DOI: *https://doi.org/10.31351/vol33iss1pp146-153*

Developing and Evaluating a Novel Drug Delivery System, Calcium-Alginate Beads loaded with Valsartan

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Abstract

Valsartan is one of the most common drugs used by chronic patients in the management of hypertension, heart failure, and diabetic nephropathy. This present study was conducted with the aim of formulating a long-acting pharmaceutical form of multiparticulate system of Valsartan in order to extend drug release where the greatest release is in the intestines (pH=6.8). The process is obtained by preparing millimeter dimensions' solid polymeric beads using the ionotropic Gelation technique by using the polymer "Alginate Sodium" (SA), and Calcium Chloride $CaCl_2$ as a cross-linking agent. Valsartan beads were studied using different concentrations of Sodium Alginate and Calcium Chloride to select the optimal formula and then were compared with locally marketed film-coated tables containing Valsartan. The formula (SA 3%, $CaCl_2$ 10%) was chosen after conducting several physiochemical tests such as shape and dimensions, swelling index, entrapment efficiency, *in vitro* drug release, and FTIR. FTIR test showed no chemical bonding between Valsartan and other excipients. Selected beads achieved a high percentage of swelling in phosphate buffer solution pH=6.8. Entrapment efficiency was also high at about 80%. Prepared beads followed the Korsmeyer-Peppas release mechanism, and eventually obtained extended-release beads which slowed drug release for 24h, Compared with the film-coated tablets, the *in vitro* release of valsartan expired after only one hour.

Keywords : Valsartan, Beads, Polymer, Crosslinking, Drug release

تطوير وتقييم نظام ايتاء دوائي حديث، حبيبات ألجينات الكالسيوم المحملة بالفالسارتان

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الخلاصة

يعتبر فالسارتان أحد الأدوية الأكثر شيوعًا التي يستخدمها المرضى المزمنون في علاج ارتفاع ضغط الدم وفشل القلب واعتلال الكلية السكري. أجريت هذه الدراسة بهدف صياغة شكل صيدلاني مديد التحرر من نظام متعدد الجزيئات للفالسارتان من أجل زيادة زمن تحرره حيث يكون التحرر الأكبر له في الأمعاء (pH=6.8) . تم تحضير حبيبات بوليمرية صلبة ذات أبعاد مليمترية عن طريق اتباع تقنية التهلم الأيوني باستخدام البوليمر "ألجينات الصوديوم" (SA) وكلوريد الكالسيوم $CaCl_2$ كعامل مصالب. تمت دراسة حبيبات فالسارتان باستخدام تراكيز مختلفة من ألجينات الصوديوم وكلوريد الكالسيوم من أجل اختيار الصيغة المثلى ، ثم تمت مقارنتها مع المضغوطات الملبسة بالفيلم المسوقة محليًا. تم اختيار الصيغة (SA 3٪ ، $CaCl_2$ 10٪) بعد إجراء العديد من الاختبارات الفيزيوكيميائية مثل الشكل والأبعاد ، ومؤشر الانتباج ، وفعالية الاحتباس ، ومعدل التحرر واختبار الأشعة تحت الحمراء. أظهر اختبار الأشعة تحت الحمراء عدم وجود روابط كيميائية بين فالسارتان والسواغات الأخرى. حققت الحبيبات المختارة نسبة عالية من الانتباج في محلول الوقاء الفوسفاتي pH = 6.8. كانت فعالية الاحتباس عالية أيضًا بحوالي ٨٠٪. اتبعت الحبيبات المحضرة نموذج تحرر Korsmeyer-Peppas . تم الحصول في النهاية على حبيبات مديدة التحرر أدت إلى إبطاء معدل تحرر الدواء لمدة ٢٤ ساعة ، مقارنة بالأقراص الملبسة بالفيلم ، والتي انتهى تحرر فالسارتان منها بعد مرور ساعة واحدة فقط.

الكلمات المفتاحية: فالسارتان، حبيبات، بوليمير، التصالب، تحرر الدواء.

Introduction

Despite the great progress in the discovery and design of new drugs, it is noted that most drugs have undesirable side effects that could be caused by the drug delivery system [(1)]. One of the most difficult challenges that can be faced and overcome by drug delivery techniques is positioning the drug at its site of action within an appropriate concentration for long periods and molding it within a specific drug delivery system [(2)]. Hydrogel Beads are multi-molecular novel delivery systems. They are three-dimensional hydrophilic polymeric networks, in the form of solid, spherical, millimeter-dimensional particles that are separated, usually consisting of biodegradable mono or co-polymers in association with a cross-linking agent. It can absorb a large amount of water and vital fluids [(3,4)]. Beads are widely used as environmentally friendly pharmaceutical formulations because they are usually biodegradable and no organic solvents are used during preparation, in addition, no toxic metabolites are formed at the end of the degradation process, which is important in the case of chronic drugs [(5)].Beads are used to improve drug bioavailability, enhance the solubility of poorly soluble drugs in aqueous media, For example: Some drugs, such as valsartan, its solubility depends on the pH of the medium, and therefore delaying its release until it reaches a suitable pH (the intestines pH=6.8)

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Received: 1/2 /2023
Accepted: 19/4 /2023

improves its total solubility instead of the immediate release in the stomach as observed in traditional pharmaceutical forms (tablets and capsules) [6], and target drugs to the site of action, for instance, delaying drug release will prevent its release in some undesirable spaces, such as the stomach, and is released when it reaches the intestines, in addition to ensuring that the drug remains at its site of action for a relatively long period of time [7], and can reduce side effects: Beads will reduce the number of doses administrated during the day and thus potentially mitigate the side effects caused by the immediate release of the drug from traditional forms, beads also lower drug dosage, and improve patient compliance [8].

Valsartan is an angiotensin II receptor blocker (ARBs) that is used in the management of hypertension, heart failure, and diabetic nephropathy [9]. Its chemical name according to IUPAC rules is (S)-N-Valeryl-N-{[2'-(1H-tetrazole-5-yl) biphenyl-4-yl]-methyl}-valine [10] (Figure 1).
Valsartan is sparingly soluble in water 0.18 mg/mol at 25°C [10]. It represents an important special case known as pH-dependent solubility, therefore, its solubility increases in alkaline solutions due to the formation of a negative binary charge, with a decrease in its affinity for fats, while its solubility is weak in acidic media with a high affinity for fats. Valsartan shows slow and incomplete release in a media similar to gastric fluid (pH = 1.2-4.5), and rapid and complete release in a media similar to the intestines (pH = 6.8), which explains the improvement in its solubility when it reaches the small intestine [11,12].
Its use is accompanied by a set of side effects that may be caused by the immediate release of the drug, or by long-term use by patients such as severe dry cough, runny nose, muscle aches, spasms, hyperkalemia, Diarrhea, blurred vision, and abdominal pain [12].

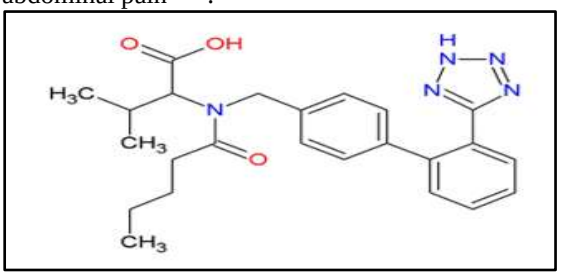

Figure 1.Valsartan structure

Valsartan is one example of poorly water-soluble drug that requires a development of its delivery system. Therefore, improving the solubility of valsartan is one of the most important challenges faced to prepare dosage forms within better bioavailability. Very little research has been conducted to improve the solubility of valsartan by encapsulating it in beads. One study was conducted by Raja *et al.* in 2012 [13], where they used expensive excipients such as xanthan gum, Soluplus, methylene bis acrylamide, and potassium persulfate. Beads achieved high entrapment efficacy in addition to the delayed release of valsartan for a relatively long time. Another study conducted by Caroline *et al.* in 2021 , used various and high-priced excipients such as sericin, alginate, and proanthocyanidin, and also achieved high entrapment efficacy and prolonged release of the drug [6].
In this research, another few and low-cost excipients were used. Results were similar to previous studies. In addition, there is a great need to conduct more studies and research on valsartan beads due to the lack of published research related to this topic and the urgent need to develop a pharmaceutical form that can improve the solubility rate of valsartan.

Materials and Methods

Materials

Valsartan was supplied as a gift sample by Medico labs (Homs, Syria), a Commercial pharmaceutical 40 mg/tab Valsartan was purchased from a Syrian local company, Sodium Alginate (BDH Chemicals Limited/ UK) was used as a polymer, anhydrous Calcium Chloride powder (Sigma-Aldrich/UK) was used as a cross-linking agent, disodium hydrogen phosphate (Fluka Steinheim/Germany), Potassium dihydrogen Phosphate (Fluka Steinheim/Germany) was used for the formulation of phosphate buffer, sodium chloride (Fluka Steinheim/Germany) Hydrochloric acid (Sigma/Germany), potassium bromide (Jasco Co./Japan) and deionized water (reverse osmosis, Gehaka, Brazil) were used in this research. All reagents used were of analytical grade.

preparation of Valsartan Hydrogel Beads

Valsartan beads were prepared using the Inotropic Gelation method which is an easy and fast technique, where the compounds of multiple electric charges are cross-linked when the compounds with the opposite charge are present. Beads were formed by dropping an aqueous solution of sodium alginate into an aqueous solution of calcium chloride [14].

Several aqueous solutions of sodium alginate were prepared using different concentrations, 40 mg of valsartan powder was homogeneously dispersed in the alginate solution using a magnetic stirrer (Labinco/the Netherlands) at a speed of 900-1200 rpm, then the formed suspension was dropped into aqueous solutions of different concentrations of accurately weighted quantities of calcium chloride using a needle (20-G) while continuing the process Stirring from a distance of 5 cm. Beads were left for 30 minutes to ensure complete curing, then filtered using a 45 µm membrane filter paper and washed with distilled water several times to get rid of the uncrossed calcium chloride residues, and then placed in the air dryer (Carbolite/England) for 48 hours at a temperature of 45 ° C [15,16].

Different concentrations of sodium alginate and calcium chloride were used (Table 1).

Table 1 Composition of Valsartan Beads

composition	F1	F2	F3	F4	F5	F6
Sodium alginate (w/v%)	**1%**	**2%**	**3%**	**4%**	**5%**	**3%**
Calcium chloride (w/v%)	**5%**	**5%**	**5%**	**5%**	**5%**	**10%**

A 40 mg of Valsartan was added to all of the previous formulations.

Characterization of Valsartan Beads

Fourier Transform Infrared Spectroscopy

FTIR was carried out by the KBR disc method within the range 400-4000 cm^{-1}, where the test was implicated on calcium-alginate beads loaded with valsartan to determine the relationship between valsartan and the excipients. The sample was well grounded and dried and then mixed with KBR at a rate of 1% (1mg sample is mixed with 100mg KBr) . Prepared beads were compressed and exposed to infrared rays [17].

Surface Morphology and particle size analysis

Beads were investigated under a Light Microscope (Olympus/Japan) to study their spherical shape, and their dimensions were determined precisely. The diameters of 10 randomly selected dried beads from each preparation were measured, then the mean diameter was calculated.

Swelling study

A swelling test was carried out on a paddle (Erweka/Germany). Several accurately weighted dry Valsartan beads were placed in the flask of the device in three different media: 500 ml distilled water, 500 ml HCl (pH = 1.2), 500 ml phosphate buffer (pH = 6.8) separately, at a stirring speed of 100 rpm and a temperature of 37 ± 5° C, then samples were chosen randomly at different intervals and were accurately weighed after placing them on a membrane filter paper for a few minutes. Swelling index was calculated following the equation [18]:

$$SI = \frac{w2 - w1}{w1}$$

Where w_1 represents the weight of Valsartan beads before swelling, and w_2 is the weight of the swollen beads. The test was performed until the beads had lost their spherical shape and become difficult to weigh.

Entrapment efficiency

A 0.1 g of each prepared formulation (Table 1) was weighed accurately, and soaked in 500 ml of phosphate buffer (pH = 6.8) for 24 hours, next, using a magnetic stirrer, the mixture was stirred thoroughly for 15 minutes until complete dissolution and filtered using a membrane filter paper. Then, 3 ml of each solution was taken from the resulting solutions and their absorbance was measured using a UV-visible spectrophotometer (Optima/Japan) at a wavelength of 250 nm. The entrapment efficiency of valsartan is calculated by the following equation [15,19]:

$$EF = \frac{\text{practical drug content}}{\text{theoretical drug content}} \times 100$$

in vitro drug release

The 500 ml of 0.1N HCL (pH=1.2) for the first 2 hours, then beads were taken out, washed with distilled water, and release was studied in another dissolution media which is similar to the intestine: 500 ml of a phosphate buffer (pH=6.8) at a temperature of 37±5°C and 50 rpm. Next, 3 ml of each sample was withdrawn at different intervals for 24 hours and their absorbance was measured using a UV-visible spectrophotometer at a wavelength of 250 nm. Finally, the cumulative percentage of the drug was calculated [6].

In vitro Release of Valsartan was conducted in triplicate for each formulation using a paddle device to determine the behavior of valsartan release. The release was first studied in a dissolution media which is similar to the gastric fluid.

Drug release kinetics

Valsartan Hydrogel beads release mechanism was investigated by using different types of erosion models as shown in (Table 2) [20].

Table 2.Mathematical equations for the study of drug release

Model	Equation
Zero order	$Q_t = Q_0 + K_0 t$
First order	$\log Q_t = \log Q_0 + K_1 .t / 2.303$
Hixon	$Q_0^{1/3} - Q_t^{1/3} = K_{hc} .t$
Higuchi	$Q_t = K_h t^{1/2}$
Korsmeyer-Peppas	$Q_t/Q_\infty = K_{kp} . t^n$

Comparison between Valsartan Beads and tablets release

The release curves of valsartan beads were compared with the release curve of valsartan 40 mg film-coated tablets. Valsartan release of tablets was obtained using a UV- visible spectrophotometer at a wavelength of 250 nm by applying the same previous conditions (dissolution media, temperature, rotation rate).

Results and Discussion

FT-IR

FT-IR spectra Figure (2) showed the main peaks of pure valsartan reported by Adriana F *et al.* (21), which are represented by the functional groups: O-H group at 3622 cm^{-1}, C-H group at 2942 cm^{-1}, C=O at 1636 cm^{-1}, C-OH at 1510 cm^{-1} were observed, in

addition to the appearance of peaks related to both CO and CN groups, and thus all the functional groups characteristic of valsartan appeared in FT-IR spectrum of the beads.

The main functional groups affiliated with Sodium Alginate were also observed, where the C=O peak appeared at 1595 cm^{-1} and an intensive peak appeared at 3850 cm^{-1} belonging to the OH group, in addition to the peaks at 1082-1023cm^{-1} belonging to the C-O-C functional group.

Thus, the chemical composition of valsartan has not changed. The bonds formed between it and the excipients are just physical bonds and there are no covalent chemical bonds between them. This bonding will not affect the effectiveness of the drug compound.

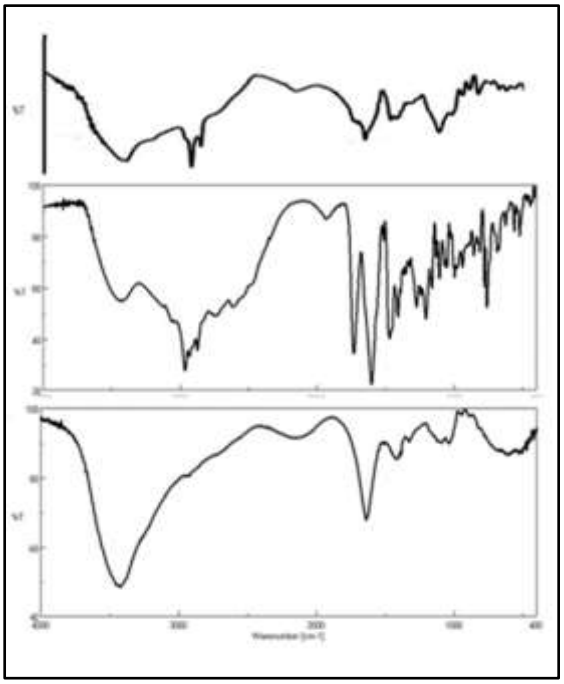

Figure 2. FT-IR spectra (a) pure sodium alginate, (b) pure Valsartan drug (c) calcium cross-linked alginate

Surface Morphology and particle size analysis

Valsartan beads showed different characteristics when changing the concentrations. F1, F2, and F4 formulations showed various shapes (Figure 3). They weren't regular nor spherical. It is not a desirable form when formulating beads with the reason that irregular shapes may affect valsartan absorption later in the living organism. It is not a desirable form when formulating beads with the reason that irregular shapes may affect valsartan absorption later in the living organism, because the more spherical and more regular the shape, the smaller the specific surface and thus the higher the absorption (22). F5 formulation showed beads with tails. This might be formed when beads fall into the calcium chloride solution, which is attributed to the large viscosity of the polymeric solution formed. Therefore, the shape of the resulting beads is also unfavorable for the same previous reasons. Whereas, F3 beads were the most spherical and regular.

The concentration of sodium alginate 3% (w/v) with a concentration of 10% (w/v) calcium chloride (F6 formulation) was also studied. F6 had spherical and regular shapes as well (Figure 3).

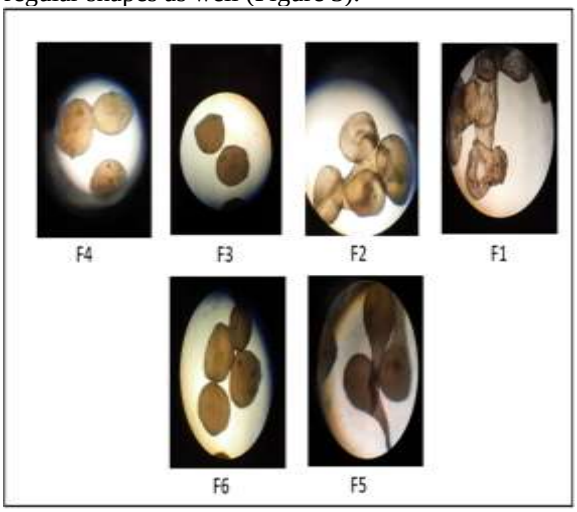

Figure 3 Microscopic photos of Valsartan beads preparations (X40, 10cm)

Beads dimensions were measured. The larger the beads, the smaller the specific surface, and thus the lower the rate of release of valsartan. The effect of sodium alginate on the dimensions was initially studied, then the effect of $CaCl_2$ on the dimensions was studied. Dimensions of the beads increase, as the increase in the concentration of sodium alginate (Figure 4). Raising the concentration of SA causes an increase in the viscosity of the alginate-valsartan mixture and consequently an increase in the density and size of the drop falling from the needle nozzle. The average diameter was increased when raising the concentration of calcium chloride (Figure 4). The reason for this is due to the increase in the beads content of additives, and as a result, the increase in the total mass.

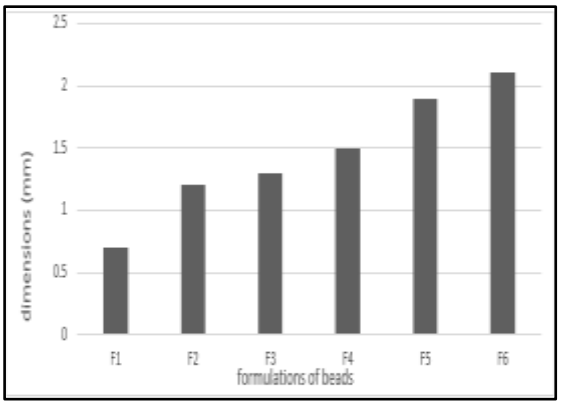

Figure 4. Impact of different concentrations of SA and $CaCl_2$ on beads dimensions

Swelling study

Preparations F3 and F6 were selected for the upcoming tests considering that the other preparations are not suitable as a pharmaceutical formula due to their irregular shape as previously shown in Figure [3].

By comparing the swelling index for both formulations F3 and F6 (Figure 5), the same swelling behavior was observed in distilled water. Both formulations swelled at a very low rate, not exceeding 4.5%, 4% of total beads weight for the formulations (F6) , (F3) respectively after 13 hours. This is similar to a study conducted by *Raja et al.* [13]. The reason for F6 swelling at a greater rate than F3 is due to the strength of the cross-linked polymeric network, which takes a long time to break the bonds within.Formulation F3 only swelled at a rate of 10% of their weight after 13 hours, while F6 swelled at a rate of 9.5% of their weight (Figure 6) in acidic media because of the three-dimensional cross-linked structure which is more robust and cohesive. Beads swelled as a result of the alginate absorbing water, and after some time, the ability to absorb water ceased. It is expected that the reason for the cessation of swelling in the acidic medium is that the negatively charged carboxyl groups of the sodium alginate present on its surface reacted with the strong acid HCl and formed the undissolved alginic acid in water and prevented water molecules from entering the polymeric network, thus preventing Valsartan beads from continuing to swell [23]. Both formulations F3 and F6 followed the same swelling behavior in the alkaline media, indicating that the beads swelled extremely, with a swelling rate reaching 82% and 80% of their weight for each of the formulas F3 and F6, respectively (Figure 7), emphasizing that F6 swelled at a slower rate than F3. This result was similar to the research conducted by Younis et al. [24].

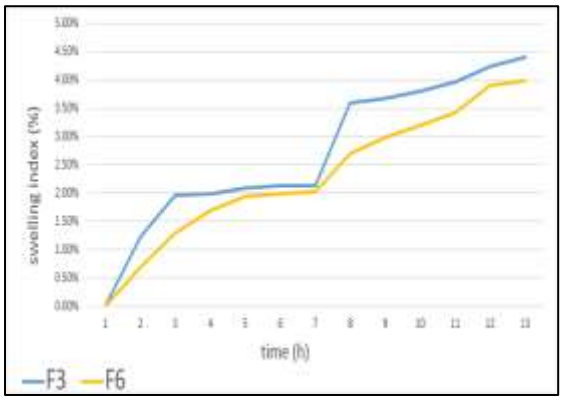

Figure 5. F6 and F3 swelling behavior in distilled water

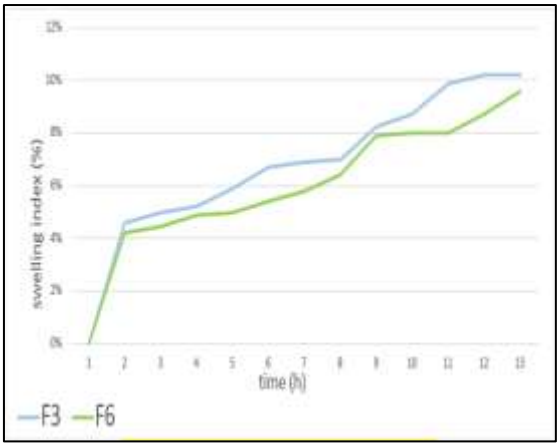

Figure 6. F6&F3 swelling behavior in HCl solution

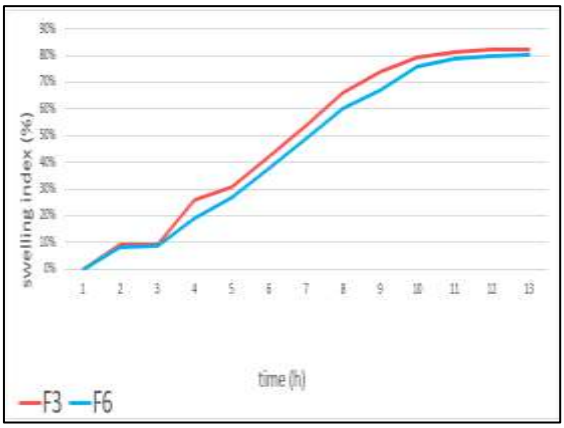

Figure 7. F6 and F3 swelling behavior in phosphate buffer solution

Entrapment Efficiency

Entrapment efficiency of valsartan beads increased when the concentration of calcium chloride increased. F6 showed an EF of 80%, which is higher than F3, which achieved an EF of 71% (Figure 8). As a result , this can be explained by the fact that the increase in the density and robustness of the cross-linked polymeric network, and the speed of formation of the sodium alginate gel caused by the increase in the concentration of calcium chloride during the droplet process hinders the leakage of the drug substance from the beads during the preparation process and reduces the percentage of valsartan lost during the cross-linking process. In contrast, a lower concentration of the cross-linking agent results in a less cross-linked and dense structure and is, therefore, more possible for valsartan to leak. A similar result was conducted by Patel *et al.* [(19)].

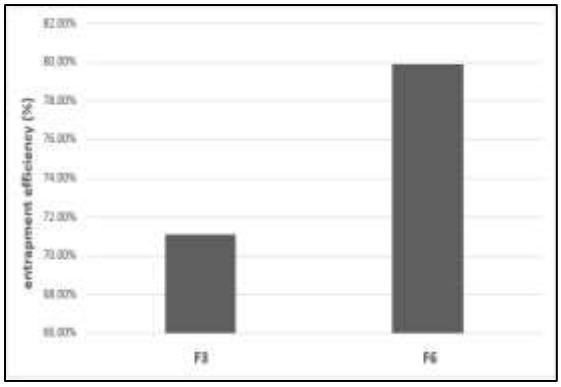

Figure 8 F6&F3 entrapment efficiency

In vitro drug release

Studying drug release is essential for predicting the behavior of the release of valsartan in the living organism, in addition, it is considered one of the most important tools when developing a new pharmaceutical formula, and controlling its quality.

Valsartan release from prepared beads was affected by the pH of the media, as not more than 3.5% (Figure 9) of the drug was released during the first two hours in the acidic media that is similar to the gastric fluid. It is expected that this amount released of the drug is encapsulated near the outer surface of the beads. Values of drug release rate (3.5%) ,(2.9%) for each of the formulations F3 and F6, respectively, after two hours, indicate the poor dissolution rate of valsartan in the studied media. In addition to the low swelling index of beads in this media. Thus, the release of valsartan in acidic media is controlled first by the diffusion of valsartan to the external media and then its dissolution. This is similar to a study conducted by Caroline *et al.* 2021 [6].

After 13 hours, valsartan release reached a clear peak (Figure 10), where (80%), (76%) of valsartan were released from each of the formulations F3 and F6, respectively. This corresponds to the swelling index test, where beads achieved the highest value in swelling after 13 hours, and therefore the continuation of beads swelling causes expansion of the pores in the three-dimensional network and weakens the bonds formed within it, and allows valsartan release, in addition to the good solubility of valsartan in alkaline media pH = 6.8. Release of the drug from the alkaline media is controlled first by beads swelling and then the diffusion of the drug to the external media and then its dissolution.

Valsartan beads continued their release at a relatively slow rate until they released (82%) , (79%) of each of the formulations F3 and F6 after 24 hours. Covering the patient's need for the drug "valsartan" which lowers blood pressure during the day, and thus the possibility of reducing the number of dosage administrated, and improving patient compliance and potentially improving drug bioavailability.

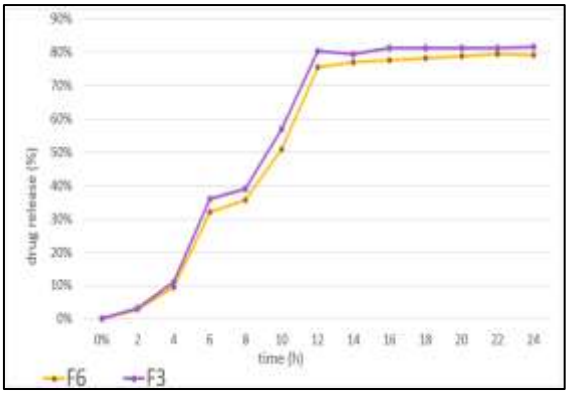

Figure 9. F6&F3 drug release

Drug release kinetics

Valsartan release followed the Korsmeyer-Peppas release model as it has the highest values of R^2, which ranged between 0.8958 and 0.901 (Table 3), and when calculating n values, F3 and F6 values ranged between 1.2241 and 1.319. This indicates that more than one mechanism is involved in valsartan release, and through the values of n, it is noted that the dominant release mechanism is super case II transport, which depends on the beads' erosion and then the relaxation of the polymeric chains.

Table 3 model fitting of drug release of valsartan beads

Korsemeyer Peppas	Higuchi	Hixon	First order	Zero order	Formulation
0.8958	0.8788	0.6243	0.6242	0.7896	F3
0.901	0.8937	0.7255	0.6443	0.8134	**F6**

Comparison between Valsartan Beads and tablets release

valsartan was completely released from tablets after only one hour, as shown in (Figure 10), in contrast to the prepared extended-release beads (Figure 11), from which the release of valsartan lasted for 24 hours.

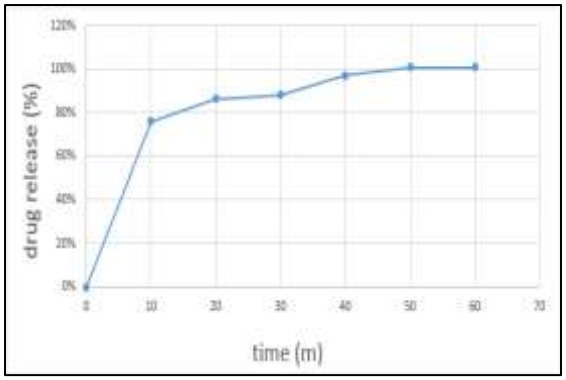

Figure 10. Valsartan-coated tablets release

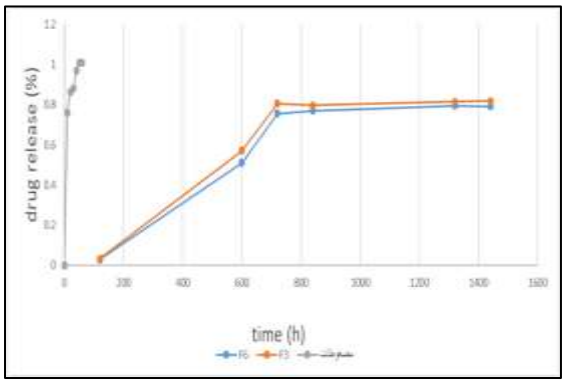

Figure 11. drug release of (a) valsartan coated tablets (b) F3 (c) F6

Conclusion

A promising form of extended-release drug delivery system for the antihypertensive drug valsartan was developed in the form of hydrogel beads using available and inexpensive excipients, namely sodium alginate and calcium chloride in different concentrations. The preparation (SA 3%, $CaCl_2$ 10%) was the most suitable pharmaceutical formula for valsartan beads. Calcium chloride concentration affected the cross-linked network, which increased the rate of swelling and the rate of release of the sparingly soluble drug valsartan. The solubility of valsartan improved when it was formulated in the form of beads due to its greater release in the alkaline media that is similar to the intestine, which is the appropriate media for the dissolution of valsartan.

Funding

The research was funded by AL Baath university in Homs-Syria.

Ethics Statements

No living organisms were handled in the research.

Conflict of interest

There is no conflict of interest.

Author contributions

PH Salwa Saad: idea of the research, practical work, data analysis, writing the article. Dr. Haifaa Alali: proofreading and supervising the article, providing research supplies.

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