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pH-Sensitive, Encapsulated, and Natural Oral Contrast Media for Enterography

Oktay Algin[1,3], Muharrem Olcer[4], Çagdas Oto[5,6]

[1]Interventional MR Clinical R&D Institute, Ankara University, Ankara, Turkey
[2]Department of Radiology, Ankara University Faculty of Medicine, Ankara, Turkey
[3]National MR Research Center, Bilkent University, Ankara, Turkey
[4]Department of Pharmaceutical Technology, Afyonkarahisar University Faculty of Pharmacy, Afyonkarahisar, Turkey
[5]Department of Anatomy, Ankara University Veterinary Faculty, Ankara, Turkey
[6]Medical Design Research and Application Center, Ankara University, Ankara, Turkey

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Corresponding author: Oktay Algin, e-mail: droktayalgin@gmail.com

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Abstract

Objective: The aim was to provide a more efficient and tolerable oral contrast agent for bowel distension with fewer side effects due to its pH-sensitive nature.
Methods: Mixtures of uncoated powder and enteric-coated granule forms of locust bean and xanthan gum (LBXG, 1 : 1 ratio) were developed. Locust bean and xanthan gum and commercially available oral contrast agents were examined using 3-tesla MR and MDCT units to determine imaging characteristics. In addition, LBXG was tested in a rabbit by a 3-tesla MR system.
Results: Enteric-coated LBXG had a minimum of 10 times water absorption and swelling in the intestinal environment (pH 4.5-7.4). The lactulose solution was hyperdense, and the other contrast agents (including LBXG) were isodense on CT images. Methylcellulose solutions showed clumping in all environments despite sufficient shaking, and this type of clumping was not observed in other solutions. All solutions were hypointense on T1-weighted images and hyperintense on T2-weighted MR images. Although the enteric-coated LBXG granules were homogeneously soluble in water and an alkaline environment, they did not dissolve and precipitated in the acidic buffer despite sufficient shaking. LBXG showed biphasic character on MR images of the rabbit.
Conclusion: Enteric-coated LBXG granules may be an effective oral contrast agent for enterography examinations. Because of its target-specific nature, it may provide fewer side effects and a higher diagnostic efficiency/toleration capacity. It can be used for enterography exams and bowel cleansing before enterography, endoscopy, and/or surgery.
Keywords: Enterography, distension, bowel cleaner, oral contrast agent, CT, MRI

INTRODUCTION

Adequate small bowel distension is essential for optimal acquisition of CT or MR enterography examinations.[1] Collapsed bowel segments may hide abnormalities or mimic pathological conditions on enterography images.[2] Several oral contrast agents have been used to provide adequate small bowel distension.[3] The most commonly used compounds are biphasic ones (such as polyethylene glycol, lactulose, methylcellulose, sorbitol, and/or mannitol).[4] However, all these oral contrast agents have disadvantages.[5] For example, methylcellulose has a high risk of clumping during preparation or drinking difficulties due to unpleasant smells. Others have dose-dependent side effects such as abdominal pain, cramping, vomiting, and excessive diarrhea. In addition, the tolerability and efficacy of these agents are limited. In summary, the question of which oral contrast agent is optimal for enterography remains unresolved. Therefore, novel oral contrast agents must be developed to overcome these limitations.

We developed a new pH-sensitive, natural, and nonabsorbable oral contrast medium containing locust bean and xanthan gum (LBXG) for enterography examinations. The recipe for the tested beverage has been deposited as a patent. We investigated the features of this oral contrast agent in various in vitro and in vivo experiments.

MATERIAL AND METHODS

Eudragit® L 100 and 12.5 (methacrylic acid, methyl methacrylate; 1 : 1; Evonik Industries, Essen, Germany) were used as the enteric polymer. Ethanol 95% (Vins Industries OOD, Bulgaria), sodium hydroxide (Emplura Merck, Germany), hydrochloric acid (Emsure ACS, ISO, Reag. Ph Eur. Sigma-Aldrich, Austria), disodium hydrogen phosphate (Emsure ACS, Reag. Ph Eur. Merck, Germany), acetone (Emir Chemistry, Turkey), and sodium hydrogen phosphate (Emsure ACS, Reag. Ph Eur. Merck, Germany) were used as analytical grade and as received without any further purification. The rabbit experiment was approved by the Partners Healthcare Institutional Animal Care and Use Committee and was conducted

under its guidelines. Our ethical board approval date and number for this study from the Ethics Committee of Veterinary Faculty, Ankara University (22nd August 2022, Number: 2022/16).

Procedures for the Preparation of Enteric-Coated Granules

Enteric-coated LBXG granules were prepared using the wet granulation method. Eudragit® L100 was dissolved in a mixture of ethanol and acetone (1 : 1). As a result, a 30% Eudragit® L100 solution was obtained. The required quantities of LBXG (Shausan Chemicals and Drugs, Mumbai, India) were weighed, mixed, and sifted through an ASTM No. 20 mesh (850 µm) sieve. Subsequently, the blend was mixed using a dry rotary mixer. Enteric-coated LBXG granules were then prepared in a rapid mix granulator. LBXG was accurately weighed, mixed, and sifted through an ASTM No. 40mesh (425 µm) sieve. Granules were prepared using the wet granulation technique. Ethyl alcohol and acetone were used as the granulation fluid. The LBXG components were mixed with 30% Eudragit® L100 in a mixture of ethanol and acetone (1 : 1). The wet mass was passed through an ASTM No. 12 mesh (1.7 mm) sieve, and the resulting granules were dried at 50˚C in an oven dryer until a loss of 0.5%-1% on drying (LOD). The amount of enteric polymer was approximately 10% based on the total weight of the powder mixture. Dried granules were further passed through an oscillating granulator using an ASTM No. 18 mesh (1 mm) sieve. The sieved and dried granules were then packed into moisture-proof polypropylene–polyethylene (PP/PE) bags.

Characterization and Analysis of Enteric-Coated Granules

The following tests were performed on the coated granules:

General appearance: he granule size, shape, color, and texture of the granule surface are visually defined.

Weight change: the loading capacity of the enteric coating agent is calculated by considering the weight of the powder mass. Before and after the granulation procedures, the weight of the granules was measured. The amount of enteric coating agent loaded into the LBXG powder was defined. The target ratio was chosen as 10% ± 0.5.

Water content: Approximately 38 mL methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric endpoint. A total of 300 mg of the powder was accurately weighed and transferred into the titration vessel, mixed, and titrated with the Karl Fischer titration reagent to the electrometric endpoint. The water content of the powder was calculated using the following formula:

Calculate the percentage of water in the sample as follows:

Percentage of water in weighed samples = (Vr × *F* × 100)/Ws

F = water equivalence of the Karl Fischer reagent

Vr = mL of Karl Fischer reagent used, and Ws = weight of the sample in mg.

Acid resistance test: enteric-coated LBXG granules were kept for 1 hour at 37˚C ± 0.5 using a 20-rpm shaker at a pH 1.2 medium. In addition, the viscosity of the solution was measured. The same experiments and conditions were repeated in a pH 7.4 medium, in the following step. Finally, the viscosities of the solutions were measured using a digital viscometer (Brookfield DV-I prime, USA).

Particle size and distribution: enteric-coated LBXG granules were dispersed in glycerin. The particle sizes and distributions were examined under a microscope.

Viscosity values in various media: the locust bean and xanthan gum were mixed in a one-to-one ratio for all experiments. The uncoated powder and the coated granule forms of the LBXG were dissolved in water, pH 1.2, pH 7.4, and their viscosities were measured. Diluted suspensions of 0.5%, 1%, 2%, 2.5%, and 3% were obtained using distilled water, 0.1 N hydrochloric acid, and phosphate (pH 7.4) buffer. The viscosity values of these diluted mixtures were calculated depending on the mixing time/speed, resistance, viscosity, and concentration.

Imaging Exams

Commercially available oral contrast agents [(polyethylene-glycol (PEG), lactulose (Duphalac), carboxy-methylcellulose (CMC)] in our country and LBXG mixtures with different buffers (distilled water, acidic, and alkaline pH) and various concentrations (0.5%, 1.0%, 2.0%, 2.5%, and 3.0%) were placed in annotated plastic tubes. The concentrations of these solutions were the same as those per mL in routine enterography examinations. The tubes were evaluated using a 3-tesla (3T) MR unit (Trio, Siemens, Erlangen, Germany) and a 32-channel birdcage head coil. Multi-detector computed tomography (128-detector, Revolution Evo, GE, USA) images with 1 mm^3 voxel sizes were also obtained.

In addition, LBXG was tested in vivo in a rabbit experiment. One hundred milliliters of a 1% LBXG solution prepared using cherry juice was administered using a 6-French nasogastric catheter. The injection rate of the LBXG solution was 20 mL/min. After 100 mL of LBXG injection, the rabbit's abdominopelvic region was scanned with a 15-channel transmit/receive type birdcage knee coil and the same 3T MR device. Acquisition details of the 3T MR exams are given in Table 1.

RESULTS

Appearance

The powder form of the LBXG mixture turned into a granular structure after coating with Eudragit®. The average particle size increased approximately 100 times. The powder and granular forms of LBXG are shown in Figure 1.

Weight Change

The loading capacity of the enteric coating material, the weight of the powder mass (before granulation), and the weight of the granules (obtained after granulation) were calculated by considering the amount of enteric coating material loaded into the system. In terms of production efficiency, a loss of up to 5% in the total powder mass was observed. However, in the amount of Eudragit covered in the powder, the target was 10% ± 0.5; while 9.5%-10.5%, the amount of Eudragit

MAIN POINTS

- The enteric-coated LBXG granules might be an effective oral contrast agent for the enterography exams.
- The enteric-coated LBXG granules may provide fewer side effects and a higher diagnostic efficiency/toleration capacity.
- The enteric-coated LBXG granules can be used for image acquisition of enterography exams and optimal bowel cleansing before the enterography, endoscopy, and/or surgery.

Table 1. 3-Tesla MRE Protocol of the Experiments

Sequences/Parameters	3D-T2W (TSE)	2D-T1W (GRE)	3D-T1W (GRE)	2D-T1W (TSE)	2D-T2W (TSE)
TR/TE (ms)	3000/579	241/5-2.5	4.17/1.59	650/9.8	999/99
Slice thickness (mm)	0.6	5	1	3	5
FOV (mm^2)	240 × 240	280 × 228	400 × 400	200 × 200	400 × 400
Acquisition time (min)	5	0.4	11	1.57	0.6
NEX	2	1	2	2	1
Slice number	240	35	224	15	26
Flip angle (°)	100°	70°	10°	150°	139°
Imaging plane	Sagittal	Axial	Coronal	Sagittal	Axial
Distance factor (%)	–	30	20	20	10
PAT factor	2	1	1	2	3
PAT mode	GRAPPA	–	–	GRAPPA	GRAPPA
Voxel size (mm^3)	0.6 × 0.6 × 0.6	1.4 × 1.1 × 5	1 × 1 × 1	0.7 × 0.5 × 3	1.25 × .125 × 5
Fat-saturation	–	–	+	–	–

FOV, field of view; GRAPPA, generalized auto-calibrating partially parallel acquisitions; NEX, number of excitations; PAT, parallel acquisition technique; TR/TE, time of repetition/time of echo.

covered was 9.8% (the difference between theoretical loading and practical loading = 0.2%).

Water Content

The moisture content of the powder form of the LBXG mixture was found to be 1.8% in the moisture determination using the Karl Fischer method, and this ratio was reduced to 1.2% in the coated granules.

Acid Resistance Test

In the acid resistance test, the viscosity values of the solution obtained when the coated granules were held for 1 hour at 37°C + 0.5 at 20 rpm using a shaking water bath at pH 1.2 are shown in Table 2.

When the same experiments and conditions were repeated at pH 7.4, it was observed that the viscosity increased significantly and was close to the values in the uncoated powder of LBXG. The enteric coating can provide resistance to acidic environments in vitro.

Figure 1. Uncoated powder (left images) and coated granular (right images) forms of the LBXG can be seen. The size of each square is 1000 µm in the upper images. The LBXG powder is in the range of about 10-20 µm, while the coated granular LBXG is in the range of 100-1000 µm (750 µm on average).

Particle Size and Distribution

The LBXG powder ranges from about 10-20 µm, while the coated granular LBXG ranges from 100 to 1000 µm (750 µm on average).

Viscosity Values in Various Media

The uncoated and coated forms of the LBXG were dissolved in deionized water, pH 1.2, and pH 7.4; and their viscosities are given in Tables 2-4.

According to the tests, the viscosities increased depending on the amount of LBXG. The density values showed a linear increase depending on the concentration, although there was no significant difference in the order of pH 1.2 < water < pH 7.4 mediums. The results are shown in Figures 2-4**.** The enteric-coated LBXG mixture exhibited a minimum of 10 times water absorption in the intestinal environment (pH 4.5-7.4). It presented increased viscosity values depending on the application concentration (range: 0.5%-3%).

Table 2. Speed Per Minute (RPM), Torque (%), and Centipoise (cP) Values of Various Formulations of Uncoated Locust Bean and Xanthan Gums (LBXG, 1 : 1) Mixtures in Water

Formula	LBXG %	RPM	Torque %	cP
F1	0.5%	5	2.4	1320
		10	2.4	880
		20	3.0	540
		50	4.0	344
F2	1%	5	5.9	4080
		10	6.0	2400
		20	7.5	1520
		50	10.8	864
F3	2%	5	20.8	17300
		10	25.1	9280
		20	32.2	6200
		50	44.7	3560
F4	2.5%	5	14.5	16500
		10	18.9	8280
		20	24.2	5200
		50	35.7	2920
F5	3%	5	16.9	35000
		10	22.1	14800
		20	26.4	6600
		50	34.0	2960

Table 3. Speed Per Minute (RPM), Torque (%), and Centipoise (cP) Values of Various Concentrations of Uncoated LBXG (1 : 1) Mixtures in the Acidic Medium (pH 1.2)

Formula	LBXG %	RPM	Torque (%)	cP
F6	0.5%	5	0.70	400.00
		10	0.90	320.00
		20	1.20	220.00
		50	1.80	136.00
F7	1%	5	2.70	2480.00
		10	3.80	1520.00
		20	4.50	1020.00
		50	7.80	616.00
F8	2%	5	10.70	9040.00
		10	12.50	5640.00
		20	18.80	3760.00
		50	25.30	2160.00
F9	2.5%	5	22.50	18 300.00
		10	25.60	11 700.00
		20	37.90	7500.00
		50	50.80	4080.00
F10	3%	5	50.00	47 600.00
		10	58.30	20 500.00
		20	68.80	12 100.00
		50	81.30	6440.00

Table 4. Speed Per Minute (RPM), Torque (%), and Centipoise (cP) Values of Different Concentrations of the Uncoated Form of the LBXG (1 : 1) Mixture in the Phosphate Buffer (pH 7.4)

Formula	LBXG %	RPM	Torque %	cP
F11	0.5%	5	2.20	3680.00
		10	2.10	1520.00
		20	4.30	840.00
		50	5.70	464.00
F12	1%	5	4.40	4480.00
		10	5.20	2120.00
		20	6.30	1320.00
		50	9.20	776.00
F13	2%	5	23.50	20 800.00
		10	29.60	12 200.00
		20	41.60	8400.00
		50	62.00	4920.00
F14	2.5%	5	28.80	24 200.00
		10	37.60	15 100.00
		20	50.00	10 100.00
		50	71.10	5720.00
F15	3%	5	33.50	28 800.00
		10	36.70	16 700.00
		20	42.90	8900.00
		50	53.00	4360.00

The viscosity values of enteric-coated LBXG (1 : 1) granules at a 1% concentration in different media are given in Table 5 and Figure 5.

Computed Tomography and Magnetic Resonance Imaging Results

The average HU values of polyethylene glycol, lactulose, and carboxymethylcellulose solutions, as well as granule forms of LBXG in neutral, acidic, and basic environments, are given in Table 6. Among these, the lactulose-based solutions were hyperdense, whereas the others were isodense on CT images (Figure 6).

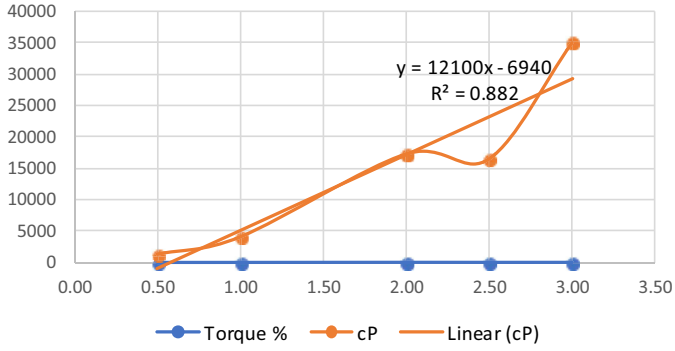

Figure 2. Viscosity graph of LBXG (1 : 1) mixture depending on its concentration in the water.

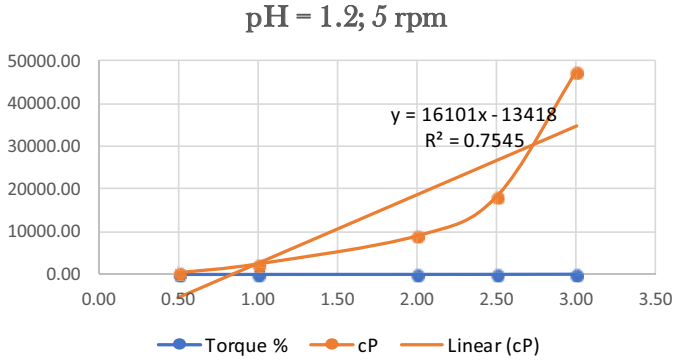

Figure 3. Viscosity graph of LBXG (1 : 1) mixture depending on its concentration in the acidic environment (pH 1.2).

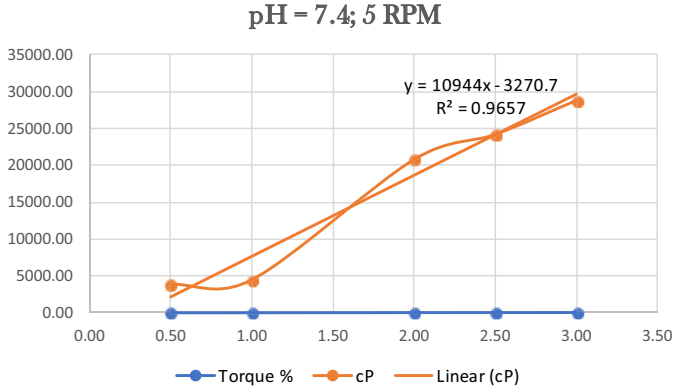

Figure 4. Viscosity graph of LBXG (1 : 1) mixture depending on its concentration in the alkaline environment (pH 7.4).

Table 5. Speed Per Minute (RPM), Centipoise (cP) Values of 1% Ratios of Coated Granules of LBXG Mixture (1 : 1) in the Water, pH 1.2, and pH 7.4

RPM	cP (water)	cP (pH 1.2)	cP (pH 7.4)
5	2025.00	810.00	4350.00
10	1210.00	475.00	2080.00
20	780.00	364.00	1276.00
50	432.00	226.00	760.00

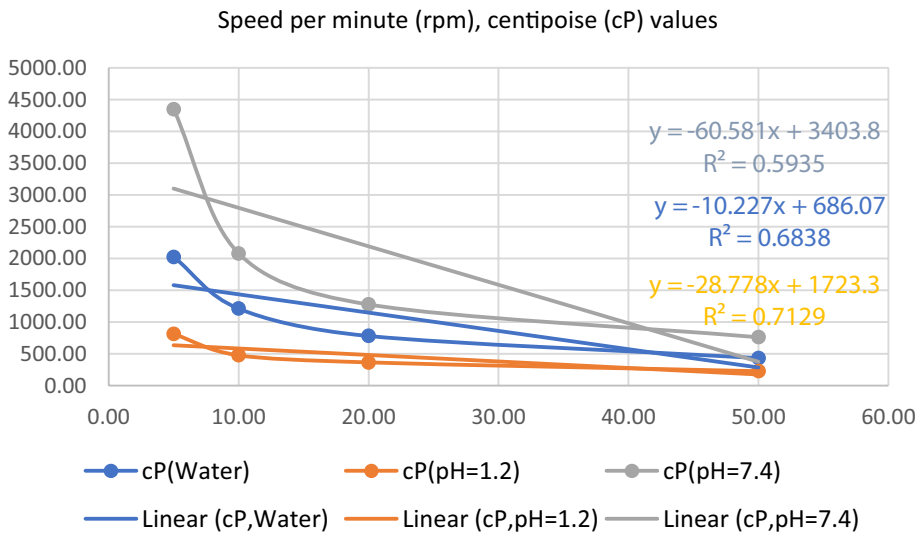

Figure 5. Graph of the viscosity values of a 1% solution of enteric-coated LBXG (1 : 1) in various media (deionized water, pH 1.2, and pH 7.4).

On CT and MR images, CMC-based solutions showed clumping in both water and acidic and basic environments despite sufficient shaking. This type of clumping was not observed in the other solutions. All oral contrast solutions were hypointense on T1-weighted images and hyperintense on T2-weighted MR images (Figure 7).

It was visually determined that the viscosity of the enteric-coated LBXG granules in water was lower than that of the enteric-coated LBXG granules in an alkaline medium. Although the enteric-coated LBXG was homogeneously soluble in water and an alkaline environment, it did not dissolve and precipitated completely in an acidic solution despite sufficient shaking (Figure 7).

After LBXG administration, an increased distention was observed in the stomach and small bowels compared with pre-contrast images on MR images of the rabbit (Figure 8). Locust bean and xanthan gum was hypointense on T1-weighted images and hyperintense on T2-weighted MR images. Vomiting was not observed in rabbits after LBXG administration. After the MR examination, no unusual situation was observed except for diarrhea. The physical examination of the rabbit was normal during the first-week follow-up visit.

Table 6. Mean HU Values of the Oral Contrast Agents in Different Environments (PEG, polyethylene-glycol; CMC, carboxymethyl cellulose; LBXG, locust-bean and xanthan gums)

	Neutral	Acidic pH	Alkaline pH
Solutions	**Mean (Range)**	**Mean (Range)**	**Mean (Range)**
Lactulose	100 (94-102)	92 (87-95)	90 (87-92)
Polyethylene-glycol	17 (15-19)	18 (15-20)	26 (20-30)
CMC	6 (4-10)	12 (8-14)	20 (17-21)
LBXG	9 (6-13)	5 (2-7)	22 (19-27)

DISCUSSION

The new enteric-coated oral contrast agent was described, and its effectiveness was investigated in this preliminary study. It has unique features for patients because of its bowel-specific nature. This natural oral contrast agent is resistant to the stomach environment and is more soluble at alkaline pH. This feature allows for more targeted dilatation of the small bowels. In addition, it would lead to a reduction in the incidence of side effects caused by stomach bloating. This will increase the patient's compliance and acceptability of the enteric-coated LBXG granules.

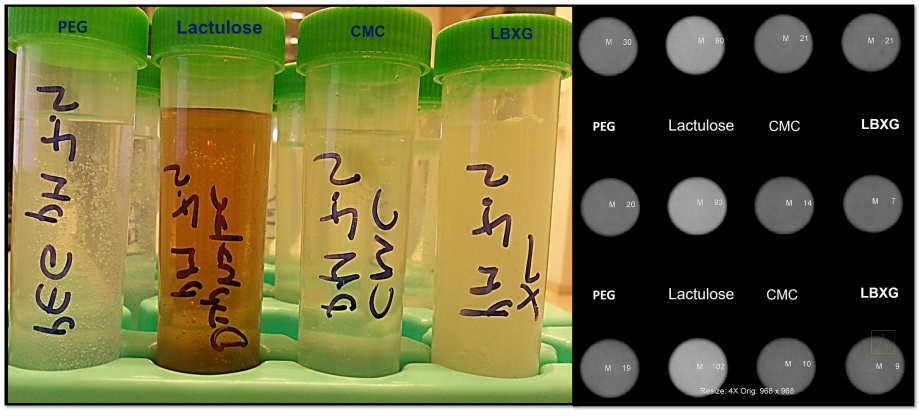

Figure 6. Mean Hounsfield units of commercially available oral contrast agent tubes [polyethylene-glycol (PEG), lactulose, carboxymethylcellulose (CMC)] for enterography and the enteric-coated LBXG granules on CT images. Lactulose-based solutions were hyperdense, while the others were isodense on CT images.

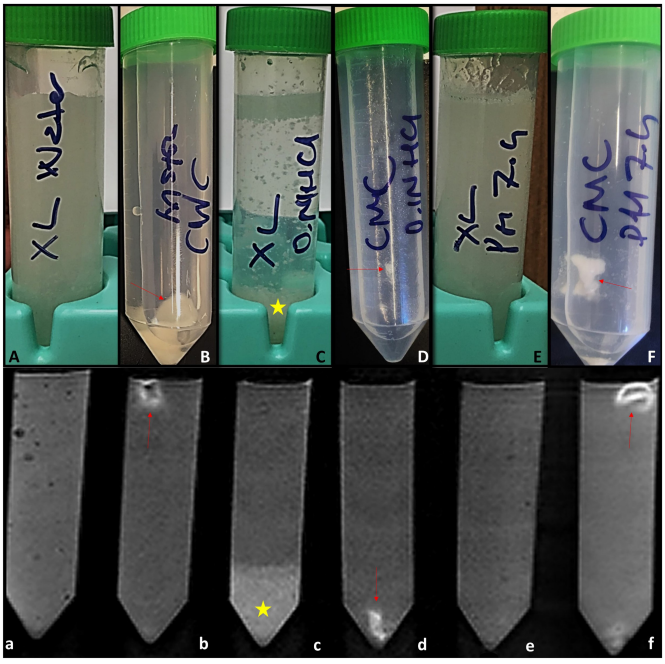

Figure 7. MR experiments of the oral contrast agents (lactulose and polyethylene glycol solutions are not shown here). Contrast agent-containing tubes were placed in a 32-channel head coil [upper line, LBXG in water (A-a), carboxymethyl cellulose in water (B-b), LBXG in an acidic environment (C-c), carboxymethyl cellulose in an acidic environment (D-d), LBXG in an alkaline environment (E-e), and CMC in an alkaline environment (F-f)]. There are many clumps in CMC solutions (arrows) on T1W MR images of the tubes (lower line). Also, a prominent aggregation was observed within the tube of the enteric-coated LBXG granules in the acidic buffer (asterisks).

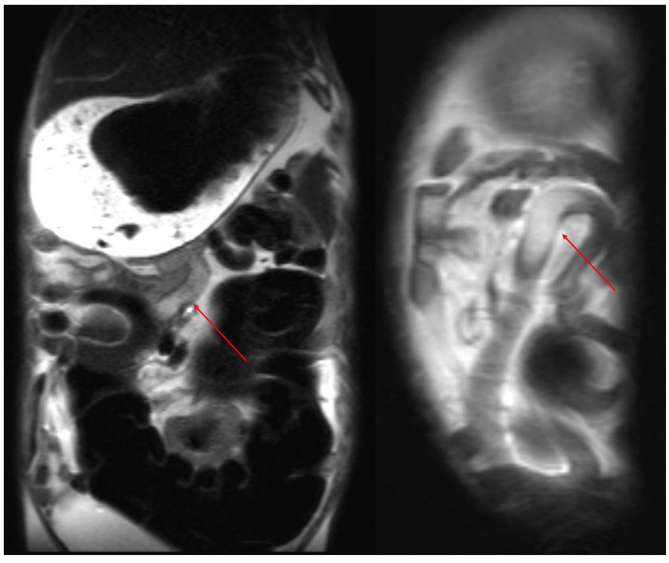

Figure 8. Coronal (left) and sagittal (right) planes T2-weighted MR images of the rabbit obtained after the LBXG administration. Small bowel dilatations were observed in these images (arrows).

Achieving proper expansion or filling of the small bowels is an essential requirement to achieve high sensitivity and specificity for detecting abnormalities on CT or MR enterography exams.[1-5] Recent advances in MRI technology have increased the role and success of MR enterography in the evaluation of the gastrointestinal system.[6] Oral contrast materials used in MR enterography are classified as positive, negative, and biphasic agents.[7] The most preferred type is biphasic (hypointense on T1W and hyperintense on T2W MR images) agents, such as methylcellulose, PEG, sorbitol, lactulose, CMC, and mannitol.[8] In addition, these contrast agents are among the most preferred oral contrast agents in CT enterography.[9] Because of some of the disadvantages or side effects (e.g., diarrhea) of oral contrast agents, the question of which contrast agent is optimal for enterography exams remains unresolved.[3,9] The enteric-coated LBXG has a biphasic character on MR images and is hypodense on CT images, similar to the clinically popular oral contrast agents mentioned above.

Xanthan gum (E-415) is an important exopolysaccharide secreted by Xanthomonas, a gram-negative bacterium.[10] Locust bean gum (LBG) is an antioxidant galactomannan vegetable gum extracted from the seeds of the carob tree (*Ceratonia siliqua*) found mostly in the Mediterranean region.[11] Locust bean gum (E-410) has a lower caloric value and a higher viscosity in vitro than starches.[12] Locust bean gum also shows a synergistic increase in gel strength when blended with xanthan gum.[13] Xanthan and locust bean gums (LBXGs) are safe and are used as gelling and thickening agents in the food and drug industry.[11] They are soluble in water and have high viscosities at relatively low concentrations.[10] Locust bean and xanthan gums can regulate the intestinal microbial balance and colonic butyrate production.[14]

Locust bean gum is a natural antioxidant and viscous soluble fiber.[13] Therefore, it may improve mucosal integrity and contribute to the reduction of intestinal inflammation.[14] Locust bean gum has a hypolipidemic effect, decreasing low-density lipoprotein (LDL) because of its high dietary fiber content.[13] It also reduces or controls diabetes and obesity because of its high gelling ability, which on ingestion causes a satiety sensation.[13] Locust bean gum can be linked with polyphenols, which cause polyphenols to reach the colon, where they can act on the gastrointestinal tract, maintain intestinal health, and prevent colorectal cancer.[15]

Enteric-coated LBXG contains non-absorbable and herbal ingredients with a biodegradable coating. Therefore, it can be used as a food supplement that does not require drug-related phase tests or a drug license. Therefore, it may also be used as an anti-constipation agent, detox therapy, liquid thickener in treating dysphagia, and/or to reduce the frequency and volume of regurgitation.

Oral intake or toleration of LBXG will be more accessible when applied by mixing it with fruit juice or yogurt. In addition, this oral contrast agent has a lower production cost than its existing alternatives because it contains easily available herbal components. The LBXG has unique features such as biodegradability, eco-friendliness, bio-acceptability, and safety, and is derived from renewable sources.

Enteric-coated LBXG may not cause significant stomach swelling because of its acid-resistant nature. It may provide more effective intestinal distension with fewer side effects and good tolerance with its alkaline pH sensitivity. The properties of our new oral contrast media may allow fast, effective, and more tolerable enterography exams. In addition, it may act as a bowel cleaner before CT/MR imaging, surgery, or endoscopy.

Because LBXG is completely natural, it may be easily removed without accumulation in the patient's body. No unusual behavior or vomiting

was observed in rabbits after LBXG administration. It may have fewer side effects for the patients.

There are some limitations to this study. The animal experiment was conducted on one rabbit. Our animal experiment model, based on 5F-guiding neurocatheter usage, is the first to be reported in the literature. Our contrast media may cause some symptoms (e.g., abdominal bloating, pain, flatulence, nausea, borborygmi, and/or diarrhea) similar to those of unabsorbed carbohydrates (such as lactulose).[16] Because we had to administer the oral contrast agent with a nasogastric tube, we limited the number of animal experiments because animal experiments could not be an adequate simulation for humans. Comprehensive preliminary human studies of the efficacy and tolerability of the new oral contrast agent are required.

Our results showed that enteric-coated LBXG granules may be more effective, safe, and tolerable for enterography exams. It may provide better luminal distension than other biphasic contrast agents. Enteric-coated LBXG may also be used as an oral bowel cleanser, and it may reduce the incidence of side effects or toleration problems.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Veterinary Faculty, Ankara University (22nd August 2022, Number: 2022/16).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.A., M.O.; Design – O.A., C.O.; Supervision – O.A., M.O.; Resources – O.A., M.O.; Materials – O.A., M.O.; Data Collection and/or Processing – O.A., M.O.; Analysis and/or Interpretation – O.A., M.O.; Literature Search – O.A., C.O.; Writing Manuscript – O.A., M.O.; Critical Review – O.A., C.O.

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