Effect Of Different Variables on The Formulation of Sodium Alginate Beads Using Prednisolone as Model Drug

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Abstract :

In this study, the possibility of encapsulating prednisolone in Na-alginate polymeric beads was investigated, as well as several factors and how they impacted the characteristics of the beads. The beads were formulated by ionotropic gelation technique, in which the Na alginate, the main polymer, was gelled with calcium ions serving as counter ions. This process created beads instantly. Eleven formulations were successfully completed, and different variables were evaluated, including Na-alginate concentration (0.5, 2, 3) w/v %, $Cacl_2$ concentration (1, 3, 5) w/v %, stirring speed (100, 300, 400) rpm, the addition of tween-80 (0, 2.5, 5) ml, washing beads with alcohol, and change curing time. The beads were assayed by bead size, morphology, drug loading, encapsulation efficiency, yield, and Fourier transform infrared (FTIR) spectroscopy. The findings demonstrated that the optimum formula was F2, which delivered a maximum EE% of 39.3. This is achieved by employing a high concentration of Na-alginate (2 w/v%), $Cacl_2$ (5 w/v%), and the addition of tween-80 (5 ml) with the slowest stirring speed (100 rpm) without increasing curing time or washing with alcohol. Also, the FTIR result revealed a shifting of the carbonyl group and a low intensity of the hydroxyl group in the spectrogram of F2, indicating potential hydrogen bond interactions that might have resulted in the creation of beads. In conclusion, $Cacl_2$ and polymer concentration are the major variables that impacted the characteristics of alginate beads together with various other variables.

Keyword: Ionotropic gelation method, Sodium alginate, prednisolone, calcium chloride, beads.

تأثير المتغيرات المختلفة على تحضير حبيبات الجينات الصوديوم باستخدام البردنيزولون كنموذج دوائي

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الخلاصة:

في هذه الدراسة، تم فحص إمكانية تغليف بريدنيزولون في حبيبات بوليمرية من ألجينات صوديوم، بالإضافة إلى العديد من العوامل وكيفية تأثيرها على خصائص الحبيبات. تمت صياغة الحبيبات باستخدام تقنية الهلام المؤين، حيث تم تبلور، ألجينات صوديوم وهو البوليمر الرئيسي، مع أيونات الكالسيوم التي تعمل كأيونات مضادة. هذه العملية خلقت حبات على الفور. تم الانتهاء من إحدى عشرة صيغة بنجاح، وتم تقييم متغيرات مختلفة، بما في ذلك الجينات الصوديوم % w/v (١, 3, 5)، كلوريد الكالسيوم % w/v (٠,٥,٢,٣)، سرعة التحريك (١٠٠، ٣٠٠، ٤٠٠) دورة في الدقيقة، إضافة توين ٨٠ (٠ ، ٢,٥ ، ٥) مل ، غسل الخرز بالكحول ، وتغيير وقت المعالجة. تم تقييم الخرزات من خلال حجم الخرزة،

والتشكل ، وتحميل الدواء ، وكفاءة التغليف ، والمحصول ، والتحليل المطيافيه للأشعة تحت الحمراء (FTIR). أظهرت النتائج أن الصيغة المثلى كانت F2 ، والتي أعطت كفاية طاقة بحد أقصى ٣٩,٣٪. يتم تحقيق ذلك من خلال استخدام تركيز عالٍ ، ألجينات صوديوم ٢%,وكلوريد الكالسيوم ٥%، وإضافة توين ٨٠ (٥ مل) مع أبطأ سرعة تحريك (١٠٠ دورة في الدقيقة) بدون زيادة وقت المعالجة أو الغسل بالكحول. أيضًا ، كشفت نتيجة FTIR عن تحول في مجموعة الكاربونيل وشدة منخفضة لمجموعة الهيدروكسيل في مخطط الطيف لـ F2 ، مما يشير إلى تفاعلات رابطة الهيدروجين المحتملة التي ربما أدت إلى تكوين الخرز. في الختام ، فإن تركيزكلوريد الكالسيوم والبوليمر هما المتغيرات الرئيسية التي أثرت على خصائص خرز ، ألجينات صوديوم مع العديد من المتغيرات الأخرى.

الكلمات المفتاحيه: طريقة الهلام المؤين، ألجينات صوديوم، بريدنيزولون ، كلوريد الكالسيوم ، خرزات

1- Introduction

Nowadays, most drug delivery systems employ biodegradable, biocompatible, natural biopolymers with rate-controlled drug release capabilities. These systems use solid dosage forms to provide various sustained and controlled release dosage forms by encasing the drugs in natural polymer and creating a gel or beads (1). To demonstrate: the muliparticulat beads dosage form are strongly cross-linked, spherical, hydrophilic particles as a drug matrix. Beads are made up of natural or synthetic polymers that have been cross-linked using a cross-linking agent to create a matrix-like network of active medicinal components (2). Multiparticulate systems have the lowest dosage dumping, the shortest stomach residence duration, and precise release patterns (3). Alginate is one of the most studied natural polysaccharides because of its cytocompatibility, biocompatibility, biodegradability, and sol-gel transformation capabilities (4). It is a linear polysaccharide copolymer in repeating units composed of guluronic (G) and mannuronic acid (M). These units create areas of M- and G-blocks and alternate structures (MG-blocks). Certain divalent (Ca, Zn, and Ba) or trivalent (Fe(III) and Al) cations can fastly interact with G-blocks of alginate, producing a 3D network in the well-known "egg-box" pattern (5). Thus, several studies formulated beads using alginate polymer, such as Sun X, L *et al*, which prepared 5-fluorouracil as microbeads for colon-targeted that based on alginate as a drug carrier. (6); also, Armutcu C, P *et al*. developed a drug delivery system based on alginate beads to treat autoimmune diseases using hydroxychloroquine as drug modeling (7). Another study was done by SY Raut, A *et al*. that formulated beads using prednisolone as drug loaded into beads (8).

Prednisolone(PRD) is a common glucocorticoid used to treat a variety of auto-immune and inflammatory conditions; nevertheless, when PRD is given orally, a significant proportion of the medication is absorbed from the upper gastrointestinal tract and reaches the systemic circulation that leads to systemic adverse effects including osteoporosis, hypertension, and adrenosppression are also brought on (9). In this work, calcium alginate gel beads containing PRD as a drug model were formulated and looked into the effect of different variables (alginate concentration, $Cacl_2$ percentage, stirring rate, tween 80 addition, washing with alcohol and curing time) on the PRD entrapment and loading percentage.

2- Experimental

2.1- Materials:

Na-alginate was purchased from Sigma-Aldraich-Switzerland. Prednisolone (PRD) was kindly gifted from Aswar Al-Khaleej – Iraq. Also, $Cacl_2$ was obtained from Thomas Baker-India.

2.1.1- Methods:

2.1.2- Preparation of Na-alginate beads loaded with PRD:

According to (Table- 1), alginate beads were prepared by making a polymer-drug solution using the ionotropic gelation method and with the help of a magnetic

stirrer at a different rotation speed and temperature of 50°C. Na-alginate was weighed and added to the beaker to be mixed with 25 ml of either water or water with tween- 80. This mixture was continuously stirred for an hour to generate a transparent viscous dispersion. Afterwards, 100 mg (PRD) was added to the transparent dispersion, the amount used in all formulations and the mixture was stirred until the drug particles dispersed. Using an 18-gauge disposable hypodermic needle, polymer solutions was added dropwise to the $Cacl_2$ solution with stirring for 15 minutes. The beads were then recovered by decantation and thoroughly cleaned with distilled water to eliminate extra Ca^{2+} ions that were unentrapped (10); this washing was for all formulations except F11, washed with alcohol to investigate the ability of further stabilization and hardening of the alginate network (11). Then the beads were filtered by (Whatman No. 42) filter paper. The beads were spread out on a Petri plate and allowed to dry at room temperature; after drying, the beads were stored in an airtight container for subsequent use (12).

Table 1: Formulation of different contents of beads, including process variables

Formula no.	$CaCl_2$ w/v %	Na-alginate w/v %	Stirring speed (rpm)	Tween 80 (ml)
F1	1	2	100	_
F2	5	2	100	5
F3	1	2	100	5
F4	3	2	100	5
F5	5	3	100	5
F6	5	0.50	100	5
F7	5	2	400	5
F8	5	2	300	5
F9	5	2	100	2.5
F10	5	2	100	5
F11	5	2	100	5

* **F10 left for 15 min in** $Cacl_2$ **before filtration.**
* **F11 washing with alcohol**
* **All formulations contained PRD 100 mg.**
* **The volume of all prepared formulations was 25 ml, and the 5 ml tween 80 addition was part of the volume.**

3- Characterization of the prepared beads:

3.1- Bead size analysis:

A digital camera was used to take images of the beads spread on a dark background while the measuring meter was present as a reference scale (13); the bead size was measured using the Image J software (14). A measurement of 30 beads' average size was made. Using the equation below to calculate the average beads diameter.

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

X = Average of particle diameter, Xi = Individual diameter of the beads, N = Number of beads (12).

3.2- Morphological analysis of the beads:
The dimensions of 30 randomly selected beads from each formulation were calculated using the Image J program using digital camera images, including their length, width and area. Afterwards, the elongation ratio (ER) and roundness were used to define the bead's morphology. The following equations (16) were used to calculate the ER and bead roundness (15):

$$\mathbf{ER}=\frac{\textbf{Major axis length}}{\textbf{Minor axis length}} \qquad \textbf{equation 2}$$

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

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

3.3- Determination of yield percentage, Entrapment efficiency (%EE) and Drug loading (%DL):
The prepared beads were removed from the filter paper and weighed using an electric scale. By comparing the final weight to the theoretical weight of the formulations, the yield % was in this case computed.

$$\textbf{Yield\%}= \frac{\textbf{Actual Weight}}{\textbf{Theorotical Weight}} \textbf{ x 100} \qquad \textbf{equation 4}$$

Entrapment efficiency (%EE) and Drug loading (%DL) were calculated to estimate the drug loaded into alginate beads. 50 mg of dry beads were accurately weighed and crushed using a mortar and pestle. The mixture was filtered after adding the crushed beads to 100 ml of phosphate buffer pH 7.4, which was magnetically agitated continuously for 60 minutes at 500 rpm until the beads burst, swelled, and dissolved. In order to compute the (EE%) and (DL%), a UV Visible spectrophotometer (Shimadzu 2000, Japan) was used after the filtrate had been diluted reads at a wavelength of PRD 245 nm (17).

$$\textbf{\%EE} = \left(\frac{\textbf{Actual drug content}}{\textbf{Theorotical drug contnt}}\right) \textbf{x 100\%} \qquad \textbf{equation 5}$$

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

3.4- FTIR spectroscopy
A possible interaction between the PRD and the Na-alginate polymer was evaluated using the FTIR analysis. For this purpose, KBR was combined with tiny quantities of pure PRD, Na-alginate, and the crushed chosen beads to press the mixture as a disc for infrared spectroscopy (Shimadzu, Japan). The obtained spectrograms scanned regions between 400 and 4000 cm-1 (18).

4- Results and Discussion:

4.1- Preparation of PRD alginate beads:
Eleven bead formulations were created successfully, and different variables were used for beads evaluation to illustrate their effect on bead formulation.

4.2- Bead size analysis:
As shown in (Table -2), the results demonstrated a direct relationship between increasing the concentrations of both Na-alginate and $Cacl_2$ with tween-80 addition resulting in larger beads in size. It was found that larger size of droplets was produced when the polymer concentration

increased and viscosity increased during the preparation of beads solution (19, 20), as this increases the chances of the Na-alginate molecules bound firmly with the help of $Cacl_2$, the cross-linking agent. Also, producing larger beads size might refer to the potential of high-degree crosslinking (12, 21, 22).

This result excludes F10 and F11 because F10 was kept in $Cacl_2$ solution for another 15 minutes (30 minutes) and showed a decrease in bead size. This finding was similar to a different work, as more extensive residence in $Cacl_2$ caused the bead diameter to decrease (23). Moreover, the washing beads in F11 using alcohol reduced bead size, which might refer to Na-alginate's insoluble nature in ethanol. Lij *et al.* used ethanol in beads washing and found a more packed polymer matrix resulting in decreased beads size and a contraction in the physical appearance (24).

Table 2: Morphological properties of the PRD alginate beads

Formula	Particle size in(mm)	ER	Roundness
F1	1.204	1.071	1.05
F2	1.466	1.18	1.04
F3	1.454	1.12	1.08
F4	1.308	1.08	1.14
F5	1.348	0.95	1.15
F6	1.124	0.85	0.89
F7	1.438	1.34	0.88
F8	1.452	1.24	0.94
F9	1.254	1.05	1.15
F10	1.248	1.04	1.1
F11	1.252	0.96	0.86

4.3- Morphological analysis of the beads:

The more beads resembling spheres, the more aesthetic standards are in pharmaceutical processing. Images with two-dimensional information were used to measure the elongation and roundness of beads, as shown in Figure 1. Every item with elongation and roundness values of around 1 has the shape of a perfect circle (15). From F1 to F11, most beads had an acceptable circularity ratio (elongation and roundness). Similar to our findings, earlier research showed calcium chloride concentration has no discernible impact on the shape of beads as F2, F3, and F4 showed the same circularity range values (25). As well, F1, F2, F9, and F10, the inclusion of tween 80 had no impact on the circularity characteristics. Unlike, the rise in Na-alginate concentration made the beads more uniformly shaped and spherical, as shown in F2, F5, and F6, and this outcome likewise Busic *et al*. study (26).

Further, an excellent round shape was produced by reducing the stirring speed to 100, as in F2, compared to F7 and F8, as their RPMs were 400 and 300, respectively. Lee coworkers studied the same factor (the stirring rate) and stated that reducing the rotation of the $Cacl_2$ solution achieved a high circularity ratio (23). Also, the beads had a non-circular form, as illustrated in F11, when rinsed with alcohol as the elongation value was greater than 1, and the roundness was less. In a nutshell, the beads with high amounts of Na-alginate and $Cacl_2$ solution showed the best circularity.

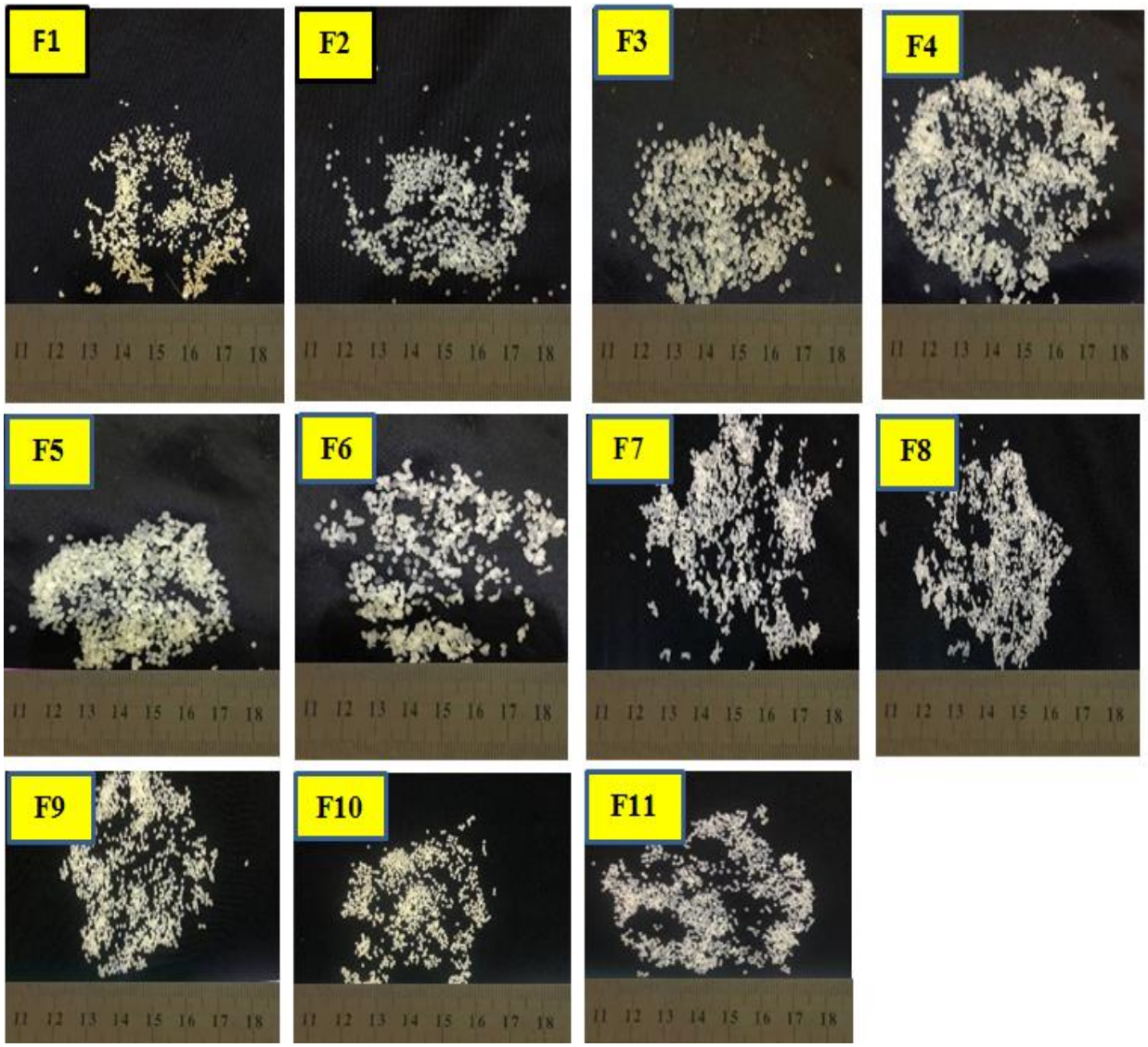

Figure 1: The images used for measuring the morphology values of PRD alginate beads as all bead's images scaled against the ruler in centimetres

4.4- Determination of yield%, entrapment efficiency and drug loading:

According to (Table-3), formulations F1 to F11 results related to yield% showed that a greater polymer concentration provided a better yield. It was noticed that F1 showed the maximum yield% of the beads formulated without tween 80. Also, prolonged curing times, higher Na alginate concentrations and calcium chloride concentrations slightly increased the yield percentage, as in F2, F3, F4, F5, F6 and F9. These results explained the variations in the intensity of cross-linking between the beads, which depend on the diffusivity of the cross-linker solution in the polymer droplet and whether calcium ions can consolidate the alginate-polymer chains into an egg-box shape (12).Another primary variables affecting the bead yield during crosslinking is the stirring rate, with extremely high stirring rates thought to cause a decrease in the yield (13).

The entrapment efficiency for the formulations varied between (3.99_39.3) %, and the low drug entrapment efficiency obtained as the concentration of Na-alginate and $Cacl_2$ solution were decreased; this may be related to drug leakage into the cross-linking solution because of the alginate-

polymer matrix's high porosity and low density as showed in F6. Other studies have discovered this decrease in Na-alginate and $Cacl_2$ caused medication loss when alginate beads are made via ionotropic gelation (12). Further, the addition (5ml) of tween 80 led to an increase in the EE%, similar to the curcumin's encapsulation efficiency, which was improved by adding surfactants and polysaccharides in the complexes(27).

Drug loading was shown to be very limited and within the range (of 0.41 to 1.48) % in all formulations; the cause of this result was that when the beads use Na alginate as a carrier often have the high porosity of the alginate matrix (28), which permits drugs to leach out beads. Additionally, other researchers have observed similar findings (12, 29).

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

formula	Yield%	EE%	DL%
F1	96	11.49	1.7
F2	50.42	39.3	1.35
F3	46.6	29.1	1.05
F4	43.47	21.55	0.82
F5	55.4	24.03	1.13
F6	16.3	3.99	0.41
F7	43.5	25.09	0.96
F8	46.4	30.11	1.13
F9	42.7	18.51	1.25
F10	52.6	38.2	1.82
F11	36.2	31.9	1.48

4.5- (FTIR) spectroscopy:

This study was conducted as evidence for beads formation at the level of the molecules, and F2 was chosen for this study. As shown in Figure 1, the FTIR analysis revealed the peak associated with the hydroxyl group in Na-alginate and PRD, corresponding to the low intensity of this peak in F2, as this was determined previously, indicating potential hydrogen bondings (30). Further, the carbonyl group, another functional group, was visible in the spectrograms of Na-alginate and PRD but with shifting positions as found in the spectrogram of F2, indicating potential hydrogen bond interactions that may have contributed to the formation of beads. Similar findings were similar to Kaddoori et al.,
as they attributed this shift to intermolecular hydrogen bonds (31).

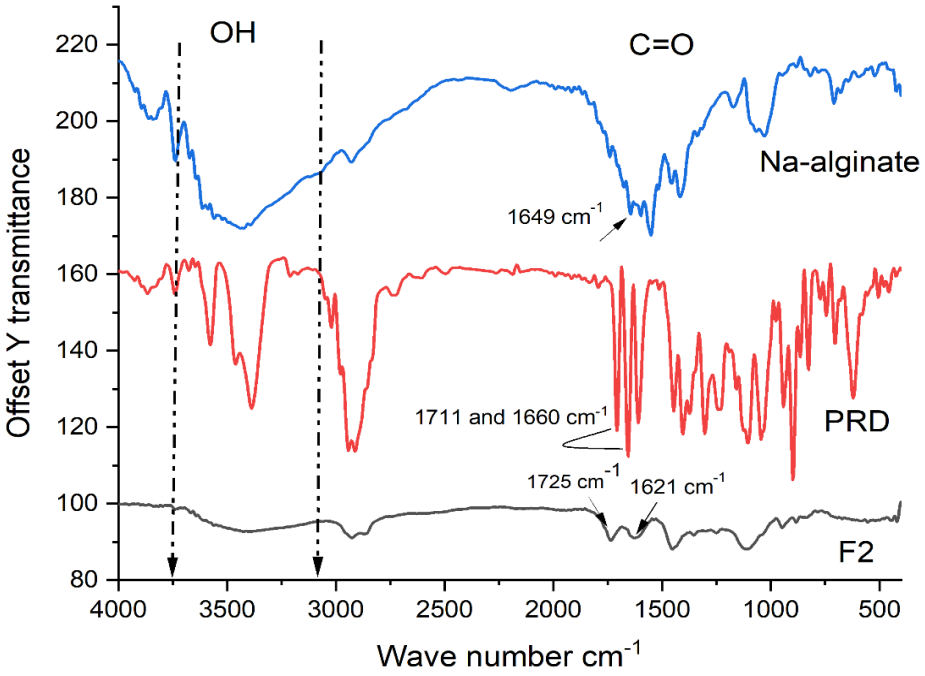

Figure 2: Spectrograms of Na-alginate, PRD, and F2 as this Figure pointed to both regions of carbonyl and hydroxyl group (1626 -1732 cm^{-1}) and (3000 to 3600 cm^{-1}), respectively.

5- Conclusion

The results indicated that the ionotropic gelation method successfully manufactured PRD beads using Na-alginate as a sole polymer. The most important variables affecting beads properties were $Cacl_2$ and Na-alginate concentration. From eleven bead formulations that were manufactured successfully, F2 was the formula with the best features as they were small spherical shape having the greatest EE% that was obtained when using a high concentration of Na-alginate, $Cacl_2$ solution, the addition of 5 ml of tween 80 and 100 rpm. Also, FTIR results presented possible interactions between Na-alginate molecules through carbonyl and hydroxyl groups.

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