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The use of golan gum in the targeted release of sulfasalazine to the large intestine based on pH sensitivity

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Abstract: Targeted drug delivery is one of the most important branches of pharmaceutical sciences, which is important for researchers in increasing the effectiveness of drugs and reducing drug toxicity by means of drug delivery carriers.

The formulation of drug delivery systems can increase the safety of the drug by reducing systemic side effects, preventing the release of the drug in the stomach and damaging it, and preventing the distribution of the drug in healthy tissues. It also prevents the decomposition of the drug and covers the bitter taste of the drug and reduces costs. The purpose of this research is to use the drug sulfasalazine to the colon in a drug delivery system based on azo hydrogels, which we cover with gellan polysaccharide, and to show its effect on the body's digestive system and the treatment of inflammatory bowel disease.

To do this, we first poured distilled water into the sample beaker and mixed it with a magnetic stirrer. Heating was done for one hour to completely dissolve gelan. Then, the ground drug was added during the dissolution of gelan. Stirring continued for three hours and after that we drained the samples in a plastic container and put them in the refrigerator. 30 ml of deionized water was added to 10 ml of each of the samples, then they were titrated separately using 10 M sodium hydroxide solution and 1 10 M hydrochloric acid. The dialysis bag was cut into several pieces, and then the bottom of the bag was closed with a piece of clean, suitable cotton soaked in PBS buffer, and 20 ml of samples were added to each bag. For each sample, 25 cc of isotonic PBS buffer with pH=0.7 was added to a 50 cc Falcon tube, and the dialysis bag and its contents were immersed in the Falcon tube. Then, optical absorption or ultraviolet light was read using a spectrophotometer in both environments inside the dialysis bag and outside the bag during different hours. Cytotoxicity test is done by several methods: NRU, CFU, MTT, XTT, in this research we used MTT test to check the toxicity of substances on cell life. We used the FTIR analysis test to identify unknown substances, determine the concentration and quality of the sample. This research, while confirming the slow release, showed that the maximum release of the drug is within 48 hours in the environment similar to physiological and isotonic conditions. The successful

development of nanoparticles for the oral method can change the treatment pattern of many diseases and have an important effect on the treatment results in the future.

Keywords: *golan gum, sulfasalazine, large intestine*

1. Introduction

Inflammatory bowel disease is a common disease in the digestive system that causes inflammation and ulceration in the inner wall of the large intestine and small intestine. This disease can be painful and sometimes debilitating and in some cases it can be life threatening. Inflammation can be limited to the intestinal wall or spread throughout the intestine, and finally it can cause another acute disease in different areas of the digestive system and anus. Sulfasalazine is one of the main drugs . The most effective ones are for the treatment of inflammatory bowel disease. It is an anti-inflammatory drug that has two parts of 5-aminosaliyl, one acid and sulfapyr-iodine, which are connected by an AZO bond, and it is taken orally. This drug is broken down in the acidic pH of the stomach and its pharmacological effect is lost. Drug release is a method in which by using the medical method and combining it with the engineering point of view, drugs or therapeutic molecules in general can be delivered more effectively to the desired target i.e. the treated area. Drug delivery to the colon is a new strategy that has received much attention. The selective release of drugs to the colon can not only control the required dose, but also reduce the systemic side effects caused by high doses. Peptide, protein, oligonucleotide drugs and vaccines can be good candidates for this route. Releasing the drug from the colon route and through the absorption of the cells of this route is another way of delivering drugs that are absorbed in small amounts from the previous parts of the digestive tract. However, there are some obstacles to choose this route for drug release. Different pH, long transit time from the mouth to the large intestine can be some of these obstacles that can be overcome by using pH-sensitive coatings. Polysaccharide di and azopolymeric coatings such as hypectin, galactomethane based systems and also azo hydrogels that can be destroyed by bacteria can be used to release the drug from the colon. Gellan Plysacar Iodine gum is biocompatible and non-cytotoxic, which is resistant to the acidic pH of the stomach, but is destroyed in the intestinal environment and causes the drug to be released at the target site. In this research, in order to deliver the drug sulfasalazine to the colon, we coated it with gellan iodide polysaccharide in a drug delivery system based on azo hydrogels.

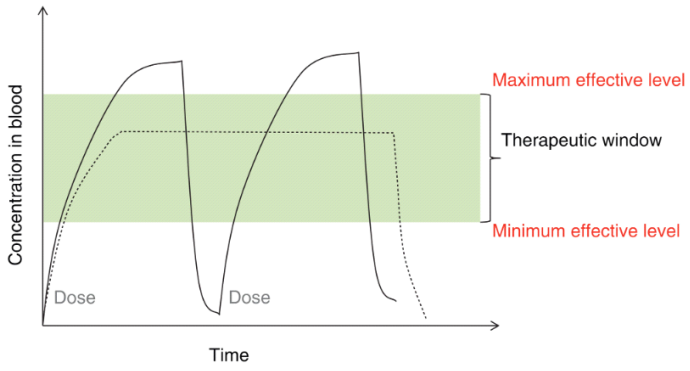


Fig 1: Showing the amount of drug concentration in blood with traditional drug delivery (dashed line) and controlled reed drug delivery (dashed line)

Controlled drug release is a targeted control system that, by means of a biological stimulus, guarantees the release of a certain amount of drug at a certain time to achieve the desired therapeutic effect [2] despite the tremendous progress in this field in recent decades, the systems Drug delivery is not a new concept. The people of ancient China and Egypt, even before the word drug delivery, used this concept in the form of polymers and waxes with active medicinal agents. Since the industrial revolution in 1970, various technologies have been developed in the field of drug delivery [4 and 3].

The formulation of drug delivery systems can increase the safety of the drug by reducing systemic side effects, preventing the release of the drug in the stomach and damaging it, and preventing the distribution of the drug in healthy tissues. It also prevents the separation of a drug and also covers the bitter taste of the drug and reduces costs. All kinds of drugs, regardless of their molecular weight and solubility in water, can be loaded into biodegradable microparticles using different production techniques. In general, a targeted drug delivery system includes a drug, a carrier and a targeted ligand.

1) Target: In this system, it is the tissue, organ or cell that needs treatment.

2) Drug carrier: drug release is possible only from the drug site. Carriers, molecules or any system

There are others who are responsible for the successful transfer or transport of the drug to the target tissue.

Carriers are specially designed to hold the drug in their structure. This is possible by encapsulating the drug, or enclosing it.

Targeting mechanisms of the drug

1: Physical targeting

Physical targeting by various external forces such as: magnetic field [9], ultrasound [10], light [11], heat [12] and electric field [13] in order to accumulate or disperse the medicinal agent in the desired location. can be It seems that among these cases, the use of magnetic field, light and ultrasonic waves has found wider use, and among these, magnetic field has found wide commercial applications due to its cheapness and ease of use [16 14]. Drug delivery by ultrasound waves is another new method of drug delivery that combines ultrasound technology with microbubbles

containing medicinal compounds and facilitates cellular absorption by using an external ultrasound field. It is depicted schematically in the form of drug release to cancer tissue by sending ultrasound waves[17]

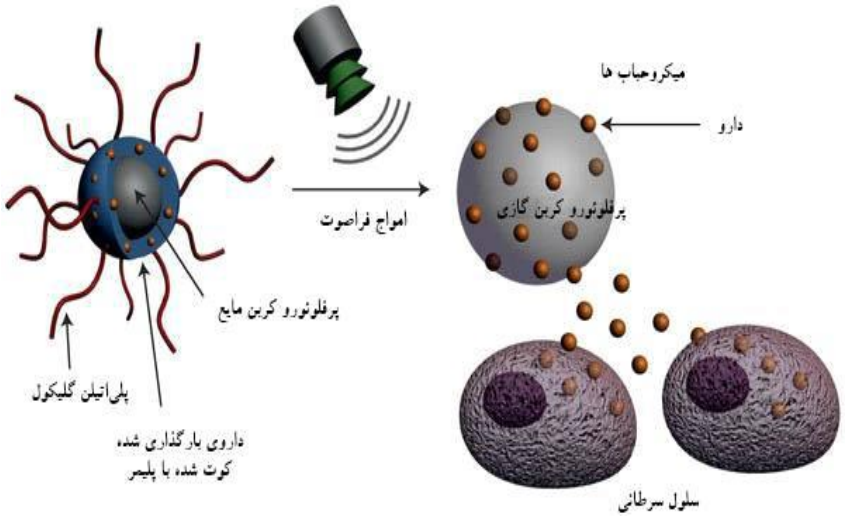


Fig 2: Sending ultrasound waves to microbubbles and drug release in cancer tissue

Controlled drug delivery systems have caused tremendous expansion and progress in the field of pharmaceuticals. In the pharmaceutical industry, one of the most vital needs is finding and making suitable drug carriers for drug delivery. As a result, the side effects of drugs are reduced due to the use of a small amount of drugs and effectiveness in certain areas. The drug delivery system without a target causes the distribution of the drug in the body and the effect of the drug on all areas of the body. This dispersion and distribution causes toxic effects on other areas as well as loss of important medicinal compounds. In medical engineering, the design of drug carriers for better diagnosis and treatment is very important in order to improve the management of diseases [23 22]. The presence of biological materials 1 is needed to design a stable and environmentally friendly drug carrier system, which can be natural polymers, metal compounds, synthetic and modified polymers. Compatibility with the environment and biodegradability of these materials have a significant effect on reducing toxic effects. A suitable drug carrier system has an effect on the absorption, distribution and rate of drug metabolism [24, 25]; This has been achieved by controlled drug delivery systems. Figure 3 shows the synthesis methods of different drug delivery systems.

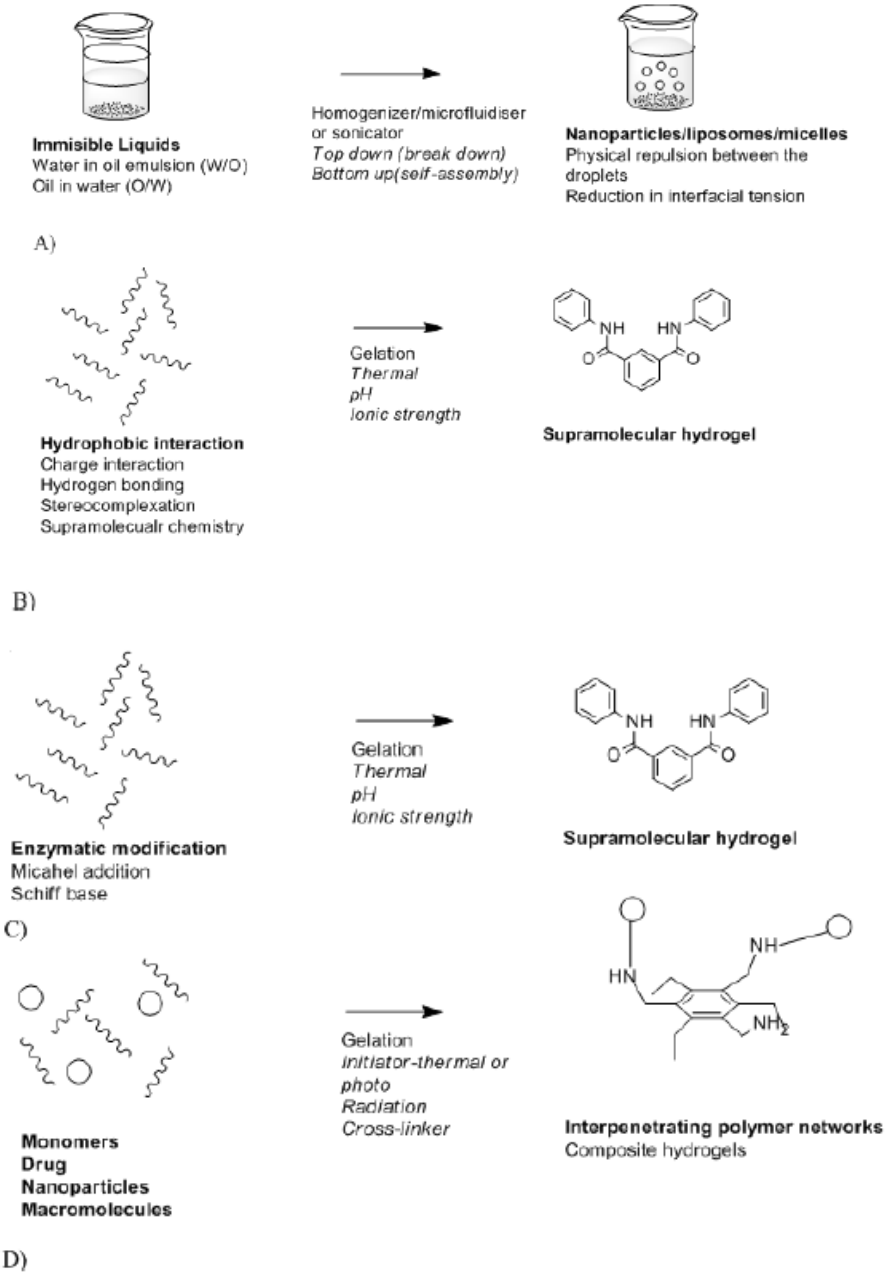


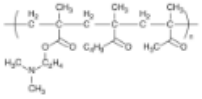
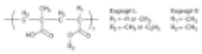
Fig 3: The different methods of synthesis of drug delivery systems.

Drug release system based on polymer

In the drug release system, polymers (natural and synthetic) are used to improve the efficiency of this system. The most important factor for choosing a polymer is its biodegradability. Because when it enters the body, after the drug release process is completed, It is easily removed from the body. Also, the radical polymerization method is used for the synthesis of these macromolecules. Bioadhesion is defined as the adhesion between the polymer and the biological structure. The existence of polymers is essential to create this state of adhesion [27]. In recent years, a number of

bioadhesive polymers have been considered very important in the drug release system: poly(acrylic acid), carboxymethyl acid. Cellulose and hydroxypropyl methyl cellulose. Among these polymers, polyacrylic acid 1 (especially in the cross-linked state) is a very good option, due to its nature. Hydrophilicity, negative charge and high flexibility are selected.

Common pH-sensitive polymers used in drug delivery.

Name	Chemical structure	Clinical indication	Refs.
Aminoalkyl methacrylate copolymer (Eudragit E)		Taste-masking	[28-32]
Poly(methacrylic acid-co-methyl methacrylate) (Eudragit L/S)		Protection of acid-degradable drugs, colon delivery	[6,35-43]
Hydroxypropyl-methylcellulose phthalate (HPMC-P)		Protection of acid-degradable drugs, colon delivery	[6]

gellan gum :

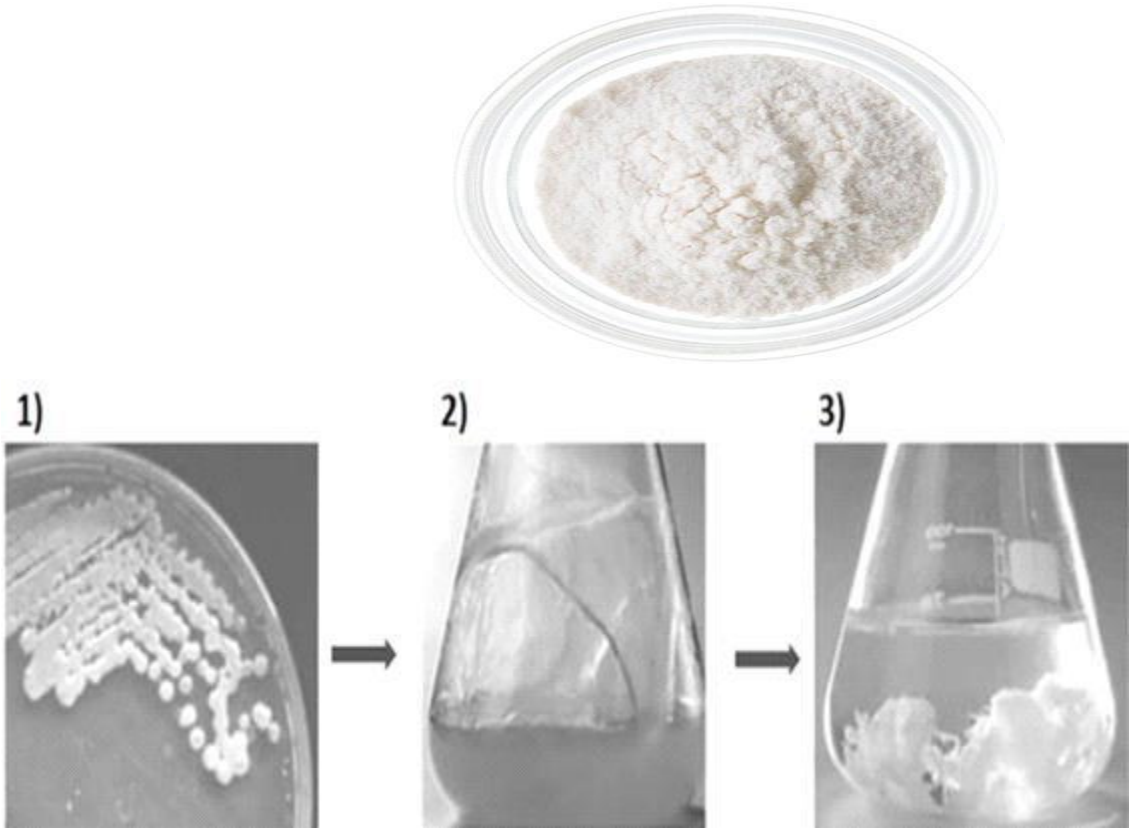


Fig 4: Gellan gum preparation.

This gum is an anionic polymer made of beta-diglucose, beta-diglucuronic acid and alpha-l-rhamnose units in a ratio of 1:1:2.

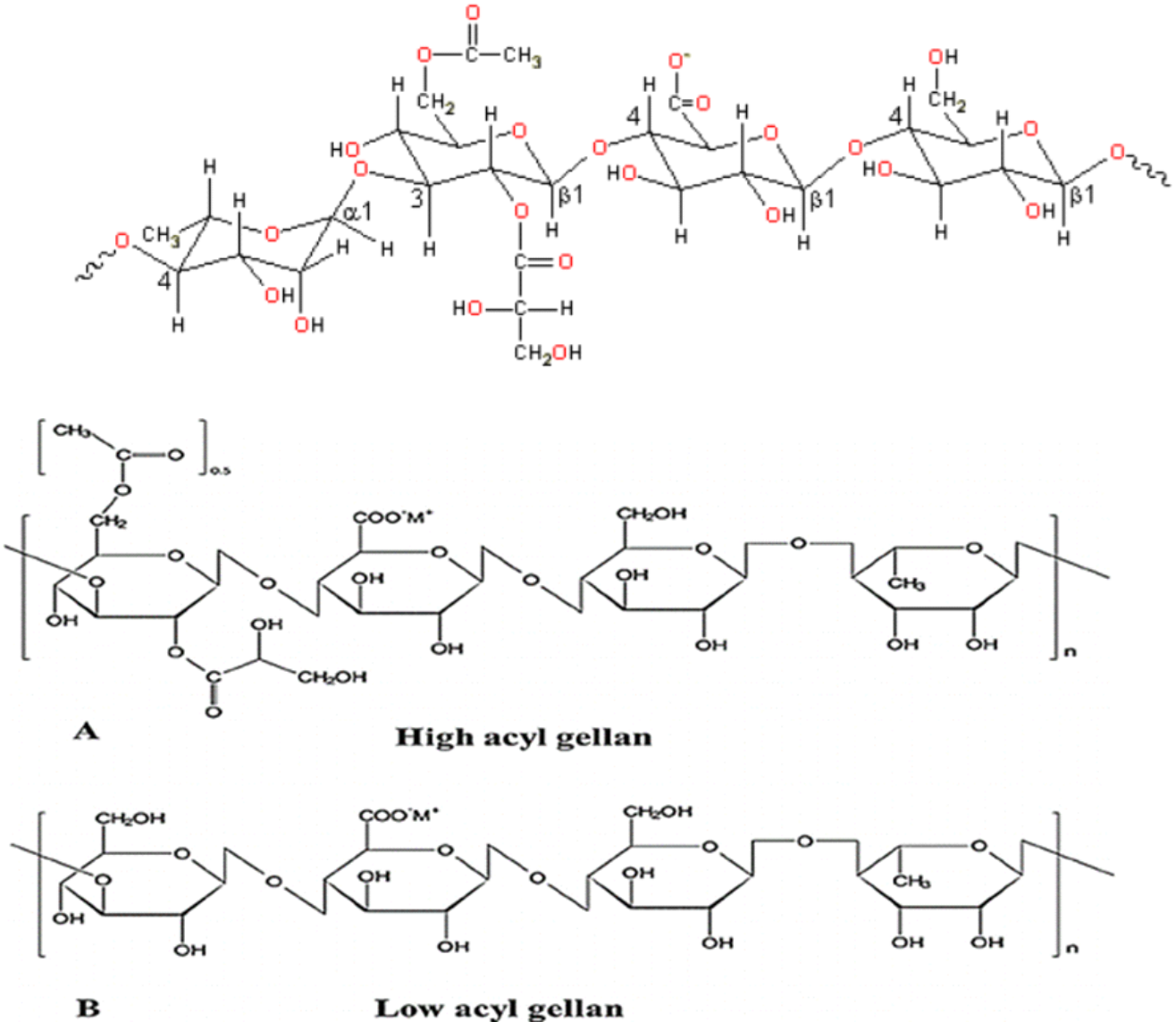
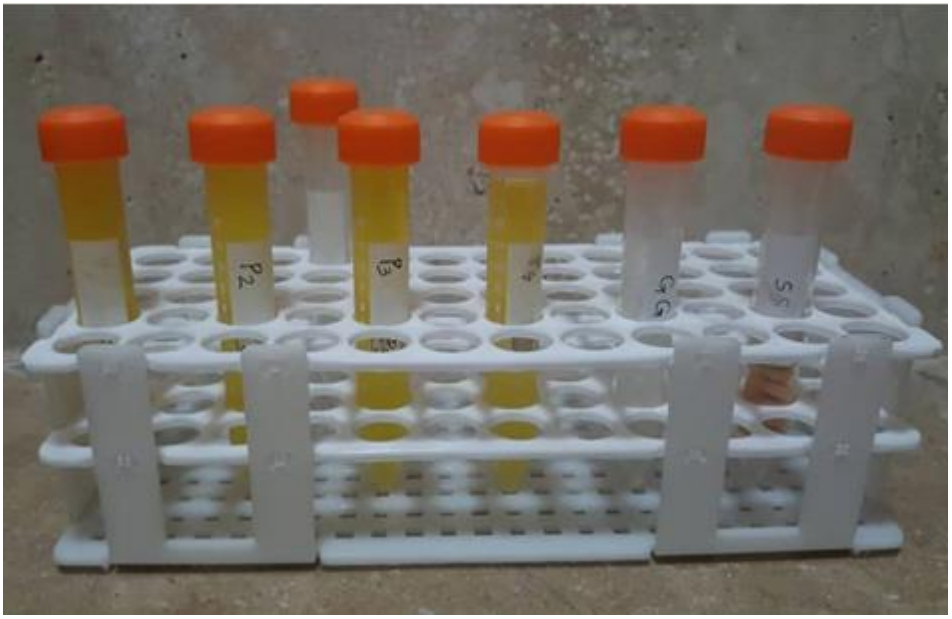


Fig 5: Chemical structure of gellan.

2. Material and method:

The gelatin sample was poured into a beaker and distilled water was added to it (Table 2). Then the beaker was covered and mixed by a magnetic stirrer. It was heated to a temperature of 90 degrees Celsius for one hour until dissolution. It is worth mentioning that 90 degrees Celsius is the temperature required to dissolve gelan gum. After one hour, the ground drug was added to it while dissolving gelan. Then for 3 hoursIt was stirred by a magnetic stirrer. The prepared samples were emptied into plastic containers and kept in the refrigerator.

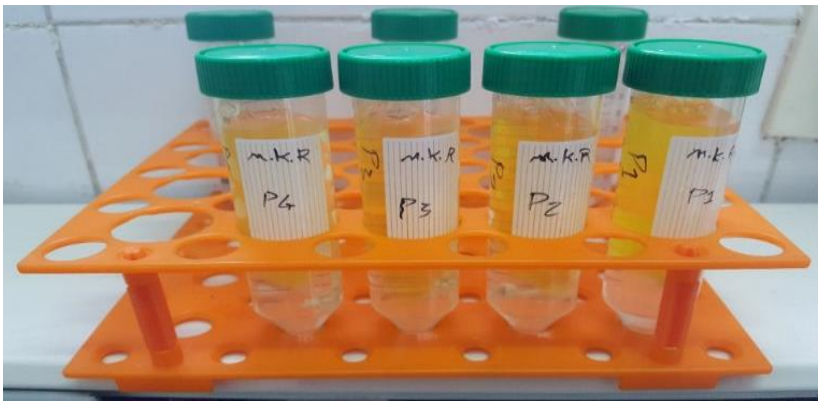

GG
SS


P2
P3
GG
SS

30 ml of deionized water was added to 10 ml of each of the samples, then they were titrated separately using 0.1 M hydrochloric acid solution and 0.1 M sodium hydroxide. It is in milliliters of acid or base consumed until the target pH is reached. A pH meter was used to measure the final pH of the samples

The pouch was cut into 17 cm pieces. Then the bottom of the bag with a piece of thread fits perfectly Cleaned and quenched with PBS buffer. 20 ml of samples were added to each dialysis bag.

For each sample, 25 cc of isotonic PBS buffer with pH = 7 was added to a 50 cc Falcon tube, and the dialysis bag with its contents was immersed in the Falcon tube.



Then absorb O.D. Absorbance (or UV light at a wavelength of 359 nm (359 nm λ) was read using a spectrophotometer in both environments inside the dialysis bag and outside the bag during 1, 2, 4, 8, 24 and 48 hours.

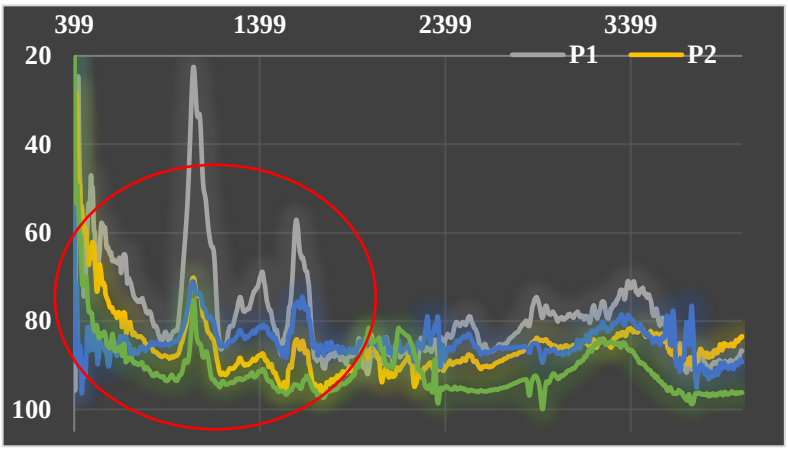
Cytotoxicity test

Cell experiments were performed at the Institute Pasteur center in the north of the country (AML) and in the cell culture laboratory. Fibroblast cells were obtained from the cell bank of the Institut Pasteur of Iran and were cultured in DMEM culture medium containing 10% FBS and 1% antibiotics penicillin and streptomycin (relative to 1 to 1) were cultured. Then the cells that have grown were separated from the culture medium with trypsin and centrifuged at 1500 rpm for 10 minutes at 4 degrees Celsius. Then 200 microliters of the cell suspension in the number of 5000 Cells were cultured in BIOFIL 96-well microplates for 24 hours (Figure 3 10) (Figure 3 11) (Figure 3 12). Next, each sample was mixed with the culture medium in the order of Table (3 4) and in each The well was added.

The microplates were placed in an incubator for 24, 48, and 72 hours at 37°C, 95% humidity, and 5% 2CO concentration (Figure 13). After 24, 48, and 72 hours, the effect Each sample on the mentioned cell line was checked by MTT colorimetric test method. The cytotoxicity test is performed according to the ISO10993-5 standard and with three methods: NRU test, CFU test, MTT test, and XTT test. The most common method in evaluating cytotoxicity is the cell survival assay using the MTT or (3-4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide) method.

3. Results and Discussion:

Diagram (4-7) compares the four Fourier transform infrared spectroscopic spectra of the four produced hydrogels in reverse Y-axis. In the area surrounded by the red circle, it can be seen that the spectra are in complete agreement and only in the amount The transmission spectrum clearly shows a change in the range of 1-Cm 2000 500. This difference in the transmission spectrum is visible in all parts of the spectrum, but it is more clear in this range.



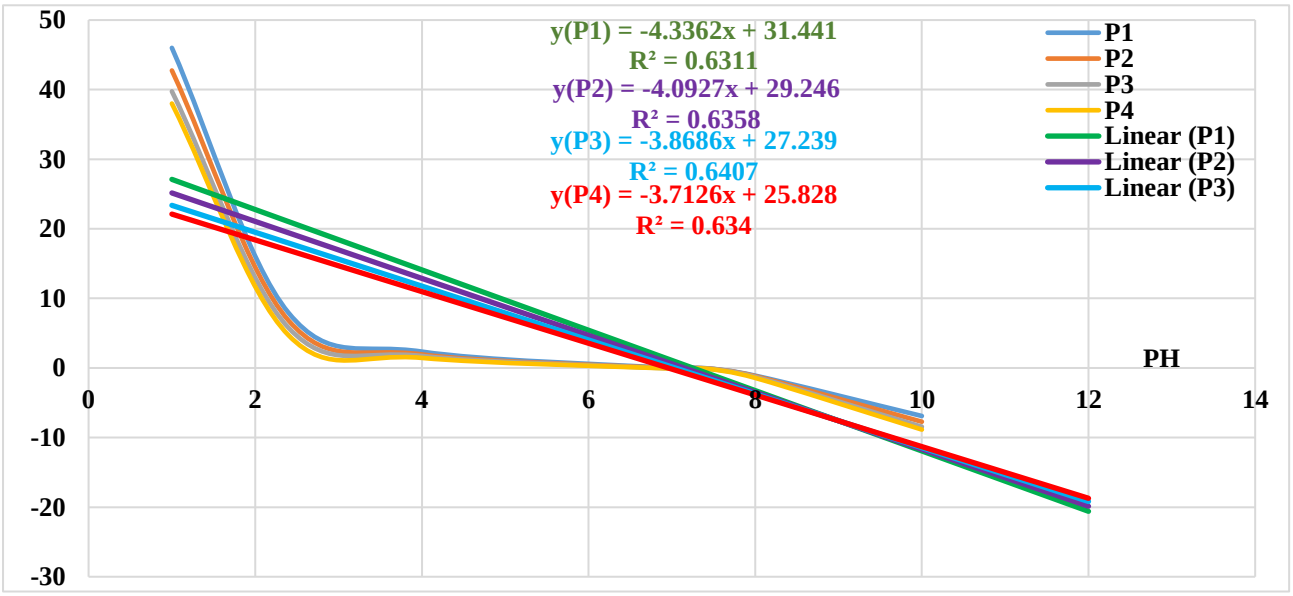


Diagram number (4-10) shows the drug release in standard conditions and in the presence of the semi-permeable barrier of the dialysis bag with a cut-off of 14 kilodaltons over time in a linear fashion. The amount of GG is far away from the product P4, which has the lowest amount of GG, and this indicates that GG is effective in releasing the drug more slowly. Also, in the first 4 hours of the study, all four products showed almost the same behavior, but in the eighth hour and later The difference between different products has become significant.

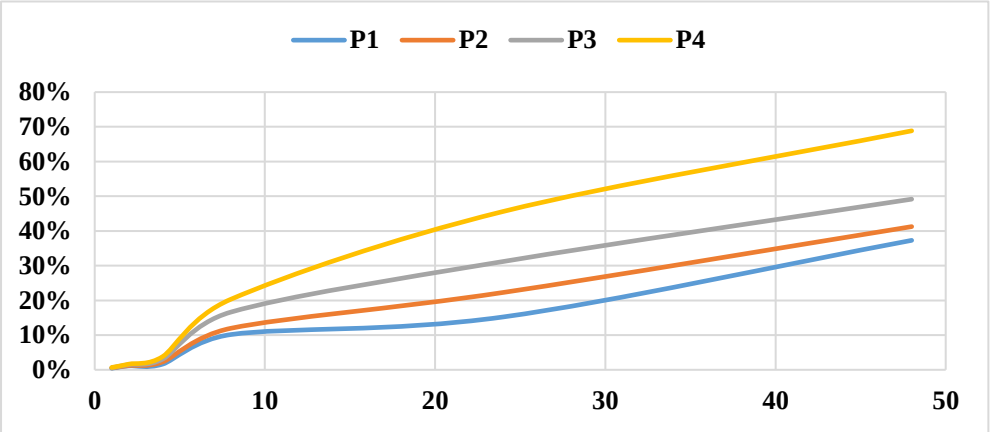


Diagram (4-10): Linear diagram of sulfasalazine drug release in four products P1, P2, P3 and P4 separately for each product

Cytotoxicity

In order to check the level of cytotoxicity of the product and the components used to make the product, normal human fibroblast cells were treated using the prepared products and sulfasalazine and gellan gum. After a period of 24, 48 and 72 hours from the proximity of cells with separate medicinal compounds and products; It was investigated using the MTT Assay method. The results of the light absorption obtained by the ELISA device along with the analysis of the results are given in tables (3-4), (4-4) and (4-5).

Conc. (µg/ml)	OD1	OD2	OD3	Viabil-ity 1	Viabil-ity 2	Viabil-ity 3	Average	SD	SEM	Cell Inhibi-tion	Ttest
P1	0.377	0.362	0.347	84.80	80.16	75.00	79.99	4.90	2.83	20.01	0.019419
P2	0.389	0.363	0.375	88.00	80.42	82.29	83.57	3.95	2.28	16.43	0.018705
P3	0.378	0.392	0.381	85.07	88.10	83.85	85.67	2.18	1.26	20.45	0.007659
P4	0.394	0.383	0.387	89.33	85.71	85.42	86.82	2.18	1.26	13.18	0.009002
G1	0.407	0.412	0.436	92.80	93.39	98.18	94.79	2.95	1.70	5.21	0.092232
G3	0.429	0.443	0.435	98.67	101.59	97.92	99.39	1.94	1.12	0.61	0.640628
SS	0.401	0.345	0.364	91.20	75.66	79.43	82.10	8.11	4.68	17.90	0.062036
Control	0.434	0.437	0.443	100.00	100.00	100.00	100.00	0.00	0.00	0.00	
Blank			0.059								

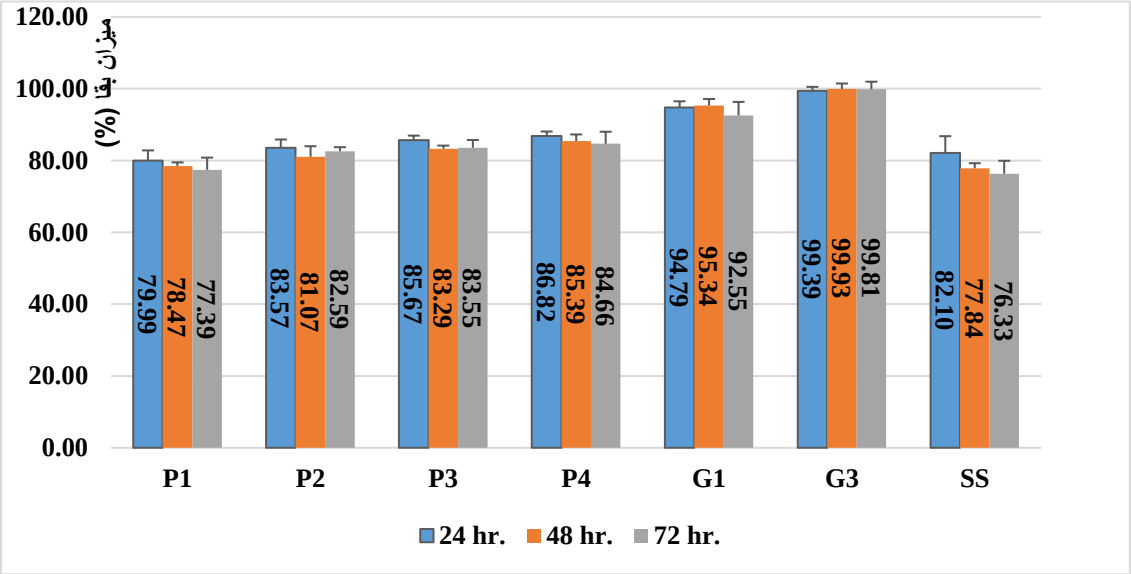
Absorption, average survival rate and inhibition of different samples and relevant statistical indicators within 24 hours of placement of human fibroblast cells in the vicinity of different samples

Conc. (µg/ml)	OD1	OD2	OD3	Viability 1	Viability 2	Viability 3	Average	SD	SEM	Cell Inhibition	Ttest
P1	0.462	0.479	0.481	76.52	79.99	78.89	78.47	1.77	1.02	21.53	0.002246
P2	0.517	0.464	0.483	86.77	77.18	79.25	81.07	5.05	2.91	18.93	0.022865
P3	0.489	0.502	0.509	81.55	84.29	84.03	83.29	1.51	0.87	16.71	0.002710
P4	0.528	0.492	0.514	88.82	82.42	84.94	85.39	3.22	1.86	14.61	0.015857
G1	0.564	0.544	0.587	95.53	92.14	98.35	95.34	3.11	1.79	4.66	0.121634
G3	0.601	0.571	0.597	102.42	97.19	100.18	99.93	2.62	1.51	0.07	0.968959
SS	0.454	0.475	0.483	75.03	79.24	79.25	77.84	2.43	1.41	22.16	0.003997
Control	0.588	0.586	0.596	100.00	100.00	100.00	100.00	0.00	0.00	0.00	
Blank			0.051								

Absorption, average survival rate and inhibition of different samples and relevant statistical indicators during 48 hours of placement of human fibroblast cells in the vicinity of different samples

Conc. (µg/ml)	OD1	OD2	OD3	Viability 1	Viability 2	Viability 3	Average	SD	SEM	Cell Inhibition	Ttest
P1	0.507	0.483	0.462	82.58	78.65	70.93	77.39	5.92	3.42	22.61	0.022115
P2	0.519	0.496	0.526	84.75	81.02	82.01	82.59	1.93	1.12	17.41	0.004093
P3	0.511	0.531	0.514	83.30	87.41	79.93	83.55	3.74	2.16	20.45	0.016836
P4	0.547	0.522	0.505	89.84	85.77	78.37	84.66	5.81	3.36	15.34	0.044650
G1	0.572	0.589	0.545	94.37	97.99	85.29	92.55	6.54	3.78	7.45	0.187439
G3	0.594	0.622	0.613	98.37	104.01	97.06	99.81	3.70	2.13	0.19	0.938277
SS	0.497	0.485	0.452	80.76	79.01	69.20	76.33	6.23	3.60	23.67	0.022317
Control	0.603	0.6	0.63	100.00	100.00	100.00	100.00	0.00	0.00	0.00	
Blank			0.052								

Absorption, average survival rate and inhibition of different samples and relevant statistical indicators during 72 hours of placement of human fibroblast cells in the vicinity of different samples



4. Conclusion:

Many new drugs are only used by injection. Alternative methods of injection, to Especially the oral method, compared to the injection method, is very desirable because it is more convenient and seeks the patient's satisfaction. Although the oral method has many challenges due to the presence of barriers in the digestive system, polymeric nanoparticles can be used to overcome the pH and enzyme barriers, but the barriers of intestinal permeability It remains an important challenge. So far, many methods have been used to overcome the intestinal epithelial barrier to effectively deliver biological drugs and nanomedicines. The tests performed in an artificial environment to check the release of salt from hydrocolloids seem reliable, acceptable and repeatable and can be compared with different structures of gels and other materials in the future. Adhesive mucilaginous materials prolong the stay time in the intestine by using the mucous layer of the intestines and increase the concentration of drugs near the surface of the epithelial cells. In addition, there are many penetration-enhancing mucosal adhesions that open tight junctions between epithelial cells so that drugs and pharmaceutical agents can pass through this barrier. Other methods on targeting routes Natural transcytosis is focused on including the M cell, the vitamin B12 pathway, and the FcRn pathway. Recent studies have shown that targeting transcytosis pathways can effectively deliver drugs and nanomedicines orally, but more research is needed before these technologies can be used clinically. Oral drug delivery system is being developed for many different applications, such as oral drug delivery of chemotherapeutic agents for cancer treatment, local drug delivery to the intestine for the treatment of inflammatory bowel disease, and mucosal oral vaccination. Many proteins, especially insulin for the treatment

of diabetes, have been loaded into nanoparticles for oral use. The successful development of nanoparticles for the oral method can change the treatment pattern of many diseases and have an important effect on the treatment results in the future. This research, while confirming the slow release, showed that the maximum drug release within 48 hours is similar to physiological conditions and isotonic conditions.

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