journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: XYZ

SUSTAINED RELEASE DELIVERY OF FAVIPIRAVIR THROUGH STATISTICALLY OPTIMIZED, CHEMICALLY CROSS-LINKED, PH-SENSITIVE

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Abstract :
In the current work, favipiravir (an antiviral drug) loaded pH-responsive polymeric hydrogels were developed by the free redical polymerization technique. Box-Behnken design method via Design Expert version 11 was employed to furnish the composition of all hydrogel formulations. Here, polyethylene glycol (PEG) has been utilized as a polymer, acrylic acid (AA) as a monomer, and potassium persulfate (KPS) and methylene-bisacrylamide (MBA) as initiator and cross-linker, respectively. All networks were evaluated for in-vitro drug release (%), sol-gel fraction (%), swelling studies (%), porosity (%), percentage entrapment efficiency, and chemical compatibilities. According to findings, the swelling was pH sensitive and was shown to be greatest at a pH of 6.8 (2500%). The optimum gel fraction offered was 97.8%. A sufficient porosity allows the hydrogel to load a substantial amount of favipiravir despite its hydrophobic behavior. Hydrogels exhibited maximum entrapment efficiency of favipiravir upto 98%. The in-vitro release studies of drug-formulated hydrogel revealed that the drug release from hydrogel was between 85 to 110% within 24 h. Drug-release kinetic results showed that the Korsmeyer Peppas model was followed by most of the developed formulations based on the R^2 value. In conclusion, the hydrogel-based technology proved to be an excellent option for creating the sustained-release dosage form of the antiviral drug favipiravir.

Keywords : iso-form , receptors , cell types

Introduction :

A sustained-release drug delivery system was intended to minimize toxicity, improve efficacy, and improve patient compliance by controlling the drug concentration at the target site [1]. Hydrogels are three dimensional pH responsive polymeric networks capable of imbibing larger volume of water in their interconnected voids. Upon exposure to a media of certain pH these systems undergo volume transitions due to chain relaxation as result of repulsion between prevalent functional groups in a system like –OH, $–SO_3H$, –COOH and $–NH_2$ etc [2].
Polyethylene glycol has various biomedical applications in drug delivery, wound dressing, and tissue engineering, because of its non-immunogenicity, biocompatibility, and resistance to the adsorption of proteins [3]. It is a synthetic polymer so its chemical and physical properties for example structure and chain length can easily be handled. It has non-cytotoxicity and powerful mechanical properties [4]. Due to the type, length, and ligand-binding properties of the hydrogel

network, PEG-based hydrogels provide substantial benefits that are required for the modulation of drug carriers [5]. Acrylic acid (AA) is used as a monomer. For the preparation of hydrogel containing AA, the free radical polymerization technique is mainly used in which acrylic acid reacted with free radicals and electrophilic agents. Acrylic acid is cross-linked to form a hydrogel having a higher absorption capacity. It is combined with other polymers to produce diverse forms of pH-responsive hydrogels [6].

Methylene bis-acrylamide (MBA) is a crosslinking agent because of its two extremely carbon-carbon double bonds. It has capacbility to react with a variety of functional groups including –COOH, $–NH_2$, and –OH while making a three-dimensional network [7]. Potassium sulfate (KPS) was used as an initiator (free radical generator) [8]. It is a white crystalline powder which can be simply dissolved in the water [9].

Favipiravir (FAV) is an antiviral drug which was permitted in 2014 in Japan against the influenza virus. It prevents viral replication by inhibiting RNA dependant RNA polymerase and is also used in COVID treatment [10]. The drug follows a very short half of 2 to 5.5 h. While the drug reaches to its maximum plasma concentration in 2 h followed by oral administration [11]. Current work aims to prepare a stable hydrogel system for oral delivery of Favipiravir using a free radical polymerization technique.

The objective of this study was to develop a dosage form, to enhance patient compliance as the drug appeared to have a very short half-life to avoid multiple dosing a sustained release formulation was developed. As hydrogels appeared to have better drug loading efficacy and drug release in a controlled manner to maintain the drug levels within the blood.

Material and method :

Favipiravir has been a gift from Pharmaceuticals. Polyethylene glycol 6000 (PEG), KPS, MBA as well as acrylic acid have been bought from Sigma Aldrich (United States). All other excipients used have been attained and distilled water was prepared in the research lab .

By the free radical polymerization process, hydrogels were prepared. The PEG 6000 required amount was dissolved in distilled water while using a magnetic stirrer . Stirring was continued until the formation of clear solution. In a separate beaker required quantity of monomer and initiator (KPS) was added and mixed it well by constant stirring. Then this monomer solution was transferred into PEG solution dropwise and mixed it well with continuous stirring. After that cross-linker (MBA) was added in it with constant mixing on a magnetic stirrer. Finally, the distilled water to make the final volume (25 ml). Sonicator was used to remove traces of any dissolved oxygen from the polymerization solution. The final solution has been shifted into the test tube and placed into the water bath at 60 °C for 3 h until the hydrogel was solidified. After that, the test tubes were taken out of the water bath and left to cool to room temperature. Then cut the hydrogel into the shape of a cylindrical discs. The discs were washed by using a mixture of water and ethanol (70:30) to eliminate the unreacted material. Washing was continued until the stable pH reading of washing solution at pH meter.

Results and discussion

PEG/AA hydrogel swelling in all trials was done at pH 7.2, 1.2, and 6.8. In all formulations, the initiator (KPS) amount was the same but the monomer, cross-linker, and oligomer amounts were different. On swelling the impact of changing concentration of the cross-linker, monomer, and PEG was studied.

The hydrogel exhibited more swelling at pH 6.8 as compared to pH 1.2 (Fig. 2). Hydrogel having AA showed a low degree of swelling at gastric pH, however when they passed into the GIT, the swelling increases as increases in pH. Acrylic acid contains a carboxyl group its structure and swelling of hydrogel was affected because of the presence of the ionized carboxylate ions at higher pH. PEG contains (–OH) groups, which make it highly appealing to water and impart it hydrophilic character. It was seen that at higher pH carboxylic groups get ionized due to which electrostatic

repulsive forces prevail between polymeric chains and results in expansion of the developed network [20].

Results exhibited that the swelling of hydrogel was increased as we increase the amount of monomer due to availability of excessive carboxylic acid groups. As presented by Sindhu et al., because of carboxylic group ionization at higher pH by increased monomer concentration, consider raised in swelling was observed [21]. Due to availability of higher ionized carboxylic groups upon incremental rise in AA contents, swelling was pronounced leading to higher uptake of swelling media. In acrylic acid addition, the amount of inorganic compound/hydrophilic polymer increased.

Gel fraction determination was done for checking the quantity of uncrosslinked ingredients which endured into the hydrogel. Gel fraction (%) of PEG-based hydrogels ranged from 88.1 to 99.3%. As we have seen that by raising the amount of cross-linker, polymer and monomer there was an enhancement in hydrogel gel fraction (%). The same result showed in the work of Barkat et al., raised in the percentage of gel fraction was seen because of the high concentration of polymer, cross-linker, and monomer. In higher concentrations of monomer, there was the presence of primary radicals [22].

Discussion

The FTIR spectrum was used to indicate the active constituent's functional groups constructed on IR spectrum peak values. FTIR spectra of favipiravir, PEG 6000, AA, MBA, KPS, drug-loaded and unloaded hydrogels disc of both polymers were conducted.

Pure favipiravir drug had shown various peaks in FTIR spectrum (Fig. 8A). At 3276 cm^{-1} one peak was observed of –OH stretching. At 1716 cm^{-1} the toughest peak was observed linked to the C=O stretching. At 1643 cm^{-1} peaks were observed C=N stretching. At 1210 cm^{-1} peaks were observed are corresponded to C–F stretching [32]. In this spectrum of PEG 6000 highest peaks were observed of C–H stretching at 2887 cm^{-1} (Fig. 8B). C–H bending peak has been detected at 1464 cm^{-1}. Band detected at 1094 cm^{-1} and 1109 cm^{-1} are attributed towards stretching of C–O–H and C–O–C [33].

In the Acrylic acid spectrum (Fig. 8C) at 2985 cm^{-1} the peak was observed of the –OH bond. At 1755 cm^{-1} the band was observed linked to the -the COOH group. The C=C and C=O stretching peaks were observed at 1635 cm^{-1} and 1697 cm^{-1} [34]. In the KPS spectrum at 1385 cm^{-1} one major peak was observed corresponding to S=O stretching [35]. In the MBA spectrum at 3305 cm^{-1} a noticeable peak was observed that revealed the N–H stretching while at 1560 cm^{-1} was seen that linked to C=O stretching vibrations as well as at 1535 cm^{-1} demonstrated N–H distortion. C–N stretching vibrations are displayed by the peak at 1301 cm^{-1}. At 965 cm^{-1} peaks were observed linked to N–C bond stretching vibrations and at 955 cm^{-1} peak exhibited C–Cα stretching.

These same peaks could be seen in the hydrogel disc that was drug loaded, indicating that the drug was well-matched with other elements. Disappearance of peaks, strengthening peak intensities, shifting of peaks and emergence of new peaks confirmed formation of a new network . There was no drug-component conflict with the hydrogel's other elements.

Conclusion

Research goal was successfully attained because favipiravir hydrogels with better drug loading capacity and the capability to deliver the drug continuously for 24 h have been created and evaluated. The use of statistical technique appeared to be beneficial because it not merely aided in evaluation and design of hydrogel formulation nonetheless also in its optimization. Experimental work has been determined to be repeatable because results of optimized formulation have been similar to those that the design expert had predicted for optimal formulation. Thus, it could be established that drug delivery system of hydrogel has been efficient at the loading the higher drug dose as well as for the loaded APIs sustained release In addition, the design expert would be a helpful tool for time as well as money savings by decreasing the need for pointless trials for formulation optimization.

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