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USING SPECIAL MULTIDRUG LOADED GASTRORETENTIVE FILMS TO TREAT H. PYLORI STOMACH INFECTIONS BETTER

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Abstract:

"We made a special kind of patch that sticks to the stomach lining and slowly releases medicine to treat infections. We used chitosan, a natural substance, and PAA to help it stick. The patch contains three medicines: amoxicillin trihydrate, metronidazole, and famotidine. We made it by mixing these ingredients together and spreading them out to dry. We experimented with different amounts of ingredients like glycerol, chitosan, and PAA to find the best combination for making the patch. We tested things like weight, thickness, and strength to make sure the patch would work well.

KEYWORDS: Gastroretention, Mucoadhesion, Diffusion, Drug release

Introduction:

Taking medicine by mouth is the easiest way. How well the medicine works depends on many things. One important thing is how long it stays in your stomach. People have been studying how to keep medicine in the stomach longer because most regular pills leave the stomach quickly. This is especially important for medicines that work best in certain parts of the intestine. Scientists have found ways to make special kinds of medicine that stick to the stomach lining and release medicine slowly. These are called gastro retentive dosage forms. They help the medicine stay in the stomach longer, which can be helpful for certain types of medicine.

The way food affects the stomach and how it moves around in there are big factors in how long medicine stays in the stomach. People have come up with different ways to make medicine stay in the stomach longer, like using special techniques and making fizzy versions of medicine. The goal of this study was to make a new kind of medicine that sticks to the stomach lining and slowly releases medicine. We used a common way to make this medicine called the solvent casting technique. This method helps the medicine stick better and release slowly. In this study, we made a sticky patch containing amoxicillin trihydrate, metronidazole, and famotidine to keep the medicine in the stomach longer and help it work better. We used chitosan and polyacrylic polymer to help the patch stick. This could help the medicine work better by keeping it in the stomach longer and improving how much of the medicine your body can use.

Material and Method:

Method:

We first prepared a chitosan solution by mixing chitosan with a 2% acetic acid solution and stirring it overnight. Then, we added specific amounts of amoxicillin trihydrate (10mg), metronidazole (5mg), and famotidine (0.15mg) to the chitosan solution and stirred it for 15 minutes using a magnetic stirrer. After that, we added glycerol to the mixture.

The solutions for making the films were stirred for 3 hours. Then, we poured them onto clean petri dishes and allowed them to dry at 35ºC for approximately 48 hours. After drying, we placed the films in a desiccator with a saturated sodium bromide solution (58% RH) at 25ºC.

Characterization of Mucoadhesive Gastro Retentive Films:

1. Film Weight: To find out how much the films weigh, we took three films from each batch and measured their individual weights. Then, we calculated the average weight of the films.
2. Thickness: To measure how thick the films are, we took three films from each batch and used a micrometer screw gauge to measure their thickness at three different spots. Then, we calculated the average thickness of the films.
3. Folding Endurance: We tested how well the films hold up by folding one film at the same spot over and over until it broke, or folding it up to 300 times. If the film didn't break after folding it multiple times, it showed good folding endurance. We repeated this test for three films from each batch and calculated the average number of times the film could be folded without breaking.

Table: 1 Physical Evaluation of the Different GR Film Formulations

Chitosan (% W/V)	**PAA (% W/V)**	**Glycerol (%)**	**Film weight (mg)**	**Thickness (mm)**	**Tensile strength (Kg mm^{-2})**
C1=2.0	**P1=2.0**	G1=20	185 1.02	0.73 0.05	2.16 0.48
		G2=30	**187 0.41**	**0.74 0.07**	**8.11 0.93**
		G3=40	194 1.64	0.79 0.02	3.67 0.13
	P2=1.0	G1=20	144 0.74	0.56 0.02	2.03 0.17
		G2=30	**148 0.12**	**0.58 0.08**	**14.83 0.34**
		G3=40	147 0.56	0.57 0.01	9.38 0.21
	P3=0.5	G1=20	113 1.53	0.42 0.06	3.68 0.20
		G2=30	**117 0.39**	**0.44 0.03**	**18.07 0.55**
		G3=40	120 0.30	0.45 0.08	14.11 0.71
C2=1.0	**P1=2.0**	G1=20	134 1.06	0.51 0.04	0.78 0.39
		G2=30	**140 0.43**	**0.55 0.07**	**4.11 0.82**
		G3=40	142 0.18	0.56 0.01	1.93 0.05
	P2=1.0	G1=20	92 0.39	0.35 0.03	0.83 0.71
		G2=30	**93 0.81**	**0.36 0.09**	**4.79 0.43**
		G3=40	95 0.69	0.38 0.05	2.04 0.50
	P3=0.5	G1=20	73 0.50	0.25 0.07	1.09 0.83
		G2=30	**77 1.32**	**0.28 0.10**	**5.53 0.66**
		G3=40	79 0.91	0.29 0.04	2.87 0.75
C3=0.5	**P1=2.0**	G1=20	119 0.82	0.45 0.09	0.39 0.04
		G2=30	**121 0.13**	**0.46 0.02**	**1.83 0.18**
		G3=40	124 1.67	0.51 0.10	0.64 0.37
	P2=1.0	G1=20	72 0.42	0.24 0.07	0.56 0.21
		G2=30	**76 1.16**	**0.27 0.01**	**2.71 0.31**
		G3=40	79 0.63	0.29 0.06	0.98 0.78
	P3=0.5	G1=20	41 0.19	0.16 0.07	0.72 0.14
		G2=30	**45 1.25**	**0.19 0.10**	**3.56 0.57**
		G3=40	47 0.94	0.20 0.03	1.81 0.69
C1=2.0		G1=20	88 0.83	0.32 0.08	4.03 0.82
		G2=30	**91 0.19**	**0.34 0.04**	**22.86 0.53**
		G3=40	93 1.56	0.36 0.03	15.42 0.20
C2=1.0		G1=20	39 0.66	0.15 0.01	1.82 0.28
		G2=30	**42 0.30**	**0.17 0.04**	**6.17 0.95**
		G3=40	45 0.57	0.19 0.02	3.43 0.74
C3=0.5		G1=20	18 0.37	0.080.03	0.75 0.43
		G2=30	**21 0.95**	**0.09 0.07**	**4.03 0.75**
		G3=40	23 1.03	0.10 0.05	1.89 0.18

The percentage (%) of plasticizer is given in relation to the total dry weight of the polymers. N=3; SD

4. **Percentage Swelling:** After finding out the initial weight and size of the film, three films of each type were placed on the surface of an agar plate inside an incubator set at 37 ± 0.2ºC. Every hour for 6 hours, the weight of the films (in groups of three) was checked to see how much they had increased.
   Calculation of percentage swelling (%S) using equation as:

$$\textbf{Percentage swelling (\%S)} = \frac{X_t - X_0}{X_0} \text{ X100}$$

Where,

X_t is the weight of the swollen film after time t,

X_0 is the initial film weight at zero time.

The mean value of three reading were calculated and reported

Table: 1 Percentage Swelling of Different GR Films Formulations

Time (h)	**Formulation code**											
	C1P1G2	**C1P2G2**	**C1P3G2**	**C2P1G2**	**C2P2G2**	**C2P3G2**	**C3P1G2**	**C3P2G2**	**C3P3G2**	**C1G2**	**C2G2**	**C3G2**
1	43.083.12	48.361.58	41.011.82	35.222.95	36.131.03	40.712.63	28.112.12	31.493.49	33.170.28	13.280.72	10.970.49	8.370.29
2	54.230.63	55.032.57	49.321.51	41.631.92	43.612.29	47.693.16	32.851.28	35.281.83	38.631.32	17.520.60	13.190.77	11.730.82
3	60.680.44	63.522.78	58.152.69	50.172.06	54.331.83	56.832.94	39.402.06	42.390.48	47.512.59	21.310.51	17.341.03	14.840.16
4	66.432.30	68.132.29	63.420.37	56.343.10	59.172.35	61.413.02	44.081.88	49.031.71	53.481.37	25.810.19	20.810.41	17.630.94
5	72.340.66	76.471.34	69.232.62	62.080.81	67.020.16	66.562.70	51.941.02	55.732.05	59.321.79	28.171.21	23.370.86	20.160.38
6	79.731.25	82.212.41	77.143.02	68.143.83	71.494.52	74.032.07	57.371.54	62.142.76	65.604.19	32.520.98	28.921.83	24.550.76

N=3; SD **Percentage Swelling of Different GR Films Formulations:**

5. Percentage moisture sorption:

Three films measuring 22 cm in size from each formulation were dried in an oven set at 30 ± 2°C. Once dry, the weight of each film was recorded. Subsequently, the films were transferred to desiccators containing saturated salt solutions of sodium nitrite, maintaining a relative humidity (RH) of 75 ± 5% at 25°C. After 1, 3, and 5 days, the films were weighed again, and these weights were noted down. Finally, the films were returned to the desiccators.

To calculate the percentage moisture sorption, we used the following formula:

$$\text{percentage Moisture sorption} = \frac{\text{Wt. of exposed film - Wt. of conditioned film}}{\text{Wt. of conditioned film}} \text{ X } 100$$

The average of the three readings was calculated and then reported.

Percentage Moisture Sorption of Different GR Films Formulations

Time (Day)	**Formulation code**											
	C1P1 G2	**C1P2 G2**	**C1P3 G2**	**C2P1 G2**	**C2P2 G2**	**C2P3 G2**	**C3P1 G2**	**C3P2 G2**	**C3P3 G2**	**C1G2**	**C2G2**	**C3G2**
1	7.03 0.18	7.32 0.92	7.94 0.25	5.82 0.69	6.14 0.50	6.65 0.98	4.83 0.12	5.12 0.35	5.46 0.22	8.69 0.92	6.97 0.81	5.64 0.16
3	9.29 0.72	9.18 0.16	9.63 0.22	7.14 0.38	8.05 0.20	8.38 0.16	6.17 0.46	6.55 0.61	6.85 0.19	10.43 0.10	8.87 0.33	6.99 0.47
5	11.62 0.55	11.90 1.28	12.71 0.87	9.53 0.41	10.18 1.82	10.89 0.49	**7.31 0.71**	8.03 1.26	8.96 1.01	**13.11 1.30**	11.14 0.97	9.07 0.83

N=3; SD

6. **Surface pH:** We used a method to find out the surface pH of the films. We used a special glass electrode for this. The films were soaked in either 1 mL of 0.1 M HCl or enzyme-free simulated gastric fluid (with a pH of 1.2 ± 0.1) for 2 hours at room temperature. Then, we measured the pH by touching the electrode to the surface of the patch and waiting for 1 minute for it to stabilize. We did this for three films and calculated the average pH value.
7. **In vitro Residence Time:** We used an IP disintegration apparatus to figure out how long the films stayed in vitro. The disintegration vessel of the test apparatus was filled with 800 mL of either 0.1 M HCl or simulated gastric fluid (SGF) with a pH of 1.2, and it was kept at 37 ± 2°C.

   A piece of rat stomach lining, 3 cm long, was attached to a vertical glass slab fixed to the apparatus. Three films from each formulation were moistened on one side using either 0.1 M HCl or simulated gastric fluid (SGF) with a pH of 1.2. Then, the moistened side was placed in contact with the stomach lining.

   The glass slab was fixed vertically to the apparatus and allowed to move up and down. This ensured that the film was fully submerged in the buffer solution at its lowest point and out of it at its highest point.

We recorded the time it took for the film to completely dissolve or detach from the stomach lining surface (n=3).**Surface pH and In vitro Residence Time of Different GR Films Formulations**

Parameters	**Formulation code**											
	C1P1 G2	**C1P2 G2**	**C1P3 G2**	**C2P1 G2**	**C2P2 G2**	**C2P3 G2**	**C3P1 G2**	**C3P2 G2**	**C3P3 G2**	**C1G2**	**C2G2**	**C3G2**
Surface pH	1.21 0.03	1.19 0.04	1.14 0.08	1.17 0.02	1.39 0.02	1.22 0.01	1.20 0.03	1.29 0.06	1.24 0.05	1.12 0.04	1.34 0.05	1.18 0.01
In vitro Residence Time (h)	8.52 0.36	7.77 0.18	6.93 0.51	6.36 0.83	5.24 0.13	4.69 0.72	4.08 0.25	3.40 0.38	2.94 0.92	6.01 0.20	3.98 0.12	2.54 0.69

N=3; SD

Result and Discussion

We made mucoadhesive gastroretentive films containing amoxicillin trihydrate, metronidazole, and famotidine using a method called solvent casting, which ensures the drugs are evenly distributed in the films. We adjusted different factors like the amount of glycerol, concentration of chitosan, and ratio of chitosan to PAA, one at a time, to see how they affected the weight, thickness, folding endurance, and tensile strength of the films.

After adjusting these factors, we tested the optimized films for various characteristics including how much water they absorbed, how much they swelled up, how long they stayed in the stomach, their pH on the surface, how evenly the drugs were spread out, and how quickly the drugs were released. The weights and thicknesses of the films, which were 2x2 cm in size and contained 20% glycerol, are shown in Table 5.1. The weights ranged from 18 ± 0.37 to 185 ± 1.02, and the thicknesses ranged from 0.08 ± 0.03 to 0.73 ± 0.05. These films are labeled as films C3G1 and C1P1G1, respectively.

Similarly, the weights and thicknesses of the 2x2 cm films with 30% glycerol are listed in Table 5.1. The weights ranged from 21 ± 0.95 to 187 ± 0.41, and the thicknesses ranged from 0.09 ± 0.07 to 0.74 ± 0.07. These films are referred to as films C3G1 and C1P1G1, respectively.

The films that measured 2x2 cm and contained 40% glycerol plasticizer had weights ranging from 23 ± 1.03 to 194 ± 1.64, and thicknesses ranging from 0.10 ± 0.07 to 0.79 ± 0.07. These films are also known as films C3G1 and C1P1G1, respectively.

Glycerol boosts flexibility and resistance, with the most significant impact seen at 30%. It reduces the stiffness of the polymer network, resulting in films with more movement of polymer chains, thus enhancing folding endurance and tensile strength. Therefore, we chose to continue the study using 30% glycerol.

The swelling behavior of a gastroretentive adhesive system is critical for achieving uniform and prolonged drug release and effective mucoadhesion. The swelling process is controlled by Donnan potential, which depends on the number of ionized groups in the polymer mixture.

Increasing chitosan content leads to higher swelling percentages. This is due to the presence of more polymer within the network structure with a significant number of pendant groups that ionize in a low pH environment, resulting in increased ionization and electrostatic repulsions.

Percent swelling was highest for the C1P2G2 film (82.21 ± 2.41) due to its regular porous nature, facilitating efficient and rapid swelling. Conversely, it was lowest for the C3G2 film (24.55 ± 0.76) due to a greater number of bonds in the network structure, hindering drug diffusion. The percent swelling was slightly lower for the C1P1G2 film (79.73 ± 1.25) compared to the C1P2G2 film, as the former was less porous and contained a higher amount of PAA and chitosan chains within the interpolymer complex, limiting solvent uptake in the network.

The swelling of films was significantly increased by the presence of both chitosan and PAA. The existence of a high molecular weight polymer in the formulation could help in facilitating the initial hydration of the films by creating an osmotic gradient, and the presence of PAA within these films could help the protonation of amine groups from chitosan causing an electrostatic repulsion among polymeric chains.

Water sorption isotherms are important for understanding the interaction mechanism between water and film components and were also determined to know the water content of the films used in the tensile experiments.

The water sorption in hydrophilic polymers is usually a non-linear process. Chitosan and PAA are hydrophilic polymers that can retain a considerable amount of water. In chitosan, we can find at least three main sites for water absorption: hydroxyl groups, the amino group, and the polymer chain end (a hydroxyl or an aldehyde group). Water absorption capacity of IPC was lower than chitosan.

Percentage water sorption was found to be high for C1G2 film (13.11 ± 1.39) and low for C3P1G2 film (7.31 ± 0.71). Water absorption capacity of films increased with increased concentration of chitosan and decreased concentration of PAA.

The surface pH of the film was found to be in the range of 1.39 ± 0.02 to 1.12 ± 0.04 for formulation C1P1G2 to C3G2. This film pH is close to the SGF pH 1.2. Hence, these films may not cause any irritation to the gastric mucosa after application. The surface pH of the film was determined to investigate the possibility of any side effects, In vivo.

A bioadhesive property of films increases with increased chitosan concentration and increased concentration of PAA. Chitosan-PAA IPC films exhibited greater bioadhesion.

The In vitro residence time of the film C1P1G2 to C3G2 on the mucosal membrane was observed, and it was noted that formulation C1P1G2 film remained on the mucosal membrane for more time (8.52 ± 0.36) as compared to other formulations. It could be due to the presence of maximum concentration of chitosan and PAA (2:2).

Drugs content uniformity was found to be in the range of 82.25 ± 2.83 to 92.38 ± 3.41 (amoxicillin trihydrate), 80.41 ± 1.97 to 91.46 ±3.81 (metronidazole), and 82.91 ± 1.31 to 91.08 ± 3.74 (famotidine) for formulation C1P1G2 to C3G2.

The In vitro drug release from the various prepared GR films was studied using the modified diffusion cell. The release profile of the drugs from different formulations indicates that the drugs release from these films follows non-fickian diffusion as the value of diffusional exponent (n) is in the range of 0.6 to 0.8. The reason for the non-fickian diffusion of the

drugs from the GR films could be due to the formation of solvent-filled pores in the matrix and erosion of the polymeric matrix at pH 1.2.

The formulation C1P2G2 film, in a ratio of chitosan: PAA (2:1), retards the rate and degree of erosion due to increased interaction between the carboxylic group of PAA and amines of chitosan. However, this effect may be limited by the ratio of chitosan and PAA. C1P2G2 film presented a suitable controlled release profile, showing 31.63 ± 1.24 of amoxicillin trihydrate, 42.20 ± 3.44 of metronidazole, and 35.55 ± 2.61 of famotidine release. These release results will ensure maximum availability of the drugs in the stomach. The reason for this is based on several factors, including the rate of erosion, the existence of a different electrostatic interaction within the network that controlled the drug release, and the presence of different kinds of structures with pores of different sizes.

The greater the PAA content in the IPC, the faster the release rate of drugs is achieved; therefore

Conclusion:

Based on the factors mentioned above, it's clear that the developed mucoadhesive films containing amoxicillin, metronidazole, and famotidine effectively stayed in the gastrointestinal tract (GIT) and kept the drugs stable at acidic pH levels. This suggests the potential use of mucoadhesive films in treating H. pylori infections.

The percent swelling was highest for the C1P2G2 film, attributed to its regular porous nature, facilitating better interaction between the matrix and solvent. Conversely, the percent swelling was lowest for the C3G2 film due to a greater number of bonds in the network structure, which slowed down drug diffusion.

Water sorption capacity was highest for the C1G2 film and lowest for the C3P1G2 film. The capacity increased with higher chitosan concentration and lower PAA concentration.

The surface pH of the films ranged from 1.39 ± 0.02 to 1.12 ± 0.04 for formulations C1P1G2 to C3G2.

Drugs content uniformity was within the range of 82.25 ± 2.83 to 92.38 ± 3.41 for amoxicillin trihydrate, 80.41 ± 1.97 to 91.46 ± 3.81 for metronidazole, and 82.91 ± 1.31 to 91.08 ± 3.74 for famotidine across formulations C1P1G2 to C3G2.

In vitro drug release from the various prepared GR films followed non-Fickian diffusion, indicated by diffusional exponent (n) values in the range of 0.6 to 0.8. This behavior could be attributed to the formation of solvent-filled pores in the matrix and erosion of the polymeric matrix at pH 1.2.**Reference:**

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