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Research Article

Fabrication and *In vitro* Characterization of Carrageenan-Based Hydrogel for Drug Delivery Application

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ABSTRACT

Controlled drug delivery system is formulated for drug delivery at predetermined rate. Disruption and any type of failure in this system may be toxic and life threatening for patients. The aim of present study was to develop controlled drug delivery system by using anti-hyperglycemic drug Acarbose. Acarbose release in intestine where it produces anti-hyperglycaemic effect by delaying the absorption of glucose rather than conventional dosage forms. The main objective of present study was to fabricate cross-linked polymeric system of Genugel Gum/Polyvinyl Pyrollidone co-poly acrylic acid hydrogels by free radical polymerization method and *in vitro* characterization for controlled delivery. Hydrogels were fabricated by free radical polymerization technique. Hydrogels were fabricated by using Genugel gum (GG) and polyvinyl pyrollidone (PVP) as a polymer, acrylic acid (AA) as a monomer and Methylene Bisacrylamide (MBA) as across linker. To initiate the free radical polymerization ammonium peroxodisulphate/ sodium hydrogen sulphite are used. Genugel gum and PVP based hydrogels were prepared with different ratios of cross linker and monomer. For structural analysis and characterization of fabricated polymeric system FTIR, TGA, SEM and DSC were performed. PH responsive behavior was investigated by *in vitro* release of drug and swelling study at both basic pH (7.4) & acidic pH (1.2). TGA and DSC confirm that fabricated hydrogels are thermodynamically stable. Interactions between monomer and polymer were revealed by FTIR analysis. By increasing concentrations of polymers, monomer and cross linker gel fraction was enhanced. Swelling studies showed that swelling behaviour was more at basic pH 7.4 as compare to pH 1.2 (acidic) which confirms that hydrogels give response to pH. GG/PVP co-poly acrylic acid-based hydrogel found to be potential candidate for controlled delivery of Acarbose for supportive treatment of diabetes.

Keywords: Hydogel; Biosensors; Polymer; Genugel gum

INTRODUCTION

Hydrogel is a water-swollen and cross-linked polymeric network, prepared by reaction of monomer/polymer/cross-linker units. It has ability to swell and retain a large amount of water in its three-dimensional network. Three-dimensional structure of hydrogel consists of polymers chain with a hydrophilic functional group that interacts with biological fluid and giving rubbery or soft nature like living tissue. Hydrophilic functional groups give swelling characteristics to hydrogel which are insoluble in water due to covalent bonds. In current days, hydrogels have great importance as controlled drug delivery applications because of their desired characteristics. In conventional drug delivery, there are a lot of problems with plasma concentration maintenance to attain a therapeutic window. This problem is overcome by a novel drug delivery system (NDDS) like hydrogel. Applications of hydrogel are increasing day by day in the biomedical field i.e., biosensor, ophthalmological devices. For NDDS hydrogel properties like capacity of drug loading, biodegradability, safety and drug release should be optimized. Hydrogels are classified on basis of drug delivery as time-controlled and stimuli- responsive. A pH-sensitive hydrogel is formed by grafting acidic or basic functional groups on the backbone of polymer. In response to external stimuli (pH), ionization occurs in these functional groups by protonation and deprotonation. Due to anion-anion repulsive forces swelling and hydrophilic nature is increased [1]. Different types of polymers are used for hydrogel formation which may be natural or synthetic. The cross-linking structure is formed by a natural polymer which should be biocompatible and biodegradable. These natural polymers give an immune response but with weak mechanical strength, while synthetic polymers have good mechanical strength, water more uptake properties and give definite shape. The Objective of Current Research is as follows combination of natural and synthetic polymer is used for controlled drug delivery. To calculate

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the effect of different concentrations of monomer and polymer as a function of pH and time on swelling index. To study the effects of Genugel Gum and PVP on drug release behaviour and check the controlled drug delivery of acarbose.

MATERIALS AND METHODS

Free radical polymerization method was used to fabricate Genugel gum and Polyvinyl pyrollidone based hydrogels. Total twelve formulations were fabricated by altered ratio of Acrylic acid (AA), Genugel Gum (polymer), polyvinyl pyrollidone (polymer), and Methylene bisacrylamide (cross-linking agent).

Preparation of genugel gum/PVP co acrylic acid based hydrogel

The required amount of Genugel Gum and Polyvinyl pyrollidone is accurately weighted and dissolved in a specific quantity of water, stirred continuously by magnetic stirrer at 25°C for 1 hour. Acrylic Acid was stirred gently until it dissolved [2]. Accurately weighed quantity of polyvinyl pyrollidone (synthetic polymer) was added in a small quantity of purified water and stirred it for one hour by magnetic stirrer to obtain clear, transparent and viscous solution. In another flask, solution of accurately weighed ammonium peroxodisulphate sulphate and co-initiator sodium hydrogen sulphite and sufficient quantity of distilled water was prepared. Accurately weighed amount of Acrylic acid (monomer) was then added to already prepared initiator and co-initiator solution. After the preparation of all solutions, polyvinyl pyrollidone (PVP) solution was added drop wise into Genugel gum (GG) solution and stirred it for half an hour using a magnetic stirrer. Solution of Monomer poured drop wise into polymer solution (Genugel gum/PVP) with constant stirring for 30-40 minutes. Then final volume was made (100 ml) by adding sufficient amount of purified water and stirred it for few minutes. Finally, methylene bisacrylamide (MBA) was carefully added to above mixture and stirred it for 3-4 minutes. This milky solution was filled in test tube and labelled and covered it. Slowly raised the temperature of water bath at 60°C and maintained for overnight. Removed the test tube from water bath and cooled it to room temperature. By breaking the test tubes fabricated hydrogel were removed. Using the surgical blades cylindrical hydrogels were cut into disc of size 8 mm in thickness [3]. These discs were placed in vacuum oven at 40°C for a week to dry up.

Characterization

Following specifications were characterized for analysis and comparison of fabricated hydrogel with monomer, polymer and cross linker contents:

Physical appearance

Hydrogel dried discs were assessed physically. Physical stability of formulation are determined by physical strength, appearance, fragile nature, abrasiveness and stickiness.

Structural analysis

To analyse the structural characteristics following test were performed:

Fourier Transforms Infrared Spectroscopy (FTIR): FTIR is used to determine the chemical structure of molecules. This technique determined the absorption bands and also helped to characterize the existence of different functional groups in prepared hydrogel. In this technique, fabricated hydrogels as well as pure materials were assayed separately to develop an effective formulation [4]. This technique enables for assaying interaction between aqueous phases and hydrogels. For spectrum recording samples were analysed in the range of 4000 to 650 cm^{-1} by ATR-FTIR spectroscopy.

Scanning Electron Microscopy (SEM): Surface morphology of prepared hydrogel is determined by Scanning Electron Microscopy. Samples were cut down in appropriate size and fixed them on a metal plate; double sided adhesive tapes were used for this purpose [5]. Samples were examined by scanning electron microscope at 250x and 500x magnification powers.

Thermogravimetric analysis: To evaluate thermal properties of prepared hydrogels, thermogravimetric analysis was performed. Samples were grounded and allowed to pass through sieve of mesh no 40. Placed 1-3 mg sample on platinum 100 µl pan, adjusted its heat from 25-600°C at heating rate 20°C /min under stream of nitrogen gas. Degradation of samples is measured by loss in sample.

Differential scanning calorimetry: The stability of ingredients in fabricated hydrogels is measured by this technique. Samples were heated in the ranges 24-600°C. Heating rate was adjusted at 20°C/min. Degradation of samples were measured by loss in weight [6].

Drug loading studies: Acarbose was taken as a model drug. By using Phosphate Buffer Solution, 1% w/v drug solution was prepared. Hydrogel discs (Dried) were dipped in drug solution at pH 7.4. Hydrogel discs were remained dipped for 72 hours, for proper loading of drug by diffusion process. After 72 hours discs were removed, washed by deionized water. Filter paper is used to remove excess liquid. Finally, these drug loaded discs were kept in oven at 40°C until weight become constant.

Drug Entrapment Efficiency (DEE): Extraction method was used to measure the drug entrapment efficiency. Hydrogel discs were immersed in a 25 ml of phosphate buffer solution for extraction of drug from formulation. Repeated the extraction process until no drug remained [7]. By using UV Spectrophotometer, calibration curve of acarbose is obtained in buffer solution of phosphate at pH 7.4 for the estimation of drug contents at λ of 266 nm. Drug entrapment efficiency is calculated by using following formula:

Percent Drug Entrapment = Drug loading /Theoretical drug loading ×100

Drug release studies: For evaluating *in vitro* release profile UV/visible spectrophotometer and USP dissolution apparatus was used. Drug release study were analysed at acidic pH (1.2) and basic pH (7.4). Drug loaded disc of every formulation dipped in 900 ml dissolution medium. The pH of Dissolution medium was maintained at 7.4 and 1.2 and temperature is maintained at 37°C. The 5ml samples were drained from every vessel of dissolution apparatus after predetermined rate and were replaced with fresh one, by using pipette [8].

Release kinetic study of acarbose: By applying kinetic modelling on results of dissolution apparatus, release mechanism of Acarbose from developed hydrogels was evaluated. Four kinetic models (Zero Order, First Order, Korsmeyer-Peppas and Higuchi) were applied.

UV analysis of acarbose: For UV analysis of model drug, both

basic and acidic buffer solution were used. To prepare the stock solution of drug phosphate buffer solution of pH 7.4 was used. USP guidelines were followed to prepare a phosphate buffer solution. To prepare stock solution in a concentration of 1000 µg/ml (1 mg/1 ml), drug acarbose was dissolved in buffer solution pH adjusted at 7.4. Prepare serial dilutions from this stock solution [9]. The λ max for Acarbose is 266 nm. Take absorbance of each serial dilution and standard curve was plotted against concentration.

Swelling studies: Fabricated hydrogel swelling behavior is evaluated by swelling studies. For this purpose, swelling behavior of fabricated hydrogel observed in buffer solution at 1.2 and 7.4 pH.

RESULTS AND DISCUSSION

Physical appearance

By using different concentrations of Polyvinyl Pyrollidone, Genugel Gum and Acrylic acid, different formulations of hydrogel were formed by free radical polymerization method. Fabricated formulations were compact and stable. Fabricated hydrogels were rubbery in nature. It was detected that fabricated hydrogel with high concentrations of Genugel gum and polyvinyl pyrollidone were milkier in appearance while formulations with fewer concentrations of polymer were slightly less milky. At high concentrations of cross-linker hydrogels were hard, less sticky and more abrasive while having low concentrations of cross-linker were less sticky in nature. Fabricated hydrogels with high concentrations of Acrylic acid were slightly transparent in appearance while others were milky in appearance. All the fabricated hydrogel displayed proper gelling with appropriate mechanical strengths and have a stable shape and structure [10].

Structural analysis

FTIR spectroscopy: At wavenumber 2896.93 cm^{-1}, polyvinyl pyrrolidone showed peak because of C-H stretching. Another peak was observed at 1310 cm^{-1} because of amide band III (C-N) stretching. Peak observed at 1632.71 cm^{-1} indicates the C=O (carbonyl stretching). Another study also reported the same peaks at 1290 cm^{-1} due to peptide bond stretching, because of C=O stretching, peak observed at 1660 cm-[2]. Genugel gum spectrum showed peaks at 2915.30 cm^{-1} because of C-H bond stretching. A strong peak appeared at 1634.30 cm^{-1} was due to C=O group stretching. Due to C-C and C-O stretching sharp peak appeared at 1020.40. Sharp peak appeared at 1020.38 cm^{-1} due to C-O and C-C stretching. At 2977 cm^{-1} broader peak of acrylic acid observed due to C-H stretching. Due to stretching vibration in C-C, a sharp peak appeared at 1295 cm^{-1}. A strong peak also appeared at 1698 cm^{-1} indicates C=O stretching. At 1243.91 cm^{-1} and 1718.02 cm^{-1} peaks observed due to imide and C=O bond respectively. The intensity of PVP/GG and Acrylic acid peaks were different in an unloaded hydrogel. Stretching of C-H band shifted from 2915.28 to 2917.07. Stretching of C=O and OH bending shifted from 1634.30 to 1704.8 cm^{-1} carboxyl group stretching and C-H bending shifted from 1540 to 1537 cm C-C stretching and OH bending shift from 1020.23 to 1156.52 cm^{-1}. CN bond shifted 1310 cm^{-1} to 1413.99 cm^{-1}. Stretching vibrations in C-C at 1295 cm^{-1} shifted to 1156.51 cm^{-1}. A spectrum of Acarbose loaded hydrogel, give characteristics peak of acarbose which confirm successful loading of the drug. Confirmation of drug stability is also observed in the prepared hydrogel [11].

Thermogravimetric analysis: TGA is performed to analyse the thermal stability of hydrogel. TGA analysis of pure Genugel gum, PVP and GG/PVP co-polyacrylic acid based hydrogels were performed to analyze thermal stability. TGA thermogram of pure GG showed heat stability and showed decomposition at 251°C to 330°C only 41.6% weight loss occured [12]. At 400°C to 485°C, PVP starts decomposing with 38% weight loss occurs. While TGA analysis fabricated hydrogel showed that thermal stability of fabricated hydrogel was enhanced when compared to its individual components. It was completely degraded at 540°C.

Differential scanning calorimetry: Differential scanning Calorimetry is used to analyse Polyvinyl Pyrollidone, Genugel Gum and fabricated hydrogel. DSC of pure Genugel Gum gives 1st endothermic and exothermic peak at 100°C and 310°C respectively. Polyvinyl Pyrollidone gives 1st endothermic peak at 100°C because of glass transition temperature. This temperature indicates that bounded water is removed. Due to solid-solid transition minor peak appeared at 210°C that exhibits due to nonspecific nature. A deep endothermic peak was observed at 390°C that showed its heat stability.

By analysis of fabricated hydrogel endothermic peak observed at 310°C due to loss of water from hydrogel of GG/PVP co-poly acrylic acid hydrogel while exothermic peak appears at 450°C because of strong fabricated polymeric network. DSC thermogram cleared that DSC pattern of the fabricated cross-linked networks showed different thermal stability pattern from pure Genugel gum and PVP. Thermal stability of formulation increases due to cross-linking between Genugel Gum and PVP which makes them fit for the delivery of different drug molecules [13].

Scanning electron microscopy: SEM is used to analyze the surface morphology of fabricated hydrogel. The result indicates the rough and irregular shape of hydrogel. The irregular dense structure of hydrogel is due to attractive forces that exist between monomer and polymer which showed better compatibility. At different magnification powers, GG/PVP co-polyacrylic acid based hydrogel showed microporous structure. The porous structure of hydrogel represents the penetration of water and entrapment of drugs. The penetration of water molecules into porous structure enhanced the swelling behaviour of hydrogel that leads to better drug release.

Swelling studies: Drug release characteristics are greatly influenced by the swelling behaviour of hydrogels so its study is necessary. The permeability and water carrying capacity of hydrogel represent its swelling behaviour. PVP/Genugel co-acrylic acid based hydrogels were studied the swelling behaviour at pH 1.2 and pH 7.4, influence of different concentrations of polymer, monomer and cross-linker. Prepared hydrogel showed more swelling at pH 7.4 as compared to pH 1.2.

Effect of media pH on swelling behaviour: GG/PVP co acrylic acid based formulations were studied for pH dependent swelling before loading of drug with buffer solution of phosphate at pH 7.4 and 1.2. The Fabricated hydrogel showed pH responsive swelling behaviour. Swelling studies were performed at both basic and acidic media to examine the effect of media pH on polymer, monomer and cross-linker. More swelling showed at basic pH due to deprotonation as compared to acidic pH due to protonation of sulphonic group. Ionisable groups present in polymeric network are responsible for swelling behaviour. Ionisable group and swelling behaviour of hydrogel showed a direct relation [14].

Effect of genugel gum on swelling behaviour: GG/PVP co-acrylic acid based hydrogels were observed at different concentration of Genugel Gum. It was observed that as the concentration of Genugel gum increased, swelling behaviour of fabricated hydrogels decreases.

Diffusion of water molecule in Interpenetrating Network of hydrogel decreased as the concentration of Genugel Gum increases. Hydrogen bonds present between carboxyl group are responsible for decreased swelling at 1.2 pH while at 7.4 pH carboxyl group under protonation which results in increase in the repulsive forces in the fabricated polymeric network as a result swelling increases. Ionisable functional groups present in the fabricated hydrogels are responsible for pH responsive behaviour of hydrogels.

Effect of polyvinyl pyrollidone on swelling behaviour: As the PVP concentration increased swelling index of fabricated hydrogel is decreased. As the PVP concentration increased, number of sulphonic acid group decreases. Due to decreased in the sulphonic acid group, repulsive force between molecules also decreased which result less number of free space in hydrogel. Free space present in the cross-linked network absorbed water which is responsible for swelling of PVP based hydrogels.

Effect of acrylic acid on swelling behavior: Acrylic acid is used as a monomer in these hydrogel. Formulations were fabricated by taking different monomer concentrations. It was observed that as the concentration of monomer is increased swelling behavior increased but upto a specific limit. A stage reached when more concentration of acrylic acid increase result in decrease in swelling behavior, As a result mechanical strength decreases resulting in collapsing of fabricated hydrogel discs. Comparison shows that hydrogel discs with increased concentration of acrylic acid have dense structure which cause difficulty in entry of water molecule and swelling decreased than those fabricated hydrogels with less concentrations of monomer [15].

Effect of MBA on swelling behavior: Fabricated hydrogel were studied at different concentrations of cross-linker. It was observed that there is inverse relation between swelling ratio and MBA concentration. As the Methylene Bisacrylamide concentration increased, swelling ratio decreases.

As the concentration of cross-linker increased, entanglement between polymer and monomer increases, result polymer relaxation decreased. Acidic nature of polymer decreased by increasing polymer cross-linking which decrease swelling behavior. Another study reports that water diffusion ability decreased as the MBA concentration increases.

***In-vitro* drug release behavior of PVP-co-poly GG/PVP co- poly acrylic acid hydrogel formulations:** Drug release percentage from PVP/GG co-polyacrylic acid by different concentrations of PVP, GG, AA and MBA at acidic and basic pH. The release of the drug was low at pH 1.2 and high at pH 7.4. These fabricated formulations not allowed quick intake of water and thus there are limited chances for sudden leaching of drug. Factors which effect drug release rate are environmental condition i.e., pH and swelling behavior and network composition.

Effect of pH media on drug release: All prepared hydrogel showed pH response, drug release percentage was low at 1.2 pH and high at 7.4 pH. On acidic pH swelling of GG/PVP co-polyacrylic acid based hydrogel is less because carboxyl groups undergo protonation in high proportion thus decreases electrostatic repulsion between carboxyl group resulting in stronger hydrogen bonding results in a minimum release of drug and less swelling.

At pH 7.4 electrostatic repulsion increases because of –COO- group resulting in increases in swelling behavior, more expansion of polymeric network and more drug release [16].

Effect of genugel gum concentration on drug release: Drug release of prepared hydrogel was studied at different concentration of Genugel Gum. Result reveals that as the as Genugel Gum concentration increased, swelling behavior of hydrogel decreases, resulting decrease in release rate of drug. Hydrogels with less concentration of Genugel Gum showed more swelling behavior and release rate of Acarbose also increased as compared to those containing high concentrations of Genugel gum.

Genugel based hydrogel swell by absorption of water which is placed in free volume of cross-linked network. Water uptake is more when less interconnecting bond, swelling is more. An increased in polymer concentration free spaces are reduced, result decreased in swelling and drug release (Talukdar and Kinget, 1995).

Effect of poly-vinyl pyrollidone on drug release: By increasing polyvinyl pyrollidone concentration in hydrogel, cross-linking density of polymer network increases, resulting decreased in swelling due to reduction in water uptake ability of hydrogel.

Effect of acrylic acid on drug release: GG/PVP co-polyacrylic acid based hydrogels were fabricated to determine the effect of acrylic acid on fabricated hydrogel. It was observed that as the acrylic acid concentration increased swelling behavior also increased but up to a specific limit after that more increase in acrylic acid concentration cause decreases in the swelling behavior because of compact mass. Fabricated hydrogels shows increased swelling at pH 7.4 resulting in increased release rate of drug as compared to pH 1.2.

Effect of methylene bisacrylamide on drug release: As the concentration of MBA was increased the cross-linking of hydrogel also increased which result decreased in swelling behaviour. At basic pH 7.4 swelling rate increased thus increased in drug release as compared to pH 1.2. However increased in concentrations of cross linker decreased release rate at both pH. By increasing the concentrations of cross-linker, inter-connected pores are reduced between monomer and polymer, resulting in decreased penetration of fluid media and hence the process of diffusion decreased [17].

Kinetic modelling of drug release: Drug release kinetics from hydrogel is determined by applying different kinetic models like Zero order, First order, Higuchi model and Korsmeyer-Peppas model. The material showed in Table 1 indicate that all prepared hydrogel is best fitted to first order modeling explaining the correlation coefficient (R^2) value ranged in 0.9806-0.9776. By applying Korsmeyer- Peppas model on all prepared hydrogels released data, the value of -n exponents and regression coefficient were between ranges 0.567 to 0.757 and 0.9491 to 0.9922. Hence, fabricated hydrogels follow Non-Fickian diffusion where drug release kinetics consists of combination of dual mechanism (polymer relaxation and diffusion of drug in hydrated matrix).

Korsmeyer-Peppas model describe release of drug from polymeric network where mechanism of drug release was revealed by -n‖ (diffusion exponent). They demonstrate that value $0.45 \leq n$ represents Fickian diffusion while value $0.45 \leq n \leq 0.89$ represents Non-Fickian diffusion. When value of n=0.89 it represents typical

Table 1: Concentration of all prepared formulations ingredients per 100 g of distilled water.

S. No	Formulation Code	Concentration of all prepared formulations ingredients per 100 g of distilled water				
		GG	PVP	AA	SHS/APS	MBA
1	GGP 1	0.12	0.32	40	0.4/0.4	0.8
2	GGP 2	0.16	0.32	40	0.4/0.4	0.8
3	GGP 3	0.2	0.32	40	0.4/0.4	0.8
4	GGP 4	0.2	0.24	40	0.4/0.4	0.8
5	GGP 5	0.2	0.32	40	0.4/0.4	0.8
6	GGP 6	0.2	0.40	40	0.4/0.4	0.8
7	GGP 7	0.2	0.32	32	0.4/0.4	0.8
8	GGP 8	0.2	0.32	40	0.4/0.4	0.8
9	GGP 9	0.2	0.32	48	0.4/0.4	0.8
10	GGP-10	0.2	0.32	40	0.4/0.4	0.4
11	GGP-11	0.2	0.32	40	0.4/0.4	0.8
12	GGP-12	0.2	0.32	40	0.4/.4	1.2

Zero order (Case II transport) release and n ≥ 0.89 represents super case II transport. Values of exponent -n as calculated according to Peppas per algorithm ranged between 0.9492-0.9923 as shown in Table 1. All fabricated formulations were following Higuchi model because value of R^2 (correlation coefficient) were also evaluated high for Higuchi model. Higuchi model demonstrates the release of drug from the polymeric network through diffusion mechanism by forming pores. In previous literature, Khalid and co-workers formulate controlled release hydrogels and similar results were observed by them as our study and their fabricated formulations were fitted best to zero order, first order, Higuchi model and Korsmeyer-Peppas model as our study [18].

CONCLUSION

The objective of present research work has been accomplished by fabricating a novel polymeric cross-linked system that can be a suitable source for control delivery of Acarbose. A biocompatible system is fabricated by using various concentrations of monomer, polymer and cross-linker. For controlled drug delivery free radical polymerization method was used. Natural polymer (Genugel gum) and synthetic polymer (polyvinyl pyrollidone) along with grafting of acrylic acid on to polymer backbone were used for developing hydrogel. This interpenetrating network provides release rate of drug for extended time period. The prepared hydrogels were analyzed by SEM, FTIR, DSC and TGA tests. Polyvinyl Pyrollidone/ Genugel Gum co-Acrylic acid-based hydrogels fabricated by using synthetic and natural polymers were successfully characterized for extended drug delivery. Fabricated hydrogels exhibited pH dependent swelling and were stable at different pH and showed maximum swelling behavior at pH 7.4. Hydrogel showed variation in their behavior by changing concentration of its ingredients. Drug release and swelling behavior of fabricated hydrogel showed that by increasing concentration of polymer swelling behavior of hydrogel decreased while with increasing concentration of cross-linker and monomer the drug release rate and swelling behavior of hydrogel decreased.

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