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Research Article

Fabrication, Characterization and *in vitro* Evaluation of Prednisolone Sustained Release Multiparticulate System for Colonic Targeting

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Abstract

Background: Prednisolone (PRD) is orally prescribed for inflammatory bowel syndrome (IBS) as the upper GIT is the main site of absorption; therefore, long-term PRD dosing decreases therapeutic effectiveness through systemic side effects. ***Objective***: This work focused on formulating sustained-release alginate beads as a multiparticulate system for colon targeting using prednisolone (PRD) to be filled in an HPMC capsule. ***Methods***: PRD beads were prepared by the ionotropic gelation technique using sodium alginate as the primary polymer and inulin, guar gum, and pectin as secondary polymers. In addition to the impact of polymer type and quantity, other factors were investigated: The $CaCl_2$ concentration and tween 80 addition Thirteen formulations were successfully prepared, and their properties, such as bead size, morphology, % of encapsulation efficiency, yield, DL, *in vitro* release study in GIT buffer media further to IBS media, SEM, and FTIR, were assessed. ***Results*:** The study showed that the beads were close in size, and the size was not an obstacle for loading the beads in HPMC capsules. Further, yield%, EE%, and DL% increased according to the bead's content increase. ***Conclusions***: The optimum formula was F3 that coated HPMC capsules with Eudragit S-100, which gave sustained release profiles in GIT and IBS simulating media, and F13 that could last the release in different pH media, pH 1.2, 6.8, and 7.4.

Keywords: Colon target beads, Eudragit S-100, Guar gum, Inulin, Pectin, Prednisolone.

التصنيع والتوصيف والتقييم المختبري لنظام بريدنيزولون متعدد الأجزاء المستدام الإطلاق لاستهداف القولون

الخلاصة

الخلفية: يوصف البريدنيزولون عن طريق الفم لمتلازمة التهاب الأمعاء حيث أن الجهاز الهضمي العلوي هو الموقع الرئيسي للامتصاص. لذلك، تقلل جرعاته طويلة المدى من الفعالية العلاجية من خلال الآثار الجانبية الجهازية. **الهدف**: ركز هذا العمل على صياغة حبات الألجينات ذات الإطلاق المستدام كنظام متعدد الأجزاء لاستهداف القولون باستخدام بريدنيزولون ليتم ملؤه في كبسولة. **الطرق**: تم تحضير حبات بردنيزولون بواسطة تقنية الهلام الأيوني باستخدام ألجينات الصوديوم كبوليمر أولي والأنيولين وصمغ الغوار والبكتين كبوليمرات ثانوية. بالإضافة إلى تأثير نوع البوليمر وكميته، تم التحقيق في عوامل أخرى: تركيز $CaCl_2$ وإضافة توين 80 تم تحضير ثلاثة عشر تركيبة بنجاح، وتم تقييم خصائصها، مثل حجم الخرزة، والتشكل، والنسبة المئوية لكفاءة التغليف، والمحصول، و DL، ودراسة الإطلاق في المختبر في وسائط عازلة بالإضافة إلى وسائط IBS، SEM، و FTIR. **النتائج**: أظهرت الدراسة أن الخرزات كانت متقاربة الحجم، ولم يكن الحجم عائقا أمام تحميل الخرز في كبسولات HPMC. علاوة على ذلك، زاد العائد ٪ ، EE٪ ، و DL٪ وفقا لزيادة محتوى الخرزة. **الاستنتاجات**: كانت الصيغة المثلى هي F3 التي غطت كبسولات HPMC ب Eudragit S-100 ، والتي أعطت نماذج إطلاق مستدامة في وسائط محاكاة GIT و IBS، و F13 التي يمكن أن تستمر في الإطلاق في وسائط الأس الهيدروجيني pH المختلفة ، 1.2 و 6.8 و 7.4.

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INTRODUCTION

Oral administration is one of the most popular methods for medication delivery; however, absorption from the gastrointestinal tract (GIT) has several significant barriers, to illustrate: Different pH along the GIT, disease status, as well as the food that restricts the absorption of active ingredients—all these together result in low bioavailability [1]. Thus, the scientific trials supported targeting the medications to overcome gastrointestinal issues [2]. A case in point is the colon-targeted drug administration that efficiently delivers medicines to the lower GIT when designing medicine for both systemic and local therapies [3] and to treat many colonic disorders like colitis and Crohn's, which are part of inflammatory bowel syndrome (IBD) [4], as well as drugs that are not stable in the stomach environment [5]. Namely, drug colon targeting can reduce the medication dose, adverse effects, dosing frequency, stomach mucosal injury, and toxicity [6]. More importantly, a multiparticulate drug delivery system is one of the strategies used for colon targeting, usually composed of hydrophilic particles of natural or synthetic polymers with cross-linker assistance to create a matrix-like network of active medicinals [7]. The current study focused on prednisolone (PRD) to be formulated as beads for colon-targeting since PRD primarily treats acute Crohn's disease and ulcerative colitis attacks. Indeed, after PRD oral administration, the highest absorbed PRD percentage was from the upper GIT, the favorable absorption site to end in the systemic circulation that deteriorates the therapeutic effect of PRD because of systemic side effects after prolonged use [8]. Thus, several studies have formulated PRD beads for colon delivery, such as Elena *et al*., who used pectin as a promising system for colon targeting [9]. Also, in a different study, the PRD beads were developed with Na-alginate and Eudragit S-100 polymer [10]. Another study used inulin, chitosan, and Na-alginate for colonic beads [11]. We wanted to make PRD beads that would stay in the colon for a long time. To do this, we first put beads into acid-resistant HPMC capsules that were made with three types of natural polymers as secondary polymers: inulin, guar gum, and pectin. Na-alginate was used as the primary polymer. The inulin, guar gum, and pectin degradation depends on normal colonic flora enzymes as well; the solubility of these polymers was affected by different pH values [12]. The second aim was to investigate the incorporation of the three secondary polymers, inulin, guar gum, and pectin, in one bead formulation. According to our knowledge, no study was done before using this combination. Third, a coating to the HPMC capsule that was already filled in beads with Eudragit S-100.

METHODS

Material

Na-alginate, inulin, pectin, and guar gum were purchased from Sigma-Aldrich-Switzerland, Transhuman Technologies-United Kingdom, Himedia Laboratories Pvt. Ltd., Mumbai, India, and Al-Kindi Co., respectively. PRD was kindly gifted from Aswar Al-Khaleej Pharmaceutical Factory, Iraq. Also, tween-80, Eudragit-S100, and $CaCl_2$ were obtained from Evonik Company, Germany, and Thomas Baker-India, respectively, and purchased from HPMC size (0) from pure CAPS USA.

Preparation of PRD alginate beads

Polymer solutions of 25 ml that contained 100 mg PRD were prepared and added dropwise using an 18-gauge disposable hypodermic needle to a 25 ml $CaCl_2$ solution while stirring for 15 minutes. The formed beads in the $CaCl_2$ solution were filtered through Whatman No. 42 filter paper. The washing step of the beads with purified water was repeated; then, the beads were spread on a Petri plate, allowing them to dry at room temperature. Finally, these beads were stored in an airtight container for later use. As shown in Table 1, different variables were included in the bead formulation: Na-alginate concentration, $CaCl_2$ concentration, tween 80 addition, and addition of secondary polymers (inulin, pectin, and guar gum) with different amounts [13].

Bead size analysis

The bead size measurement was done by taking images with a measuring ruler in cm as a reference scale of the beads using the Image J software [14]. The average size of 30 beads was recorded, and the bead's average diameter was determined using the following formula [13]:

$$X = \frac{\Sigma (Xi)}{N}$$ ---- equation 1

As the X=Average of particle diameter, Xi = Individual diameter of the beads, and N = Number of beads.

Morphological analysis of the beads

The length, width, and area of 30 randomly chosen beads from each formulation in taken images were measured using the Image J software. The shape was then determined using the elongation ratio (ER) and roundness. The ER and roundness of the beads were computed using the following equations [15]:

$$ER=\frac{\text{Major axis length}}{\text{Minor axis length}}$$ --- equation 2

Beads with ER = 1 is considered perfectly spherical, while ER > 1 indicates deviation from sphericity [16].

$$\text{Roundness} = \left(\frac{4 \times \text{Area}}{\pi \times (\text{Major axis length})2} \right)$$ --- equation 3

Table 1: Formulations of different contents of prednisolone alginate beads

Formula no.	$CaCl_2$ w/v %	Tween 80 (ml)	Secondary polymers (mg)
F1	5	5	Inulin 100
F2	5	5	Inulin 200
F3	5	5	Inulin 300
F4	5	5	Pectin 100
F5	5	5	Pectin 200
F6	5	5	Pectin 300
F7	5	5	Guar gum 100
F8	5	5	Guar gum 200
F9	5	5	Guar gum 300
F10	1	5	(Inulin+ pectin+ guar gum) 50 of each
F11	5	5	(Inulin+pectin+ guar gum) 50 of each
F12	5	0	(Inulin+pectin+ guar gum) 50 of each
F13	1	0	(Inulin+pectin+ guar gum) 50 of each

Na-alginate was 2% w/v in all beads formulations. The volume of all prepared formulations was 25 ml, and the 5 ml tween 80 addition was part of the volume.

Determination of yield (%), Entrapment Efficiency (%) and Drug loading DL (%)

The prepared beads were taken out after drying and weighed on an electric balance, where the yield percentage was calculated by comparing the final weight to the theoretical weight of the formulations according to equation 4.

$$\text{Yield\%} = \frac{\text{Actual Weight}}{\text{Theorotical Weight}} \times 100 \quad \text{---- equation 4}$$

The EE% and DL% were computed using a mortar and pestle with a precise weight (50 mg) of dry beads, then crushing beads. The crushed beads were added to 100 ml of phosphate buffer pH 7.4 and magnetically stirred continuously for 60 minutes at 500 rpm until the beads burst, swelled and dissolved completely, followed by filtration. If required, the filtrate was diluted before being spectrophotometrically examined at 245 nm using a UV Visible spectrophotometer (Shimadzu 2000, Japan) using the equations shown in *in vitro* release study to compute the EE % and Drug Loaded (DL%)

$$\text{EE(\%)} = \left(\frac{\text{Actual drug content}}{\text{Theorotical drug contnt}}\right) \times 100\% \quad \text{equation 5}$$

$$\text{DL(\%)} = \left(\frac{\text{Amount of drug loaded in the beads}}{\text{Total weight of the beads}}\right) \times 100\% \quad \text{equation 6}$$

In vitro release studies

An amount of the prepared beads equivalent to 5 mg PRD was filled in acid-resistant capsules (HPMC) and placed in stainless steel baskets suspended in screw-capped containers containing 500 mL of different media to examine the release profiles resembling the GIT environment. The beads placed within the capsules were pre-incubated for two hours in simulated gastric media at 0.1 N HCl, pH 1.2, then for four hours in phosphate buffer pH 6.8, and finally for a further twenty-four hours in phosphate buffer pH 7.4 [17]. Samples were taken at a predetermined time, then filtered and spectrophotometrically subjected to reading their absorbance at a wavelength of PRD 245 nm. The PRD amount was calculated at pH 1.2, 6.8, and 7.4, depending on y= 31.643x + 0.13443, y= 46.243x -0.0015, and y= 56.229x + 0.0077, respectively. These equations were constructed from absorbance values corresponding to different concentrations and showed high regression coefficients.

In vitro release studies at pH 4

The same procedure described previously was executed with a change of phosphate buffer pH 7.4 to acetate buffer to obtain pH 4.0 to simulate the IBD colon pH for analyzing the PRD release of selected formulations [17]. A calibration curve of PRD in pH 4 of acetate buffer at 245 nm was constructed as its equation was y = 66.291 +0.0085, and the R^2 was 0.9993.

Field emission scanning electron microscopy (FE-SEM)

The FESEM study was carried out to probe the surfaces of the selected beads using an Inspect TM F50 electron microscope that was operating at an accelerating voltage. The surface morphology was examined with different magnifications of 5 µm to 2 mm.

Fourier-transform infrared spectroscopy (FTIR)

Small amounts of pure PRD, Na-alginate, inulin, tween 80, pectin, guar gum, and the randomly selected beads were mixed with KBR to be pressed as a disc in infrared spectroscopy (Shimadzu, Japan). The collected spectrograms scanned regions from 400 to 4000 cm^{-1}.

RESULTS AND DISCUSSION

The successful beads gelation was in 13 formulations, while F4 and F6 formulations did not give beads. F4 with low pectin amount of 100 mg did not help to form beads on the other side; the high viscous pectin dispersion was like a pest in F6, which was challenging to dropwise by the syringe as the quantity of pectin was 300 mg. Indeed, the suitable pectin amount that assisted in the formulation of beads was 200 mg, as in F5. Small particles are highly promising for colon drug delivery that could improve solubility and dissolution, showing the high surface area; hence, the multiparticulate system is favorable [18]. Table 2 lists the average bead sizes for various batches; the results showed that the size of the beads varied along with the type and amount of polymer added. Still, the beads got bigger as the polymer content and tween 80 additions went up.

Table 2: Morphological properties computation of the PRD alginate beads

Formula	Particle size (mm)	Elongation	Roundness
F1	1.809	1.02	0.79
F2	1.830	1.15	1.02
F3	1.942	1.06	1.04
F5	2.367	0.78	0.64
F7	2.149	0.84	0.74
F8	2.159	0.87	0.65
F9	2.745	0.89	0.73
F10	2.173	1.26	1.03
F11	2.333	1.37	0.99
F12	1.218	1.03	1.02
F13	1.213	1.06	1.0

This could be because there were two polymers in the mixture. A study of beads formulated from S. tura gum, guar gum, and locust bean gum showed the same trend of increased size with an increase in the amount of the polymer [19, 20]. Despite the differences in bead size, the HPMC capsule was filled with beads equivalent to the PRD amount for all the successful formulations. A spherical shape can provide reasonable control over the processes of drug dosage manufacturing. Additionally, the more spheres bead in shape, the more aesthetic requirements there are in the drug industry [21]. Bead sphericity was measured regarding elongation and roundness, as shown in Table 2, and representative images of prepared beads are illustrated in Figure 1.

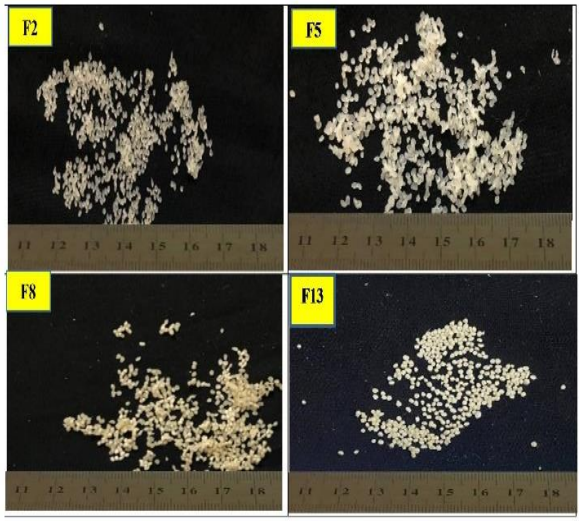

Figure 1: Images illustrated the morphology of PRD alginate beads as all beads images scaled against the ruler in centimetres.

The results showed that the shape of the beads got better as the amount of inulin went up, as seen in F1, F2, and F3. On the other hand, by lengthening and making the pectin beads F5 less round, all of the guar gum beads had a low circularity ratio. Further, the beads of the three polymers, F10 and F11, exhibited the best circularity properties. To sum up, the beads with high amounts of inulin and those containing the three polymers with no tween 80 gave the best morphology. The yield%, EE%, and DL% are essential to count, representing the bead's constitution and drug entrapment. As seen in Table 3, generally from F1 to F13, the yield%, EE%, and DL% increase in their values as the amount of the secondary polymer increased. The best result was in F13, composed of the 3 polymers, and interestingly, the tween 80 was not included, and the $CaCl_2$ concentration was decreased to 1% w/v. We think the absence of tween 80 assisted in constituting beads of tightly cross-linked polymers with no water attraction, which is the tween 80 property, to the inside of the beads. Additionally, the 1% w/v $CaCl_2$ in this F13 was very suitable, as revealed in the increased yield%, EE%, and DL% values. A similar observation of the appropriate $CaCl_2$ concentration in the pectin beads led to the loss of beads when the $CacCl_2$ solution concentration changed from 100 mm to 300 mm [22]. Different studies showed that adding pectin to Na-alginate increased the ranitidine encapsulation of the beads [20].

Table 3: The yield%, EE%, and DL% of successful alginate beads formulations

Formula	EE%	DL%	Yield%
F1	46.4	1.56	57.2
F2	58.7	1.68	58.62
F3	63.18	1.76	60
F5	28.06	1.16	40.4
F10	64.77	1.76	60
F11	45.34	1.27	58.2
F12	69.2	2.86	89.3
F13	75.88	10.53	96

This positive effect on entrapment could be attributed to the two protective layers of polymers in bead formulations that assisted in keeping the PRD [23]. It was F13 that had the best yield%, EE%, and DL% results because it had all three polymers, a low concentration of $CaCl_2$ solution, and no tween 80. The *in vitro* release investigation of beads at different pHs (1.2, 6.8, and 7.4), which represent the gastrointestinal segments of gastric media, small intestine media, and colon media, respectively, was essential for our research work to investigate the beads' ability to last until colon media [24]. This study excluded the guar gum beads F7, F8, and F9 due to their non-bead-like structure and transparent appearance. PRD release at different pHs was applied by loading the prepared beads in the HPMC capsule to overcome the release of PRD in gastric environments. The *in vitro* release studies in Figures 2, 3, 4, and 5 indicated no PRD was released at pH 1.2. Starting with Figure 2, the results of F1 and F2 contained 100 mg and 200 mg of inulin, respectively, which released the PRD to the pH media at 7.4, whereas F3 (inulin 300 mg) burst the whole PRD at 6.8. Ati *et al*. looked into the beads made from inulin and alginate polymers together. At pH 6.8, they found beads that were unstable and had a lot of holes in them. These findings support the idea that having a lot of inulin in the network makes the egg box structures less stable.

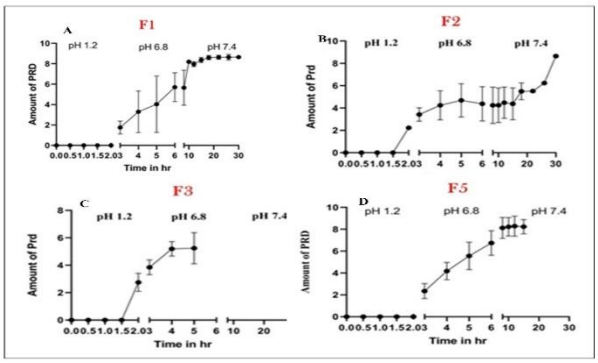

Figure 2: *In vitro* PRD beads release in pH 1.2, 6.8 and 7.4 for 30 hours with different amounts of the secondary polymer inulin, (A) 100 mg amount of inulin (B) 200 mg amount of inulin (C) 300 mg amount of inulin (D) 200 mg of pectin beads: 5% w/v $CaCl_2$, 2% w/v Na –alginate and 5 mL tween 80.

This makes the polymeric networks weaker until they break down at pH 6.8, which makes it easier for all the material inside to be released [25]. Also, the results showed that F1 and F3 released more than 5 mg of the acquired amount, which was not seen in F3. Thus, F3 was chosen for further upcoming studies to sustain the PRD release. Also, Figure 2 regarding the beads of pectin in F5 (pectin 200 mg) presented good PRD persistence at pH 7.4, but with high PRD release. This agreed with a previous study demonstrating high $CaCl_2$ concentration during beads manufacturing, leading to slow drug release like the 5% w/v of $CaCl_2$ in F5 [26]. To conclude, the beads of pectin as secondary polymers did not achieve our goal. Figure 3 shows what happened when the concentration of $CaCl_2$ in the solution changed between F10, F11, F12, and F13 in the three polymer formulations. It wasn't possible for F10 and F11 to keep the PRD release going until pH 7.4, but F10 did a good job. This meant that a low concentration of $CaCl_2$ solution (1% w/v) could be used with the last two formulations, which were made up of the three polymers. In line with this finding and to improve the in vitro dissolution in three media, tween 80 was not added to F12 and F13 while they were being made.

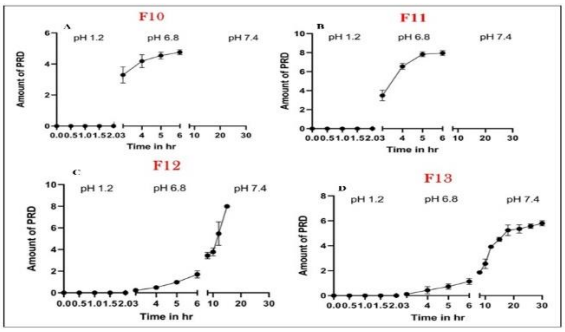

Figure 3: *In vitro* PRD release in pH 1.2, 6.8 and 7.4 for 30 hours of addition of 3 polymers (inulin, guar gum, pectin) (A) 1% w/v $CaCl_2$ (B) 5% w/v $CaCl_2$, 2% w/v Na-alginate with 5 ml tween 80 addition (C) 5% w/v $CaCl_2$, 2% w/v Na-alginate (D) 1% w/v $CaCl_2$, without 5 ml tween 80 addition.

As illustrated in Figure 3, both F12 and F13 persisted the PRD release till pH 7.4 with the improved total PRD content in F13, as this evidence of decreasing $CaCl_2$ concentration helped in lasting the release till pH 7.4. Further, the formulation of beads using the three polymers together by avoiding tween 80 addition enhanced the PRD content of the beads. It appears the tween 80 avoidance in F12 and F13 enhanced the persistence of PRD release, and this could be due to adding a higher surfactant concentration, making a tiny side cavity that was not seen in those with zero tween 80 concentrations. Also, the beads might distort this when they come into contact with the surface of the $CaCl_2$ solution. This could make the three-dimensional polymer matrix that forms when calcium ions touch it less stable [27]. Thus, F13 showed the desired amount of PRD and was chosen for future study in this current work. To sum up, the PRD in vitro dissolution of several formulations optimized for colon-targeting drug delivery systems had the best in vitro release profile when the $CaCl_2$ concentration was lowered to 1% w/v and tween 80 was not added, as shown in F13. Eudragit S-100 is a pH-sensitive polymer with free carboxylic groups and ester groups in its structure. It dissolves at a pH of 6 or above, protecting the drug core in the stomach and, to some extent, in the small intestine before releasing the medication in the colon [27]. And the aim of using Eudragit S-100 as a coating polymer for the HPMC capsule of F3 was the possibility of this formulation targeting the colon and preventing PRD beads from being released in the upper GIT, as this formulation showed uniform PRD loading, which is similar to the previous study that used the same aim of coating the HPMC capsule with Eudragit for the treatment of ulcerative colitis [28]. The *in vitro* release study, as shown in Figure 4, presented the coated HPMC capsule with Eudragit S-100 that already contained beads constructed of Na-alginate and inulin 300.

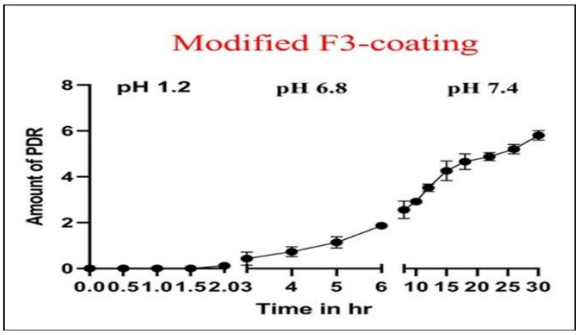

Figure 4: *In vitro drug* release pH 1.2, 6.8, and 7.4 for 30 hours of modified F3- coating.

The result revealed a good release profile, as this formulation lasted the PRD on the media with a higher pH than the uncoated HPMC capsule of F3, as the release profile did not reach the higher pH. The possibility of PRD release at a pH lower than 7 could be attributed to the probability of some cracks on the outer Eudragit S-100 coating of the HPMC capsule

that helped in the PRD leak. Inflammatory bowel diseases (IBDs) include ulcerative colitis and Crohn's disease, which lead to gastrointestinal problems and inflammation in the digestive tract. IBDs cause the intraluminal colonic pH to decrease to 2.3–5.5, and PRD is one of the drugs that treat these cases. Thus, the *in vitro* release study at pH 7.4 was replaced with pH 4. As shown in Figure 5, modified F3 (coated HPMC capsule) and F13 were subjected to *in vitro* drug release tests in pH mediums (1.2, 6.8, and 4). Both formulations do not exhibit drug release at pH 1.2, as the HPMC capsule and the Eudragit S-100 prevent PRD release in acidic media.

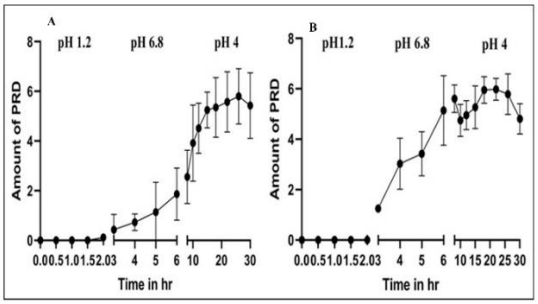

Figure 5: *In vitro* drug release pH 1.2, 6.8, and 4 for 30 hours (A) coated F3 beads, (B) F11 beads.

The release pattern of both formulations had not changed at pH 6.8; however, the modified F3 (coated HPMC capsule) showed a gradual release of PRD at pH 4, while F13 released PRD faster at pH 4 compared with the modified F3. In conclusion, both formulations, the modified F3 and F13, shield the PRD from the stomach, and PRD release started upon arrival to the small intestine and colon media to provide the local action. It could deliver site-specific release for the IBS colon. This study was used to look at the shape of the beads' surfaces, as seen in Figure 6. Images of the chosen beads (F13 and F3 from Table 1) were taken at different magnifications, ranging from 5 to 2000 µm, to help compare and describe their surfaces. The results showed clear differences in the outside structure of the beads that were studied. Images scaled at 5 and 100 µm showed that F13 had a surface with many small scattered particles that looked like they had been smashed, while F3 had a surface that was wrinkled. At a scale of 500 µm and 2 mm, the images of F13 showed the structure of the beads; still, the surfaces were covered with tiny particles that stayed at the surface. The F3 at low magnifications presented smooth surfaces, which were wrinkled at high magnifications. Like F13, in another study by Nachiket Patel and his group, Na-alginate-bead-coated cellulose acetate phthalate surfaces were rough and sandy [13]. In addition, the F3 containing inulin as a secondary polymer's surface was close to a different study surface for inulin beads [13]. In conclusion, the findings of the SEM investigation demonstrate that two images of the studied formulations showed an approximately spherical shape of the generated beads with different surfaces that might be related to the secondary polymer in the formulations.

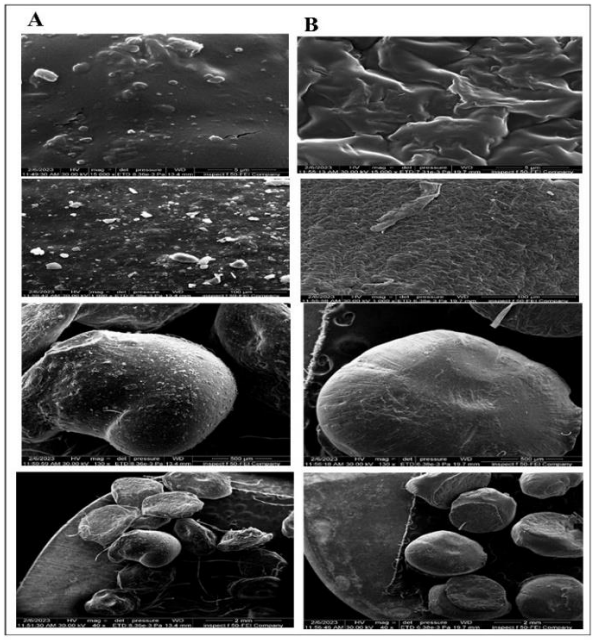

Figure 6: SEM images where Columns A and B represented F13, F3 (uncoated formulation) respectively in magnification scale of 5 µm, 20 µm, 500 µm, and 2 mm.

The functional groups expected to be involved in inter- or intramolecular interactions are the hydroxyl and carbonyl groups of all polymers, including pectin, inulin, guar gum, and Na-alginate; thus, this study applied, as shown in Figure 7, to selected beads that showed better *in vitro* release profiles. The pure polymer spectrograms in Figures 7 (A) and (B) focus on the areas of hydroxyl and carbonyl groups. We start with the hydroxyl groups. The peaks related to the hydroxyl group in the F13 and F3 spectrograms disappeared compared with their pure spectrograms, indicating the high possibility of the hydroxyl group's interaction between molecules of all polymers in F13 and F3, which assisted in beads formation; this outcome was similarly reported by Dakhil *et al.* [29]. The same trend was observed with the carbonyl groups that are part of the carboxylic group and were observed in all spectrograms of pure polymers; however, these peaks in F13 and F3 shifted as this indicated hydrogen bonding with different molecules. This shift in the carbonyl group was mentioned in a further study indicating hydrogen bonding [30]. The pure PRD spectrogram presented the peaks associated with the stretching of the hydroxyl and carboxyl groups. The peak related to the hydroxyl group almost vanished, and the carbonyl-related peak shifted from 1708 to 1725 cm^{-1} and 1734 cm^{-1} compared with the spectrograms of F13 and F3, respectively. Both changes suggested an interaction of hydrogen bondings [29], as these changes suggested hydrogen bonds of PRD with different polymers that might assist PRD capture within beads [31].

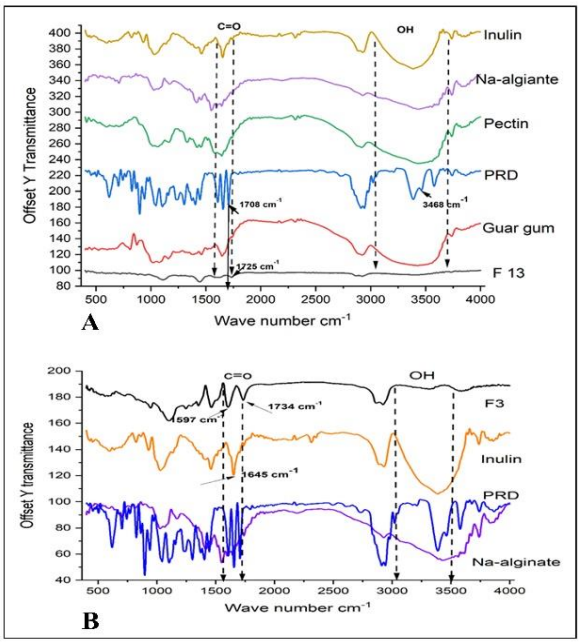

Figure 7: A and B Spectrograms of inulin, Na-alginate, pectin, PRD, guar gum and F13 with F3, respectively, pointed to both regions of carbonyl and hydroxyl group.

Conclusion

The size of the beads varied along with the type and amount of polymer added, but all formulations successfully filled the HPMC capsule. The beads with high amounts of inulin and those containing the three polymers with no tween 80 gave the best morphology, while beads of guar gum and the pectin beads gave bad morphology. The best formulation was that included inulin, pectin, Guar gum, and Na-alginate. Decreased $CaCl_2$ concentration to 1% w/v, without tween 80 addition gave the best yield%, EE%, and DL% and the best *in vitro* release profile that ensure reach to the colonic media.

Conflicts of interest

There are no conflicts of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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