Jordan Journal of Pharmaceutical Sciences, Volume 15, No. 4, 2022

Preparation and Characterization of Hydrogel Beads for Controlled Release of Amoxicillin

Rasha Almasri*[1], Amin Swed[2], Haifaa Alali [1]

[1] Department of Pharmaceutical Chemistry and Quality Control, Faculty of Pharmacy, Albaath University, Syrian Arab Republic.
[2] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Albaath University, Syrian Arab Republic.

ABSTRACT

Amoxicillin trihydrate-loaded hydrogel beads were prepared and characterized as a controlled drug delivery system to improve patient compliance. An ionotropic gelation process was used to prepare the hydrogel beads using calcium chloride (CaCl2) as a crosslinking agent. The effects of CaCl2, sodium alginate, poloxamer 407 (PL) concentration, and preparation temperature were investigated. Spherical hydrogel beads were obtained with high encapsulation efficiency (85.74±1.09) %. FTIR analyses confirmed the compatibility of amoxicillin with the used excipients. In vitro swelling and cumulative drug release studies were performed over 24 hours in HCl medium, pH 1.2. Prepara-tion temperature was found to influence both the index of beads swelling (SI) and the cumulative release of amoxicil-lin. The study demonstrated the capability of PL to enhance the cumulative release of amoxicillin, correlating with swelling behavior. The proposed hydrogel beads have the potential as a promising drug delivery system for controlled release of amoxicillin, over 24 hours, and thus reduced dosing frequency.

Keywords: Controlled drug delivery, Sodium alginate, Hydrogel beads, Poloxamer 407, Amoxicillin.

INTRODUCTION

Amoxicillin trihydrate (α-amino-hydroxybenzyl penicillin) is a semisynthetic, orally absorbed, broad-spectrum antibiotic [1]. It is used to treat many infections, such as respiratory, urinary, and genital infections [2]. Amoxicillin has been widely used in triple therapy for gastric *Helicobacter pylori* infection in combination with a second antibiotic and a proton pump inhibitor [3], [4]. It has a short half-life of 61 min, thus it has been used at 500 mg every 8 hours [5]. Because of the high patient compliance, Llor *et al* mentioned that nearly 80% of users did not adhere to the amoxicillin dosage regimen [6]. Controlled drug delivery systems have many advantages over the immediate release dosage forms including (i) the reduction in drug plasma level, fluctuation and adverse side effects, (ii) the improvement in patient tolerability and compliance, (iii) and finally, the reduction in healthcare costs [7].

Hydrogels are of special interest in the development of controlled drug delivery systems due to the ease of drug dispersion in their matrices, their soft tissue biocompatibility and the high level of controlling the drug release compared to other systems [8]. Hydrogels are crosslinked polymers capable of absorbing a large volume of water due to the abundance of hydrophilic groups in their network structure. [9]. In the controlled swelling systems, a drug is dispersed in the polymer, however, when the water uptake occurs the polymer swells and the drug diffuses out. The release rate of drug depends on the rate of water diffusion and chain relaxation [9]. Hydrogels are being used for the encapsulation of several drugs as drug delivery vehicles and controlled release systems for different medicines including amoxicillin [10]. Moreover,

*Corresponding author: Rasha Almasri
r.almasri@albaath-univ.edu.sy
Received: 21/8/2020 Accepted:19/3/2022.
DOI: https://doi.org/10.35516/jjps.v15i4.675

Narkar and co-workers have successfully employed gellan hydrogel beads as an effective vehicle for the sustained delivery and release of amoxicillin [11].

In this study, hydrogel beads have been formed using sodium alginate (SA). SA is a linear polysaccharide copolymer which is composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) of repeating units linked by a 1→4 linkage [12]. SA can be composed of one or more units, or alternating sequences of M blocks, G blocks, or heterogeneous blocks of MG [13]. It is rich in carboxylic groups, which facilitate the formation of a three-dimensional gel structure (or so-called Egg box model). This can be achieved by interacting with multiple many positive triple or double electrolytes such as barium, zinc, aluminum and finally calcium (Ca) which is preferable due to its non-toxicity [12].

However, there are some problems challenged the drug release from Ca-sodium alginate matrix. First, the low of encapsulation efficiency during the crosslinking process (gel formation) which is time-consuming (i.e. takes long time). Second, the gel porosity which could result in a burst release of the loaded drug [14 15]. Therefore, many efforts are being currently made to improve the performance of Ca-sodium alginate hydrogel beads as controlled drug delivery carriers [15]. The attempts include the addition of other polymers, such as, chitosan and sodium carboxymethyl cellulose (Na CMC) [16].

In this research, poloxamer 407 (PL) (Pluronic F127) was added, a non-ionic and a synthetic triblock copolymer consisting of poly (oxyethylene-propylene oxide- ethylene oxide) (POE-POP–POE) where POE units is 70% and POP units is 30% [17]. PL is being currently employed in mucosal drug delivery because of its thermo-sensitive properties at the physiological temperature [18 19].

PL has a low toxicity [17], therefore it can be used for developing injectable drug delivery depot matrices [20 21]. Because of its thermal sensitivity, PL has been used for controlled drug delivery system. However, the excess of aqueous fluids causes the packed PL micelles to dissociate resulting in a loss of gel integrity [17]. Considering the mentioned challenges of both polymers, PL was added during the crosslinking process to improve the performance of hydrogel beads as a drug carrier. This was found to increase encapsulation efficiency and improve the controlled release of amoxicillin.

MATERIAL AND METHODS

Sodium alginate extracted from Laminaria Hyperborea with MW of 1.97 × 105 and M/G ratio of 0.59 was purchased from BDH Chemicals Limited, UK. Amoxicillin trihydrate was purchased from DSM Sinochem Pharmaceutical India Pvt. Ltd, India. Poloxamer 407 was purchased from BASF, USA. $CaCl_2$ was purchased from Eurolab, Great Britain. Water used to be of high purity deionized and double distilled. All other chemicals used were of analytical grade.

Preparation of hydrogel beads

Hydrogel beads were prepared by ionotropic gelation method using (1, 5, 10) % $CaCl_2$ concentration as a cross-linker. Briefly, sodium alginate was hydrated into 100 mL of distilled water overnight. Two g of amoxicillin were dispersed in the alginate solution and stirred with magnetic stirring to form a viscous coarse dispersion. Six mL of the resulting dispersion was then dropped into 60 mL of $CaCl_2$ solution (as gelling agent) at 15 and 25°C. Considering that temperature affects the viscosity of suspensions and solutions in our case it was necessary to consider the

temperature change as a parameter to be studied. Preliminary studies were done to compare between 25 and 4 ºC. It was found that at 4 ºC, the viscosity of the suspension was very high, and the preparation process became complicated and took a long time. So it was tried another temperatures like 15 and 25 ºC. A vibration bathroom (Biobase, China) was used to control the temperature of 15 ºC.

In some formulations, poloxamer 407 was added into $CaCl_2$ solution. Thus, hydrogel beads were formed and allowed to complete the crosslinking reaction for 30 min

before being filtered and washed once by soaking with 60 mL of distilled water. All collected hydrogel beads were finally dried in an air convection type oven (Carbolite LHT4/30, England) at a temperature of 35°C for 24 h [22 23]. Totally, 11 formulations were prepared as it showed in Table 1.

Characterization of hydrogel beads

Particle size analysis

Particle size was determined using a Trinocular stereo microscope, smz-143, Motic, China. 20 dried hydrogel beads were randomly sampled from each formulation and measured. The results were expressed as mean values ± standard deviation of 20 measurements.

Mass testing

To determine the average mass, 20 dried hydrogel beads were randomly sampled from each formulation and accurately weighted using Precise scale 320 XB balance (220A, Switzerland). The results were expressed as mean values ± standard deviation of 20 measurements.

Fourier transform infrared (FTIR) spectral measurements

FTIR spectra were obtained using Nicolet (IRAffinity-1S, Shimadzu,Japan) instrument to confirm the formation of composite structure as well as to confirm the compatibility of the drug with polymers used to prepare hydrogel beads. FTIR spectra of amoxicillin loaded hydrogel beads, placebo hydrogel beads, and pure amoxicillin were all taken by grinding them separately with KBr and making pellets under a hydraulic pressure. The spectra were acquired over the wavenumber of the range of 4000–500 cm^{-1} at ambient temperature.

Drug content

Three weighted hydrogel beads were grounded to get the powder using an agate mortar and placed in a beaker containing 25 mL of the fresh phosphate buffer pH=6.8 for 24 h to allow their complete dissolution using a shaker (Heidolph, Germany). Samples were then filtered using the Through Whatman filter paper (0.45μm). The polymeric debris was washed twice with 10 mL buffer to extract any adhered drug. The filtrate was analyzed at 272 nm by UV spectroscopy (SP-3000 Plus, Optima, Japan).

The encapsulation efficiency (EE%) and drug loading (DL%) were calculated using the following equations, respectively:

$$EE\ \% = \frac{\textbf{actual drug content in beads}}{\textbf{Theoretical drug content}} \times \mathbf{100}$$

$$DL\ \% = \frac{\textbf{actual drug content in beads}}{\textbf{weight of beads}} \times \mathbf{100}$$

Swelling study and drug release study

Swelling and release studies were carried out in HCl solution pH=1.2 (stomach condition) during 24 hours at 37±0.5°C using a USP rotating basket apparatus (ERWEKA DT 600 HH, Germany) at 100 rpm. In each experiment, 30 hydrogel beads were weighted and placed in the apparatus vessel containing 500 mL of the swelling or the dissolution medium. For the swelling study, hydrogel beads were carefully taken out at time intervals, drained with filter paper to remove excess water and weighted. Mass changes were calculated using the following equation:

$$SI\ \% = \frac{\textbf{weight swollen beads} - \textbf{weight dry beads}}{\textbf{weight dry beads}} \times \mathbf{100}$$

In a separate experiment, samples of tested medium were with-drawn at the same time intervals, filtered and the released amount of amoxicillin was determined by UV spectroscopy (SP-3000 Plus, Optima) at 272 nm.

Analysis of in vitro drug release and mechanism

In order to predict and correlate the release behavior of amoxicillin from these hydrogel beads, it was necessary to plot in different models of data treatment as follows:

1. Dependent-model method [24]. 2) Independent-model method (data analysis) [25]

Similarity factor (f_2) dissolution profile comparisons are used to assess the similarity of the dissolution

characteristics of the two formulations.

$$f2 = 50 \times \log[(1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} (R_t\text{-}T_t)^2)^{-0.5} \times 100]$$

where *n* is the number of time points, *R* is the dissolution value of the reference at time *t*, and *T* is the dissolution value of the test at time *t*.

Statistical analysis

Statistical significance was measured using the Student's t-tests and one-way analysis of variance (ANOVA). All values were presented as the mean ± standard deviation (STD). Each experiment was repeated at least three times. Values of $p<0.05$ were regarded as statistically significant (*).

Scanning electron microscopy

Scanning electron microscopy (SEM) images of the typical external structure of the dried hydrogel beads F4 were taken using Vega TC TESCAN, UK operated at an accelerating voltage of 20 kV under low-vacuum mode.

RESULTS AND DISCUSSION

Hydrogel beads size analysis

The dimensions of the amoxicillin-loaded beads were measured are an important parameter for characterizing the release rate. The beads measured 919.45±41.16 µm, 1002.58±34.11 µm, 1173.85 ±25.14 µm at 1, 5, and 10% $CaCl_2$, respectively. They were significantly impacted by the increase in $CaCl_2$ concentration, as shown in (Figure 1A) ($p<0.05$). There were consistent with a previous study [26]. Ca^{2+} cross-linkage with the poly-G and/or MG blocks generates a gel of a characteristic structure, called an egg-box structure contrary poly-M [23], which may interact with the calcium ions by synergistic interactions. Therefore, increasing the concentration of calcium ions may occupy more space within the beads, expanding their dimensions.

Similarly, SA was found to significantly affect the beads' size ($p< 0.05$), which is in agreement with an earlier study [27]. The particles measured 1173.85±25.14 µm and 1269.05±18.34 µm at 3 and 4 % SA concentrations, as depicted in (Figure. 1B). This increase can be reasoned to the improved dispersion viscosity which makes the droplet size bigger [28]. SA solution with a higher concentration, 5%, was previously investigated earlier, however, the high viscosity made the preparation process time-consuming.

Interestingly, inclusion of PL was demonstrated to significantly reduce the hydrogel beads' size ($p< 0.05$), measuring 1229.33± 20.08 µm and 1258.67±18.02 µm at 10% and 15% PL, respectively. The value however was 1359.80±23.08 µm at 5% PL, yielding insignificant amoxicillin release ($p< 0.05$). These observations correspond with previously published data [29], and can be attributed to the PL being a surfactant, that increases the intra- and inter-interactions of SA chains and thereby reduces the water molecules available between the chains. This increases the interactions between SA and amoxicillin as a consequence, resulting in an improvement of the cross-linking effectiveness between SA and calcium ions.

Furthermore, as shown in Figure. 1C, elevating the preparation temperature (from 15°C to 25°C) significantly increased the beads' size ($p< 0.05$). This can be attributed to the enhanced viscosity of the dispersion, since the lower temperatures facilitate a slower reaction of calcium ions with SA. The data is consistent with an earlier report where the hydrogel beads prepared at 8°C exhibited bigger sizes than those at a higher temperature, 25°C [30]. The statistical analysis indicated that the effect of both factors (preparation temperature and PL concentration) together was significant ($p< 0.05$), a result that could be explained by the temperature impact on the PL solution viscosity.

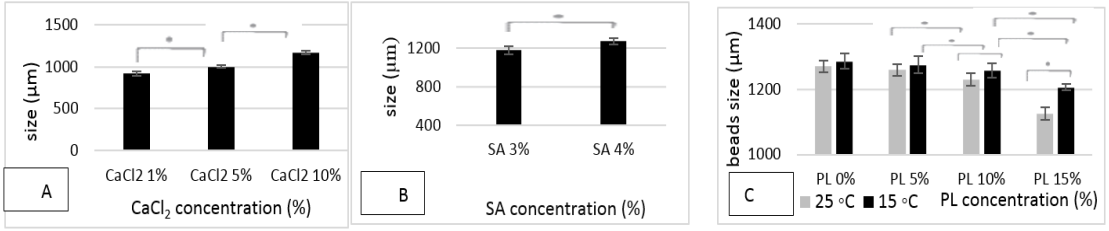

Figure 1: Determination of beads' size prepared under different condition. The effect of (A) CaCl2, (B) SA, (C) PL concentration and preparation temperature on the beads' size. The data shows the mean values ±SD (n=20). * Significantly statistical difference (p<0.05).

Hydrogel beads mass

The mass of hydrogel beads was determined to validate the earlier observations on beads' size. The beads' weighted 2.52±0.47, 3.49±0.37 and 4.35±0.29 mg at 1, 5, 10% $CaCl_2$ concentration as shown in figure 2A. As Figure. 2B presents, the average mass of dried beads at 3 and 4% SA concentrations were 4.35±0.29 mg and 5.64±0.20 mg. This can be justified by the hygroscopic properties of Ca^{2+} [23] and the hydrophilic properties of SA, which led to the corresponding increase in the droplet content of water. The concentration effect of SA was more noticeable compared to $CaCl_2$, since the molecular weight of SA is 47000-370000 g/mol [31]. A significant mass of amoxicillin was shown in (figure. 2A and 2B) using both $CaCl_2$ and SA concentrations *(p<0.05)*. As per figure 2C, the differences were significant *(p<0.05)* only at 10 and 15% PL concentrations. The beads' weighted 5.5±0.12 mg, 5.15±0.15 mg and 4.67±0.13 mg at 5, 10 and 15 PL, respectively. This could be linked to the hydrogel beads' size and their water content. Finally, the decrease in medium viscosity, achieved at the higher temperature 25°C, could be responsible for the significant drop in the beads' mass (Figure. 2C). The statistical analysis indicated that the effect of both factors (preparation temperature and PL concentration) together was significant (p< 0.05).

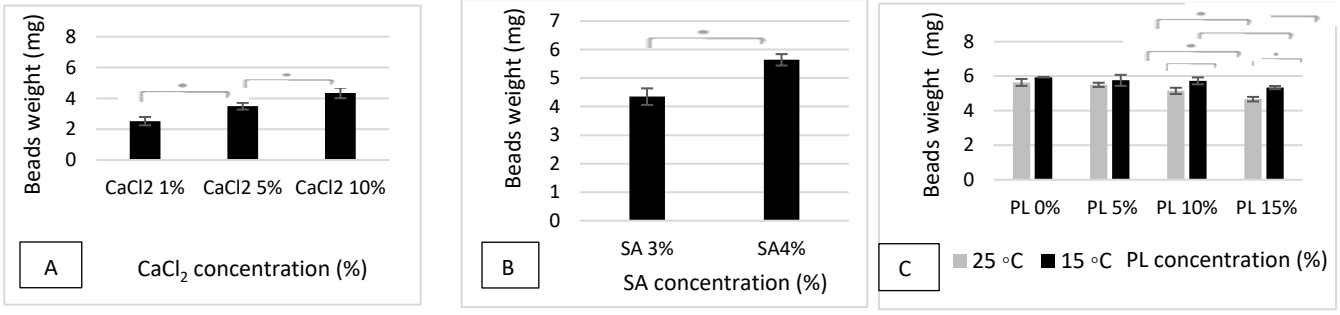

Figure 2: Determination of beads' mass prepared under different conditions. The effect of (A) $CaCl_2$, (B) SA, and (C) PL concentration and preparation temperature on the beads' mass. The data shows the mean values ±SD (n=20). * Significant statistical difference *(p<0.05)*.

FTIR spectroscopy

The FTIR spectra of (a) amoxicillin only, (b) alginate placebo beads, (c) amoxicillin-loaded alginate hydrogel beads, (d) alginate and PL beads, (e) amoxicillin-loaded alginate and poloxamer beads are shown in Figure 3. The major peaks of amoxicillin were observed in the pure

powder, F4, spectrum A and F9 spectra. In F4 spectrum, the peaks are recognized at 3460 cm^{-1} (OH of amoxicillin and SA) (peak-1 in Figure 3C), 2970 cm^{-1} (CH of amoxicillin and SA) (peak-2 in Figure 3C), 1778 cm^{-1} β lactam CO stretch (peak-3 in Figure 3C), 1640 cm^{-1} (carboxylic C=O to amoxicillin and SA) (peak-4 in Figure 3C), 1519 cm^{-1} (benzene ring C=C stretch) (peak-5 in Figure 3C), and finally 1334 , 1257 , 1284 and 1028 cm^{-1} (CO either of amoxicillin and SA) (peaks 6, 7, 8. 9 in Figure 3C). This results were compatible with previous reports [16] [11].

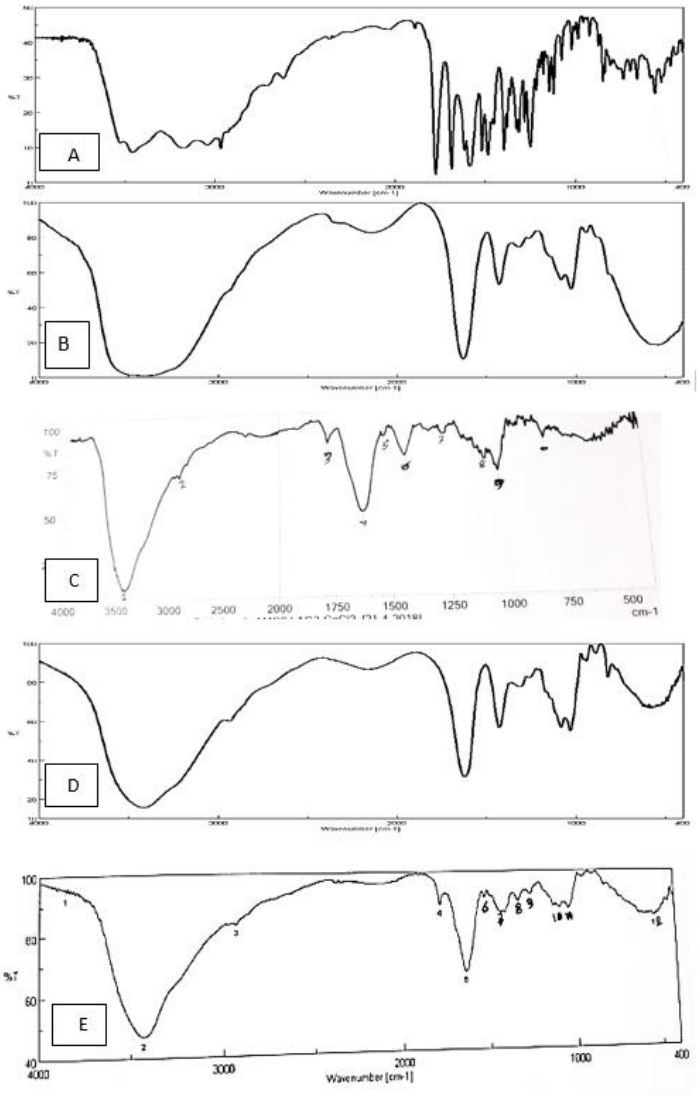

Figure 3: (A) FTIR spectra of amoxicillin, (B) Ca-alginate placebo beads, (C) amoxicillin loaded Ca-alginate beads (F4), (D) Ca- alginate-PL placebo beads, (E) amoxicillin loaded Ca-alginate-PL beads (F9).

In F9 spectrum, the peaks observed at 3450 cm^{-1} (OH to amoxicillin and SA) (peak-2 in Figure 3E), 2970 cm^{-1} (CH to amoxicillin, SA, and PL) (peak-3 in Figure 3E), 1778 cm^{-1} β lactam CO stretch (peak-4 in Figure 3E), 1640

cm^{-1} (carboxylic C=O to amoxicillin, and SA) (peak-5 in Figure 3E), 1519 cm^{-1} (benzene ring C=C stretch) (peak-6 in Figure 3E), and finally 1325 , 1252 , 1282, and 1031 cm^{-1} (CO either to amoxicillin, SA and PL) (peaks 7, 8, 9. 10 in Figure 3E). Thus it was supposed that the interactions might be Van der Waals and dipole interactions between amoxicillin, SA and PL.

Encapsulation efficiency

The beads' encapsulation efficiency (EE) of amoxicillin was determined using a spectrophotometer at 272 nm. (Figure. 4A suggests a correlation between $CaCl_2$ concentration and EE, as reported previously [32]. This observation might be due to (i) the improved density of the three-dimensional network (that produced smaller pore size) and (ii) the increased rate of bead formation, these altogether resulted in a significantly efficient encapsulation of amoxicillin *(p<0.05)* . EE values were 28.69±2.45 %, 36.93±2.82 and 44.70±0.59% at 1%, 5%, and 10% $CaCl_2$, respectively.

Using higher concentrations of SA was found to significantly improve the EE of amoxicillin (p< 0.05) , corresponding with previously published data [27]. As Figure. 4B shows), EE was 61.70±2.52 % at 4% SA concentration. This was probably because of the increase in dispersed viscosity and number of hydrogen interactions between the SA strands, yielding smaller internal and external bead' pores, which limited the elusion of amoxicillin during crosslinking stage.

Moreover, PL was added to the $CaCl_2$ solution in some formulations to improve the encapsulation efficiency. PL significantly *(p<0.05)* increased EE only at 10% and 15 % concentrations as shown in (Figure. 4C). EE values were 65.16±1.51 %, 71.07±3.76% and 76.40±3.27 % at 5, 10, and 15 % of PL concentration, respectively. This may be due to an increase in the viscosity of the crosslinking solution, emulsifying more amount of amoxicillin, and reducing the pore size. On the other hand, at 15°C, EE was significantly (p<0.05) increased as shown in (Figure. 4C). This might be due to an increase in the SA dispersion viscosity, leading to a slower leakage of amoxicillin during crosslinking process. Again, the statistical analysis indicated that the effect of both factors (preparation temperature and PL concentration) together was significant (p< 0.05).

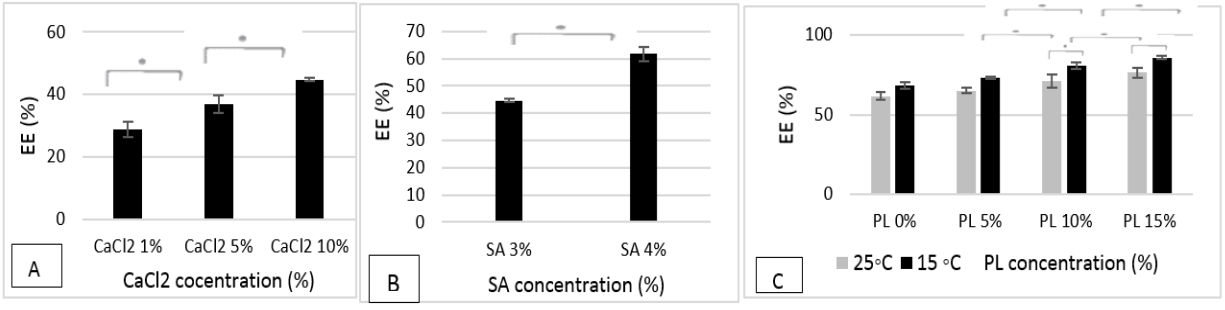

Figure 4: Determination of beads' encapsulation efficiency prepared under different conditions. The effect of (A) $CaCl_2$, (B) SA, and (C) PL concentrations and preparation temperature on the beads' EE. The data shows the mean values ±SD (n=3). * Significant statistical difference *(p<0.05)*.

Drug loading

Drug loading related to the hydrogel beads' mass and the amount of amoxicillin loaded in it. Therefore, all previously studied parameters that affect one or two of these factors will inevitably affect them. Such as increasing both $CaCl_2$ and SA concentrations contributed to a significant (p< 0.05) decrease in drug loading as shown in (Figure 5A) and (Figure 5B), respectively. It was

found that DL decreased from 15.35±0.77 % to 12.21±0.25 % when the concentration of $CaCl_2$ increased from 1 to 10 %. This can be linked to the fact that both $CaCl_2$ and SA concentrations contributed to the increase of the hydrogel beads' mass. In contrast, DL significantly increased (p<0.05) with increasing PL concentration as shown in (Figure 5C). The differences were significant only at 10 and 15 % PL concentrations (p<0.05). The results were 11.26±0.22 %, 13.29±0.32 %.

This may be due to decreasing hydrogel beads' mass and increasing the amount of amoxicillin within them. These results contradict an earlier research [33] because of different way of adding PL, leading to decrease the EE which related to DL results. Similarly, preparation temperature significantly increased DL (p< 0.05), may because of its contribution to increasing the amount of amoxicillin within the hydrogel beads. The statistical analysis showed that the effect of the two factors (preparation temperature and PL concentration) together was significant (p< 0.05).

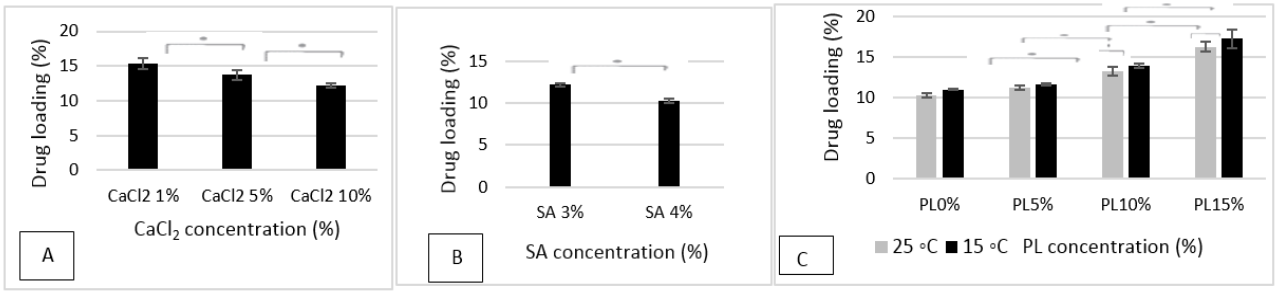

Figure 5: Determination of beads' drug loading prepared under different condition. The effect of (A) $CaCl_2$, (B) SA, (C) and PL concentrations and preparation temperature on the beads' DL. The data shows the mean values ±SD (n=3). * Significantly statistical difference (p<0.05).

Swelling study and drug release study in vitro

First, F4 and F8 were selected to perform swelling study and drug release study. The aim here was to study of the effect of only temperature preparation. It was found that all studied hydrogel beads had the same swelling profile as shown in (Figure 6A) and (Figure7A), respectively. They absorbed amount of water during the first 2 hours resulting from increasing SI. It may be because of the hydrophilic properties of hydrogel beads. In this context, Pasparakis and Bouropoulos reported that calcium-alginate hydrogel beads swelling was achieved in a period of time due to the equilibrium between the osmotic pressure and the forces of the crosslinking bonds that hold the 3D network 33. This explains how the osmotic pressure is higher than the force of the crosslinking bond, which causes rapid release of amoxicillin 34 existing on the surface and in the surface layers. Then, it was observed that the SI was decreased and the hydrogel beads dissolved releasing the remaining amount of amoxicillin existing in the core of them (their core). No significant decrease in SI and cumulative amoxicillin release were observed among formulations (F4, F7) as shown in (Figure 6A). This was confirmed by the f2 of the drug release profile considering the formula F4 is the reference formulations. f2=75.76 is an acceptable result as it was in the acceptance range (50-100) 25. This may be because the crosslinking reaction is slightly slower at 15°C than 25°C.

A 25°C was selected as temperature because the viscosity of solutions and suspensions was less at this temperature, and thus the preparation was easier. So, the studies were completed with hydrogel beads (F4, F5, F6 and F7) to know the effect of PL on SI and cumulative amoxicillin release. As shown in (Figure 7 A) and (Figure

7 B), respectively, that the dissolution study was consistent with the swelling study. The SI and cumulative amoxicillin release increased with increasing PL concentration (5, 10, 15%). That can be linked to the fact that PL was a surfactant and a hydrophilic polymer, resulting from adsorbing more amount of water and emulsifying more amount of amoxicillin. In this case, PL has been reported that the largest factors contributing to solubilization of drug by poloxamers are the number of micelles that would form in the solution and the micellar core surface area accessible to drug molecules 35. This is due to the amphiphilic structure of PL acting like a self-emulsifying system 36. Significant differences were observed between formulations F4, F6 and F7.

It was calculated f2 considering the formula F4 is the reference formula. It concluded from Table 2 that F5 and F6 were similar to F4 (80.12) and (63.95), respectively. On the other hand, F7 had (f2= 42.40). It was out of the acceptance range (50-100) 25.

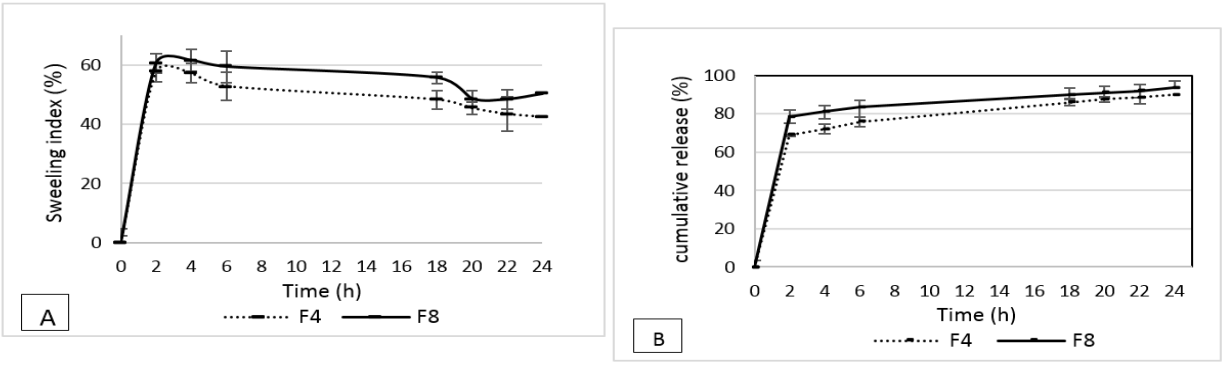

Figure 6: Effect of preparation temperature on SI (A) and cumulative release (B), F4 at 25°C and F8 at 15°C.

The initial fast release (burst effect) was attributed to the diffusion of the drug particles from the coating layer of the hydrogel beads, while subsequent release was due to slow diffusion of the entrapped drug from the interior core of the alginate matrix.

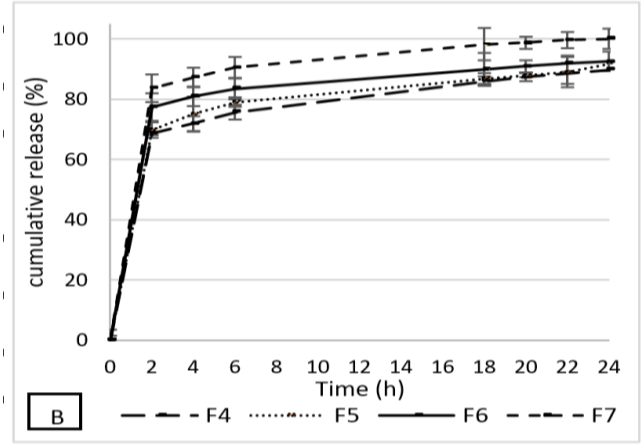

Figure 7: Effect of PL concentrations on SI (A) and cumulative release (B) at 25°C.

Scanning electron microscopy

It was chosen the best formulation as shown later to know the surface morphology and to investigate the presence of pores. Obtained hydrogel beads were spherical and homogenous regardless with small crystals probably due to partially crystallized amoxicillin formed during the drying step (Figure 8A). Scanning electron micrograph showed relatively rough surface with some pores (Figure 8B).

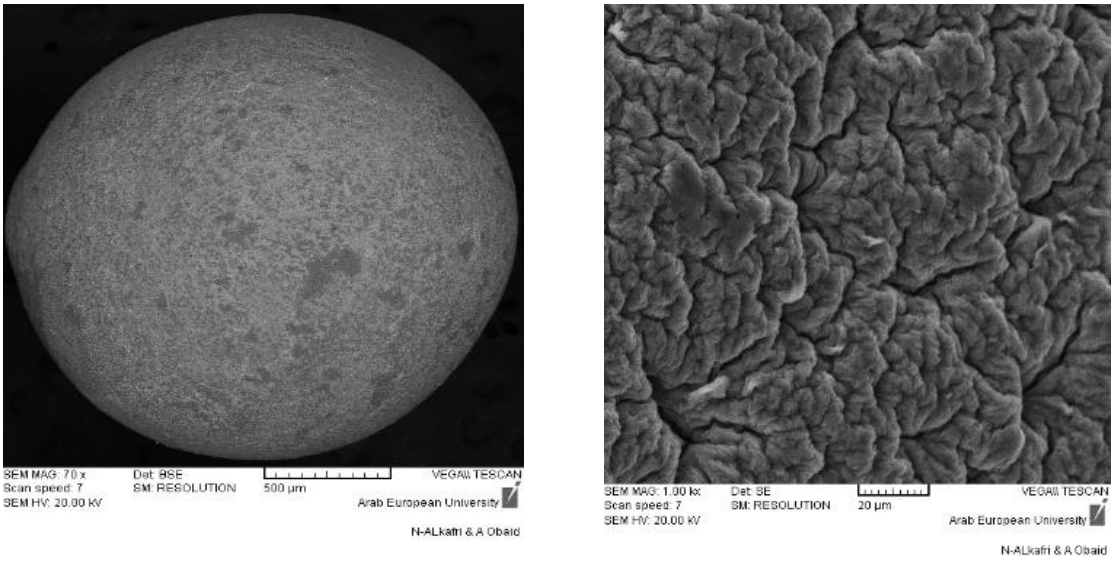

Figure 8: SEM image of (a) dried beads F4, (b) the surface of F4.

CONCLUSION

The amoxicillin-loaded hydrogel beads were prepared using an ionotropic gelation process. SA, CaCl2, PL concentrations and preparation temperature were investigated in order to understand their effects on beads properties. Poloxamer was added to improve the encapsulation efficiency and amoxicillin release profile. The SEM data confirmed that the hydrogel beads were spherical. FTIR analyses demonstrated the compatibility of amoxicillin with the used excipients. Sodium alginate, calcium chloride, poloxamer and preparation temperature had significantly increased encapsulation efficiency and drug loading. In vitro swelling and drug release studies in HCl pH=1.2 over 24 h revealed insignificant decrease in swelling index and drug release over a range of temperature degrees. Poloxamer concentration contributed to increase swelling index and cumulative drug release. These hydrogel beads containing amoxicillin can be a promising drug carrier to improve patient compliance and reduce frequency of dosing.

Amoxicillin release profiles can be further confirmed by performing in vivo release studies.

REFERENCES

1. Dey, S. K. et al. Floating mucoadhesive alginate beads of amoxicillin trihydrate: A facile approach for H. pylori eradication. International Journal of Biological Macromolecules. 2016; 89: 622–631.
2. Al-Degs, Y. S., El-Sheikh, A. H. & Harb, D. M. Accurate Quantification of Amoxicillin in Different Drug Formulations using Advanced Chemometric Methods. Jordan Journal of Pharmaceutical Sciences. 2020; 13: 19-27.
3. Cammarota, G., Sanguinetti, M., Gallo, A. & Posteraro, B. Review article: biofilm formation by Helicobacter pylori as a target for eradication of resistant infection. Alimentary Pharmacology & Therapeutics. 2012; 36: 222–230.
4. Alfaqeer, R. H., Albakain, R., Rasheed, M. & Makahleh, A. Development of Novel HPLC Method for Analysing Drugs Used in H-Pylori Treatment. Jordan Journal of Pharmaceutical Sciences. 2021; 14: 473-486.
5. Thambavita, D. et al. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Amoxicillin Trihydrate. J Pharm Sci. 2017; 106: 2930–2945.
6. Llor, C. et al. A study of adherence to antibiotic treatment in ambulatory respiratory infections. International Journal of Infectious Diseases. 2013; 17: e168–e172.
7. Michael E. Aulton & Kevin M.G. Taylor. Aulton's pharmaceutics: the design and manufacture of medicines; Churchill Livingstone: Elsevier, New York. 2013, p 552.
8. El-Mahrouk, G. M., Aboul-Einien, M. H. & Makhlouf, A. I. Design, Optimization, and Evaluation of a Novel Metronidazole-Loaded Gastro-Retentive pH-Sensitive Hydrogel. AAPS PharmSciTech. 2016; 17: 1285–1297.
9. Kalshetti, P. P., Rajendra, V. B., Dixit, D. N. & Parekh, P. P. Hydrogels as a Drug Delivery System and Applications: A REVIEW. International Journal of Pharmacy and Pharmaceutical Science. 2012; 4:1-7.
10. Altinisik, A. & Yurdakoc, K. Chitosan/poly (vinyl alcohol) hydrogels for amoxicillin release. Polym. Bull. 2014; 71: 759–774.
11. Narkar, M., Sher, P. & Pawar, A. Stomach-Specific Controlled Release Gellan Beads of Acid-Soluble Drug Prepared by Ionotropic Gelation Method. AAPS PharmSciTech 2010; 11: 267-277.
12. Motwani, S. K. et al. Chitosan-sodium alginate nanoparticles as submicroscopic reservoirs for ocular delivery: formulation, optimisation and in vitro characterisation. Eur J Pharm Biopharm. 2008; 68: 513–525.
13. Giri, T. K. et al. Alginate based hydrogel as a potential biopolymeric carrier for drug delivery and cell delivery systems: present status and applications. Curr Drug Deliv 2012; 9: 539–555.
14. Parhi, R. & Suresh, P. Alginate-Poloxamer Beads for Controlled Release of Metoprolol Succinate. Turkish Journal of Pharmaceutical Science. 2015; 12: 59-66.
15. López-Cacho, J. M., González-R, P. L., Talero, B., Rabasco, A. M. & González-Rodríguez, M. L. Robust Optimization of Alginate-Carbopol 940 Bead Formulations. The Scientific World Journal. 2012; 4: 1–15.
16. Angadi, S. C., Manjeshwar, L. S. & Aminabhavi, T. M. Novel composite blend microbeads of sodium alginate coated with chitosan for controlled release of amoxicillin. International Journal of Biological Macromolecules. 2012; 51: 45–55.
17. Moebus, K., Siepmann, J. & Bodmeier, R. Alginate–poloxamer microparticles for controlled drug delivery to mucosal tissue. European Journal of Pharmaceutics and Biopharmaceutics. 2009; 72: 42–53.
18. Giuliano, E., Paolino, D., Fresta, M. & Cosco, D. Mucosal Applications of Poloxamer 407-Based Hydrogels: An Overview. Pharmaceutics. 2018; 10 (3): 159.
19. Mansuri, S., Kesharwani, P., Jain, K., Tekade, R. K. & Jain, N. K. Mucoadhesion: A promising approach in drug delivery system. Reactive and Functional Polymers. 2016; 100: 151–172.
20. Swed, A. et al. Sustained release of TGF-β1 from

biodegradable microparticles prepared by a new green process in CO2 medium. International Journal of Pharmaceutics. 2015; 493: 357–365.

21. Swed, A., Cordonnier, T., Fleury, F. & Boury, F. Protein Encapsulation into PLGA Nanoparticles by a Novel Phase Separation Method Using Non-Toxic Solvents. Journal of Nanomedicine & Nanotechnology. 2014; 5: 1-8.
22. Khoder, M., Tsapis, N., Domergue-Dupont, V., Gueutin, C. & Fattal, E. Removal of residual colonic ciprofloxacin in the rat by activated charcoal entrapped within zinc-pectinate beads. European Journal of Pharmaceutical Sciences. 2010; 41: 281–288.
23. Dalaty, A. A., Karam, A., Najlah, M., Alany, R. G. & Khoder, M. Effect of non-cross-linked calcium on characteristics, swelling behaviour, drug release and mucoadhesiveness of calcium alginate beads. Carbohydrate Polymers. 2016; 140: 163–170.
24. Nayak, A. K. & Pal, D. Development of pH-sensitive tamarind seed polysaccharide–alginate composite beads for controlled diclofenac sodium delivery using response surface methodology. International Journal of Biological Macromolecules. 2011; 49: 784–793.
25. Shargel, L. & Yu, A. B. C. Applied biopharmaceutics & pharmacokinetics; Mc Graw Hill Education: New York. 2016, p 435.
26. Smrdel, P. The Influence of Selected Parameters on the Size and Shape of Alginate Beads Prepared by Ionotropic Gelation. Scientia Pharmaceutica. 2008; 76: 77–89.
27. Arora, S. & Budhiraja, R. D. Chitosan-alginate microcapsules of amoxicillin for gastric stability and mucoadhesion. J Adv Pharm Technol Res. 2012; 3: 68–74.
28. Jeong, C., Kim, S., Lee, C., Cho, S. & Kim, S.-B. Changes in the Physical Properties of Calcium Alginate Gel Beads under a Wide Range of Gelation Temperature Conditions. Foods. 2020; 9 (2):180.
29. Morakul, B., Suksiriworapong, J., TraidejChomnawang, M., Langguth, P. & BurapacheepJunyaprasert, V. Dissolution enhancement and in vitro performance of clarithromycin nanocrystals produced by precipitation–lyophilization–homogenization. European Journal of Pharmaceutics and Biopharmaceutics. 2014; 88: 886–896.
30. Huang, S.-L. & Lin, Y.-S. The Size Stability of Alginate Beads by Different Ionic Crosslinkers. Advances in Materials Science and Engineering. 2017; 1: 1-7.
31. Florence, A. T. & Attwood, D. Physicochemical principles of pharmacy; pharmaceutical press: London. 2007, p 297.
32. Lotfipour, F., Mirzaeei, S. & Maghsoodi, M. Evaluation of the effect of CaCl2 and alginate concentrations and hardening time on the characteristics of Lactobacillus acidophilus loaded alginate beads using response surface analysis. Adv Pharm Bull. 2012; 2: 71–78.
33. Pasparakis, G. & Bouropoulos, N. Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate-chitosan beads. Int J Pharm. 2006; 323: 34–42.
34. Morris, N., Razak, F., Kennedy, J. & Murphy, A. Development of Amoxicillin loaded microspheres for anti-Helicobacter pylori infection using Ionic Gelation method. 2017; 2: 56-67.
35. Croy, S. R. & Kwon, G. S. The effects of Pluronic block copolymers on the aggregation state of nystatin. J Control Release. 2004; 95: 161–171.
36. Martín-Villena, M. J. et al. Novel microparticulate systems for the vaginal delivery of nystatin: development and characterization. Carbohydr Polym. 2013; 94: 1–11.

تحضير وتوصيف حبيبات هلامية مائية تحرِّر الأموكسيسيلين بشكل مضبوط

رشا المصري* [1]، أمين سويد[2]، هيفاء العلي[1]

[1] قسم المراقبة الدوائية والكيمياء الصيدلانية، كلية الصيدلة، جامعة البعث، حمص، الجمهورية العربية السورية.

[2] قسم الصيدلانيات والتكنولوجيا الصيدلانية، كلية الصيدلة، جامعة البعث، حمص، الجمهورية العربية السورية.

ملخص

تصف هذه الدراسة تحضير وتوصيف الحبيبات الهلامية المائية والمحمَّلة بالأموكسيسيلين ثلاثي الماء، وذلك بهدف استعمالها كنظام إيتاء مضبوط من أجل تحسين مطاوعة المريض. تم تحضير الحبيبات الهلامية المائية بطريقة التهلم الأيوني، وذلك باستخدام كلوريد الكالسيوم كعامل مصالِب (CaCl2). تمت دراسة تأثير تركيز كلاً من CaCl2 والجينات الصوديوم والبولوكزامير 407 ودرجة حرارة التحضير. تم الحول على حبيبات هلامية مائية كروية الشكل مع كفاءة كبسلة عالية (85.74 ± 1.09) ٪. أثبت تحليل FTIR التوافق ما بين السواغات والأموكسيسيلين. تم إجراء كلاً من اختبار الانتباج والتحرر التراكمي للدواء في وسط HCl (pH=1.2) خلال 24 ساعة. أثّرت درجة حرارة التحضير معنوياً على كلاً من منسب الانتباج والتحرر التراكمي للأموكسيسيلين. ساهم الـ PL في زيادة التحرر التراكمي للأموكسيسيلين، وتوافق ذلك مع دراسة الانتباج. يمكن اعتبار هذه الحبيبات الهلامية المائية الجديدة نظام إيتاء واعد، يحرر الأموكسيسيلين بشكل مضبوط خلال 24 ساعة ويقلل عدد مرات التجريع.

الكلمات الدالة: إيتاء الأدوية بشكل مضبوط، ألجينات الصوديوم، الحبيبات الهلامية المائية، البولوكزامير 407، الأموكسيسيلين.

* ***المؤلف المراسل: رشا المصري***

r.almasri@albaath-univ.edu.sy

تاريخ استلام البحث 2020/8/21 وتاريخ قبوله للنشر 2022/3/19.