaks at temperatures of 375 °C, 425 °C and 550 °C. These results exhibited that loading of drug in GG-co-AA polymeric network formulation improved its thermal stability. Similar results were described by Gomes et al., in 2020 (Gomes et al., 2020).

Scanning Electron Microscopy (SEM)
Fig. 7 presented SEM micrographs (surface morphology) of lyophilized GG-co-AA polymeric networks. These photomicrographs confirmed that synthesized polymeric network (GG-co-AA) had a porous structure. These interconnected pores could be suitable for controlling drug release by swelling and diffusion (Sadeghi, 2011). In fig. 8 SEM images of GG-co-AAm polymeric network have shown loose network structure, an uneven and coarse surface with fibrillar structure (Warkar and Gupta, 2015). In fig. 9 interlocked porous structural network of GG-co-MAA was detected in SEM micrograph. Increase in porous architecture and geometry aids in augmented water uptake followed by swelling and drug release (Rai et al., 2016).

Swelling analysis
Effect of acrylic acid on swelling behavior of Guar gum based polymeric networks
The swelling ratios and percent equilibrium swelling of GG-co-AA at pH 1.2 and 7.4 were illustrated in fig. 10 and 11, respectively. The swelling ratios of GG-co-AA polymeric networks at varying pH values relied upon the extent of polymer matrix relaxation and availability of hydrophilic ionizable groups e.g. COOH group of AA. AA has pKa of 4.5 and thus, tends to dissociate at a pH > 4.5 enhancing the ionization and osmotic pressure inside the polymeric networks. Therefore, at pH 7.4, the ionic concentration of carboxylate ions inside the polymeric network matrix increased promptly causing repulsion between the networks which consequently resulted in matrix relaxation and thus rapid increase in the swelling ratio. With an increase of AA content, the equilibrium swelling ratios of the GG-co-AA polymeric networks were also increased at pH 7.4 (Rashid et al., 2019). While at pH 1.2, polymeric network was in non-ionized state due to the hydrogen bonding interactions between the carboxylic hydrophilic groups of AA and hydroxyl groups of GG leading to decreased availability of free hydrophilic groups of polymer with increasing acrylic acid content that ultimately resulted in reduced swellability (Tulain et al., 2018). Xanthan gum (XG) grafted acrylic acid (AA) (Xg-co-AA) based nexus was formulated for targeted delivery of perindopril erbumine which depicted pH dependent swelling and shrinkage. Hydrogel shrinks at pH 1.2 and swell in pH 7.4 (Ijaz et al., 2018).

Effect of acrylamide monomer on swelling of Guar gum based polymeric networks
AAm is a versatile hydrophilic monomer. In acidic (pH 1.2) and physiological (pH 7.4) media, there was no major difference in swelling ratio of guar gum based acrylamide polymeric networks due to its non-ionic nature. Percentage swelling of the matrix was controlled by the intermolecular hydrogen-bonding effects between the hydrophilic hydroxyl groups of GG and hydrophobic amide groups of AAm, which decreases the hydrophilicity of the matrix by decreasing the availability of free hydrophilic hydroxyl groups for water absorption and thus swelling was also decreased with increasing AAm concentration (Mahmood et al., 2022). Sabbagh et al., 2018 formulated AAm/NaCMC/MgO hydrogels and depicted the fact that swelling is attributed to carboxylic (COOH) and hydrophilic amide (NH2) groups (Sabbagh et al., 2018)

Effect of methacrylic acid monomer on swelling behavior of Guar gum polymeric networks
MAA is an ionizable hydrophilic monomer. It depicted pH dependent swelling behavior (fig. 12 and 13). According to Bartil et al., these polymeric networks swelled in great degree at alkaline pH (7.4) than acidic pH owing to the availability of free carboxylate ions of MAA and resulting electrostatic repulsion between these charged ionized groups at alkaline pH (7.4) while at pH 1.2 polymeric network was in non-ionized state due to the hydrogen bonding interactions between the carboxylic hydrophilic groups of MAA and hydroxyl groups along the polymer network chains (Tulain et al., 2016).

Equilibrium Swelling Ratio
Equilibrium Swelling Ratio (ESR) shown in Fig. 12 and 13 which showed same pattern of equilibrium swelling as that of dynamic swelling ratio. Acrylic acid and methacrylic acid depicted pH dependent swelling in pH 7.4 as compared to pH 1.2.

Drug loading
In fig. 14 maximum drug loading (141 mg/g disc) was found in GG-co-AA polymeric networks (M2). Among MAA based systems, amount of drug incorporated was maximum in 35 % MAA polymeric network formulation (M8) having maximum concentration of monomer which showed maximum swelling. Drug loading in all other

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Table 1: Composition of guar gum based hydrogel formulations per 100 g

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Guar Gum (g)</th>
<th>MBA (% w/w of monomer)</th>
<th>KPS (% w/w of monomer)</th>
<th>Monomer Amount (g)</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>15</td>
<td>Acrylic acid</td>
</tr>
<tr>
<td>M2</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>20</td>
<td>Acrylic acid</td>
</tr>
<tr>
<td>M3</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>12.5</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>M4</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>15</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>M5</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>17.5</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>M6</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>25</td>
<td>Methacrylic acid</td>
</tr>
<tr>
<td>M7</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>30</td>
<td>Methacrylic acid</td>
</tr>
<tr>
<td>M8</td>
<td>1</td>
<td>0.35</td>
<td>0.3</td>
<td>35</td>
<td>Methacrylic acid</td>
</tr>
</tbody>
</table>

Table 2: Impact of various monomers on drug release of GG based polymeric network at pH 7.4

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero order model</th>
<th>First order model</th>
<th>Higuchi model</th>
<th>Korsmeyer-Peppas model</th>
<th>Hixson-Crowell model</th>
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<tr>
<td></td>
<td>R²</td>
<td>K₀</td>
<td>R²</td>
<td>Kᵣ</td>
<td>R²</td>
</tr>
<tr>
<td>M1</td>
<td>0.79</td>
<td>2.93</td>
<td>0.91</td>
<td>0.04</td>
<td>0.98</td>
</tr>
<tr>
<td>M2</td>
<td>0.88</td>
<td>3.24</td>
<td>0.96</td>
<td>0.05</td>
<td>0.98</td>
</tr>
<tr>
<td>M3</td>
<td>0.68</td>
<td>5.87</td>
<td>0.86</td>
<td>0.18</td>
<td>0.98</td>
</tr>
<tr>
<td>M4</td>
<td>0.48</td>
<td>6.58</td>
<td>0.86</td>
<td>0.32</td>
<td>0.95</td>
</tr>
<tr>
<td>M5</td>
<td>0.42</td>
<td>6.84</td>
<td>0.84</td>
<td>0.39</td>
<td>0.94</td>
</tr>
<tr>
<td>M6</td>
<td>0.66</td>
<td>2.89</td>
<td>0.84</td>
<td>0.04</td>
<td>0.99</td>
</tr>
<tr>
<td>M7</td>
<td>0.68</td>
<td>3.27</td>
<td>0.88</td>
<td>0.06</td>
<td>0.99</td>
</tr>
<tr>
<td>M8</td>
<td>0.73</td>
<td>3.48</td>
<td>0.92</td>
<td>0.06</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Where, Kᵣ, K₀, kᵣ, k₇C and k₇C are the release rate constants for first-order, zero-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell model, respectively.

formulations was also exactly in accordance with the swelling pattern of polymeric networks. This was due to the fact that higher hydrophilic ionic monomer content resulted in an increase in porosity of formulation, which resulted in assimilation of higher drug contents (Malik et al., 2021).

D. In vitro drug release

In vitro drug release from GG-co-AA polymer networks

In response to the external pH, swelling of the monomer played a major role in the drug release kinetics as shown in fig. 15-17. Swelling of the acrylic acid (AA) monomer was more in the alkaline pH due to the ionization of the ionizable groups and action of electro-repulsive forces. In alkaline medium (pH 7.4), hydration of the polymeric networks increased due to the electrostatic repulsive forces between the charged groups of the acrylic acid and lead to swelling but in acidic environment (pH 1.2), electrostatic forces vanished between uncharged carboxyl groups and caused the decrease in the hydration thus low swelling and in turn restricted the release of the Losartan potassium in the medium. Formulation M1 showed 71.71 % drug release at pH 7.4 while M2 showed 82.99 % release within 24 hrs, so formulation M2 was considered to have best drug release profile. In these polymeric network formulations, drug release pattern was directly related to AA content (Rashid et al., 2020). It was observed that all formulations followed Korsmeyer-Peppas kinetic model. All the formulations of GG-co-AA polymer network showed “n” values between 0.5 and 1 (Table 2) suggesting Losartan potassium release from GG-co-AA polymeric network followed non-Fickian transport (Malik et al., 2020).

In vitro drug release from GG-co-AAm polymer networks

As shown in fig. 16, among all the GG-co-AAm polymeric networks, the initial rate of release was higher at pH 1.2 but gradually decreased by augmenting the acrylamide monomer. Formulations M3 and M4 containing acrylamide monomer i.e. 12.5 and 15% respectively showed controlled release of drug up to 14 hrs followed by 100 % release of drug within 18 hrs while M5 that contained higher content of acrylamide i.e. 17.5 % showed controlled release of drug up to 18 hrs followed by 100 % release of drug within 22 hrs. But, M3 was considered as an ideal one for controlled drug release from GG-based polymeric network formulations as it depicted maximum drug release i.e. 99.96 % at pH 7.4 as compared to 98.97 % and 88.42 % of M4 and M5, respectively. Thus, as reported by Panda et al., 2014 by comparison of the R² values of all models, Korsmeyer-Peppas was considered to be most appropriate (table 2) and released drug by diffusion (Mahmood et al., 2022).
**In vitro drug release from GG-co-MAA polymeric networks**

The GG-co-MAA polymeric network depicted minimum swelling at pH 1.2 and maximum swelling at pH 7.4 (fig. 17) which indicated that the carboxyl groups of MAA were in the non-ionized state at pH 1.2 thus drug release was reduced owing to the hydrogen bonding. Conversely, the polymeric network progressively swelled due to ionization of carboxyl groups at pH 7.4 resulting in higher drug release. According to the results presented in fig. 17, the formulation M8 containing 35% of methacrylic acid monomer showed best drug release profile at pH 7.4 as compared to other formulations containing varying ratios of methacrylic acid monomer, as M8 showed 67.30% release while M6 and M7 showed 55.41% and 63.67% drug release respectively, within 24 hrs. The ‘n’ values (the exponent of release) (table 2) indicated that GG-co-MAA followed Fickian mechanism for release as reported by Li et al. (2008). Fig. 18 is cubic structure indicating influence of monomer on drug release. Whereas fig. 19-21 showed RSM graph, contour plot and interaction of all monomers on drug release (Laraib et al., 2022).

**CONCLUSION**

Chemically cross-linked Guar gum based graft polymeric networks were successfully formulated by the method of free radical polymerization of guar gum with acrylic acid, methacrylic acid and acrylamide separately using KPS as an initiator. The impact of three different monomers on the swelling and release behavior of formulated polymeric networks at the pH of 1.2 and 7.4 was studied. Losartan potassium was incorporated as model drug. Both nature and concentration of monomers were observed to have substantial impact on the rate of drug release from polymeric networks. However, among all the formulated polymeric networks, maximum swelling ratio and optimal prolonged drug release was observed for GG-co-AA (M2) polymeric networks but formulations prepared with acrylic and methacrylic acid give pH responsive release but with acrylamide formulations give pH independent swelling and drug release. Thus, a polymeric network preparation of Losartan potassium for optimum controlled drug release having an advantage of reduced frequency of dosing and thus improved patient compliance was effectively formulated in vitro. Though, in vivo studies can also be carried out to ascertain its appropriateness for clinical applications.

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