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Effect of Pluronic F127 on the Preparation of Intranasal Mucoadhesive in Situ Gel Containing Lomustine Nanoemulsion

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Abstract

The anticancer drug lomustine has poor oral bioavailability in addition to its serious side effect, therefore, developing more effective drug delivery with direct targeting towards the brain through intra-nasal administration applying nanoemulsion-based-in situ gel technology is a promising alternative. Pluronic F127 is one of the widely used thermoreversible gelling agent, and used in sol-to-gel transformation. It has been used to localize drug delivery such as nose-to-brain delivery which allows the direct targeting of drug molecules bypassing the systemic effect and BBB (Blood Brain Barrier). The work involved preparation of Lomustine as in situ gel using Pluronic F127 and study the effect of the polymer on sol-to-gel transition temperature, gelation behaviour, spreadability, mucoadhesive force, residence time and drug percentage remaining on the tissue, as well as in vitro drug release. The results showed acceptable pH and high drug content, beside increased Pluronic percentage (from 15 to 20%) led to reduced gelation temperature from 33°C to 27°C and spreadability, improved gelling properties from + to +++, increasing mucoadhesive force from 4965.33 to 9866.30 dyne/cm^2 as well as prolonged residence time from 30 to 66 min and in vitro drug release where was 120 min for 100% drug release from F1 that contained 15% of the polymer to 210 min for F3 with 20% polymer. Therefore, modifying the Pluronic F127 percent in the in situ formulas could optimize the required formula for targeting the anticancer to treat brain cancer via nose-to-brain delivery.
Keywords: Pluronic F127, Brain, Tumour, Lomustine, in-situ gel.

تأثير تركيز بلورونيك F127 على تحضير المحلول الانفي المتحول الى جل لاصق الذي يحتوي على مستحلب دواء اللوموستين النانوي

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الخلاصة

يتميز عقار اللوموستين المضاد للسرطان بالتوافر الحيوي الضعيف عن طريق الفم بالإضافة إلى تأثيره الجانبي الخطير ، لذلك فإن تطوير نظام توصيل دواء أكثر فاعلية مع استهداف مباشر للدماغ من خلال الإعطاء داخل الأنف باستخدام تقنية الهلام الموضعي القائمة على مستحلب النانو هو بديل واعد. يعد بلرونك ف١٢٧ احد المواد واسعة الاستخدام و من أهم عوامل التبلور القابل بالتأثير الحراري ، حيث يستخدم في تحويل المحلول الى جل. ولقد تم استخدامه في توصيل الأدوية من خلال طرق استخدام مختلفة منها التوصيل من خلال الأنف إلى الدماغ والذي يهدف الى الايصال المباشر للدواء الذي سيتجنب التأثير المحيطي خارج الدماغ وكذلك حاجز الدم في الدماغ. تضمن العمل على تشكيل دواء لومستين على هيئة هلام موضعي بعد وضعه داخل الانف باستخدام مادة البلرونك ومن ثم دراسة تأثير هذه المادة على درجة حرارة انتقال المحلول الى هلام وسلوك تكوينه وقابلية انتشاره وقوة التصاقه ببطانة الانف ومدة بقائها داخله ونسبة الدواء ، وكذلك تحرر الدواء خارج الجسم في المختبر. أظهرت النتائج أن الرقم الهيدروجيني مقبول ومحتوى عالٍ من الدواء ، إلى جانب ذلك وجد ان زيادة نسبة بلرونك (من ١٥ إلى ٢٠٪) أدت إلى انخفاض درجة حرارة التكوّن من ٣٣ درجة مئوية إلى ٢٧ درجة مئوية وقابلية الانتشار ، وتحسين خصائص التبلور من + إلى +++ ، وزيادة قوة اللاصق المخاطي من ٤٩٦٥,٣٣ إلى ٩٨٦٦,٣٠ داين / سم^2 ووقت بقاء الهلام من ٣٠ إلى ٦٦ دقيقة وتحرر الدواء خارج الجسم الحي في المختبر كان ١٢٠ دقيقة لتحرر ١٠٠٪ من دواء لومستين للصيغة الدوائية F1 والتي احتوت على ١٥٪ من بوليمر البلرونك وكانت ٢١٠ دقيقة للصيغة F3 والتي كانت تحتوي على ٢٠٪ من نفس البوليمر . لذلك يمكن أن يؤدي تغيير كمية البوليمر بلرونك في الصيغ الموضعية إلى تعديل وتحسين الصفات المطلوبة لغرض استهداف مضاد السرطان اللومستين لعلاج سرطان الدماغ عن طريق توصيله من الأنف إلى الدماغ.
الكلمات المفتاحية: بلرونك ف١٢٧، السرطان، الدماغ، لومستين، هلام في الموضع.

Introduction

A drug delivery system known as an in situ gel demonstrates sol-to-gel transition in formula phases as a result of a change in certain physicochemical parameters as temperature, ionic strength, or pH. Thermo-responsive in situ gel formulations may be carried as a fluid and solidify at body temperature. They have both solid and liquid-like characteristics. The benefit of the formulation is prevention anterior dosage form leaking, lessens the taste impact, and increases nasal absorption [1].

There are three different types of heat sensitive polymers including negative type polymers like poly-N-isopropyl acrylamide (PNIPAAm) that contract as temperature rises (negative temperature response), positive type polymers like polyacrylic acid (PAA) that swell as the temperature rises (positive temperature response) and reversible type by temperature, such as tetronics and poloxamer, which expand and contract as the temperature changes [2-4].

The mostly often used mucoadhesive polymer in these formulas is poloxamer 407 (Pluronic F127) that micellizes and gels as temperature rises. Pluronic F127 may be used alone; or with other polymers in order to change the temperature of gelling. Pluronic F127 is investigated as a suitable gelling agent due to its negligible toxicity, suitable release pattern of drug, compatibility with other involved chemical agents, non-irritating effect on the mucosal lining, and prolonged residence time at a specific drug site of delivery, as well as reduction in the therapeutic dose, and side effects [5, 6] . Due to Pluronic's ability to form micelles and its improvement of drug solubilization, significant quantities of these medications may be solubilized in a small volume of the formula, making it appropriate for intranasal usage [7]. Pluronic, as non-ionic surfactant that lowers mucosal viscosity and flexibility and also disturbs the lipid membrane, enhances lipid leakage through it, also boosts medication absorption through the mucosal surface [8].

The Pluronic gelling capacity was resulted from the micellar number change with temperature where the solubility negative co-efficient of block copolymer micelles lead them to generate more micelles as the temperature rises and eventually pack so densely then gel is created. The gelation phenomena will be affected by conformational changes in the methyl group's orientation in the side chains of the polyoxypropylene (POP) polymer chains that make up the micelle's core and by the hydrating water expulsion from the micelles [9].

Lomustine is an alkylating chemotherapeutic agent for treatment of glioblastoma multiform (GBM) that is administrated orally. However, lomustine undergoes significant liver metabolism with a short half-life of 94 min [10, 11]. It is relatively insoluble in water (<0.05 mg/ml) with a pKa of 14.05 (Strongest Acidic) and -5.3 (Strongest Basic). Lomustine orally is not selectively directed to cancer cells therefore causes serious systemic toxicity [10, 11]. Therefore, targeting the drug directly to the brain via nasal cavity could be an alternative route. Nose-to-brain delivery via olfactory region has many advantages of rapid onset of action, reduced systemic effect and toxicity, bypass the BBB and enhanced targetability [12, 13].

The aim of this study is to prepare an intranasal mucoadhesive in-situ gel containing lomustine nanoemulsion using Pluronic F127 as gelling agent and investigating its effect on sol-gel transition temperature, and other parameters reaching to the optimum formula that may be considered as a potential alternative to the oral dosage form.

Materials and Methods

Materials

Lomustine was purchased from Aladdin Industrial Corporation, China. Eucalyptus oil was from Wuhan Senwayer Century Chemical Co., Ltd, Wuhan, China. Cremophore EL was from Shanghai Ruizheng Chemical Tech Co, Ltd, Shanghai, China. Chitosan of 200-400 mPs, methanol and Pluronic F127 were purchased from Sigma-Aldrich, USA. Triton X-100 was purchased from Dow, USA.

Experimental work

Lomustine in situ gel preparation containing Lomustine nano-emulsion

Lomustine nano-emulsion was prepared using probe sonicater. It was composed of 10% eucalyptus oil, 40% of Triton X-100: Cremophore El as Smix in a ratio of 3:1, as explained in the previously published work [14].

The mucoadhesive agent (chitosan) was added directly to 25 mL of the prepared nano-emulsion containing 625 mg Lomustine (5 mg/ 200 µL formula) and mixed using a magnetic stirrer (Stuart U.K) for enough time until the clear formula was obtained, then it was cooled in ice bath. Pluronic F127 in different percentages, as shown in Table 1, was added on the cool formula with continuous stirring at 500 rpm for 2h. Finally, the formulated solution was kept at 4°C overnight in refrigerator [15].

Table 1. In situ gel-based nano-emulsion of Lomustine formulas.

Ingredient	F1	F2	F3	F4	F5	F6
Lomustine NE (mL)	25	25	25	25	25	25
Pluronic F127 (%w/v)	15	18	20	15	18	20
Chitosan (%w/v)	-	-	-	0.5	0.5	0.5

Characterization of formulated mucoadhesive in situ gel

Determination of sol-gel transition temperature of the formulas

Two millilitre of each formula were added to a test tube (with a 10 mL capacity), which was then parafilm-sealed and kept in a water bath at 15 °C. The water bath was gradually heated by increment of 1°C, maintaining equilibrium for 5 minutes at each temperature adjustment, until the formula gelled and remained as a gel even when the test tube was tilted 90 degree [16].

Determination of in situ gel pH

In order to protect the formulas from dangerous bacteria, prevent irritating the nasal mucosa, and maintain normal physiological ciliary activity, the nasal preparation pH is essential. The apparent pH of each in situ gel formulas (F1-F6) was determined using pH meter (Hanna Instruments Ltd. Singapore) at room temperature [17].

Drug content

Precisely, one mL of each formulation was transferred into a 100 mL capacity volumetric flask, and then methanol (70 mL) was added. A dispersion was attained after sample sonication for about half an hour, then diluted with methanol to the desired concentration, centrifuged for 15 minutes at 3000 rpm (Fanem, 206-R Centrifuge, Brazil), and then filtered through a syringe filter of 0.22 mm. An UV-Visible spectrophotometer (Shimadzu 1650 PC-Japan) was used at the drug wavelengths (230 nm) to measure the contents of Lomustine spectrophotometrically [18, 19].

Osmolarity determination

The isotonicity of the nasal preparation is one of the important properties that preferred to be within specific limit to avoid nasal mucosa irritation and damage. It could be measured by a molecular weight method by calculating the drug concentration for all formulas using the equation below [20]:

$$\frac{mOsmol}{L} = \frac{Drug\ concentration\ \left(\frac{g}{L}\right)}{Molecular\ weight\ of\ the\ drug} \times Ionic\ species\ number \times 1000$$

The drug concentration was obtained from the percentage of drug content and Lomustine molecular weight is 233.695 g/mol.

Gelation behaviour

Precisely, 5 ml of each formula was poured to 50 ml PBS (phosphate buffer saline; pH 6.4) in a beaker with a gentle stirrer of 50 rpm at 32°C±2 [21]. Gelling behaviour was measured in three groups based on the stiffness and the duration of the gel. Where, in (+) gelation happens after few minutes and stays for short time (few minutes that rapidly dispersed). While, (++) the gelation occurs immediately and stays for few hours (4-6 h). In (+++), the gelation happens immediately and stays for long period (more than 6 h) [22, 23].

Spreadability test

Spreadability of formulas was calculated in square meters per second (cm^2/s) at room temperature in order to determine the ability of the formulas to spread or distributed in nasal olfactory region before gelling to ensure larger area covered in this region to enhance direct contact of loaded drug in NE in situ gel with it. It was performed by using a micropipette, 0.2 ml of each formula (after being colored with methylene blue for visual observation) was placed at the center of a filter paper placed in a petridish at a 2 cm distance from the tip of the micropipette. The surface area that the formula covered on the paper at a set time period of 20 second was calculated to determine spreadability [24].

Determination of in situ gel mucoadhesive force

The detachment force required to separate the gel sample from the fresh sheep nasal mucosal tissue was used to calculate the mucoadhesive strength of each prepared formula. This test was carried out utilizing a modified mucoadhesive measuring equipment (Figure 1) and tissue samples were taken from the sheep nasal mucosa that were obtained from a slaughterhouse. The apparatus was a two-arm balance. On the right arm, there were upper and lower glass platform. On the lower platform, there was fixed nasal mucosa of the sheep (moisten with PBS of 6.4 pH) on which the 1 g of formula applied. Then, the upper slide was allowed to attach the formula on the nasal sheep. After that, on the left arm, water was gradually added until upper slide was detached from the lower. The weight of added water was used to calculate the mucoadhesive force using the following equation [25]:

$$Detachment\ Stress\ \left(\frac{dyn}{cm2}\right) = \frac{m * g}{A}$$

Where, 'm' is the weight required to detach the two glass plates, 'g' is the acceleration by gravity (980 cm/s^2) and 'A' is the tissue area, 3 cm^2.

Figure 1. Modified mucoadhesive force measuring equipment.

Ex-vivo residence time and percentage of drug remaining on tissue

The residence time for the all the formulas (F1-F6) were determined using the modified apparatus shown in Figure 2. One millilitre of colored (with methylene blue for identification) prepared formulation was added to the surface of the sheep nasal mucosa (5x3 cm). PBS was manually allowed to flow over the formula and mucosa at a rate of 1.2 mL/min at ≈ 34°C±2 and collected in a petri-dish. The time required for the formula to disappear from the mucosa (based on color disappearance) was determined as residence time and analysed for percent of drug remaining on the tissue. After that the mucosa was sliced to smallest possible size and homogenized in 10 mL methanol for 3 h then centrifuged for 5000 rpm for 10 min. The sample taken from the supernatant was analyzed spectroscopically to determine the percent of Lomustine remained on the mucosa [26].

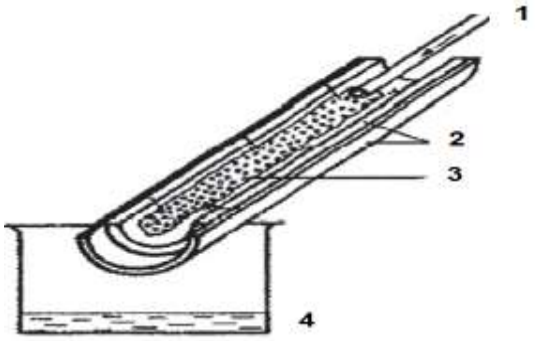

Figure 2. Schematic diagram for the apparatus used to determine the formulas' residence time. 1) PBS supplied in rate of 1.2 ml per min, 2) plastic support, 3) sheep nasal mucosa 5 cm long, and 4) collector for the washing [26].

In vitro drug release study

Lomustine release from all formulated in situ gels (F1-F6) was measured using rotating paddle dissolution apparatus and a dialysis bag (MWCO 12000 Da). The sealed dialysis bag containing 200 µL of in situ gel (containing 5 mg Lomustine) was immersed into 200 mL PBS (pH 6.4) as a dissolution medium at 50 rpm and the medium's temperature was kept at 34±0.5° C [27]. Samples of two millilitre aliquots were drawn at a specific time intervals of (5, 15, 30, 45, 60, 90, 120, 150, 180, 240, and 360 min) and promptly replaced with fresh dissolution medium [28]. A UV-Vis spectrophotometer was used to measure the drug concentration at its $\lambda_{maximum}$ (230 nm) [19].

Statistical analysis

The paired t-test was used to assess the differences between the data that were acquired. When $p \leq 0.05$, the differences were deemed significant.

Results and Discussion

In situ gel evaluation

Sol-gel transition temperature ($T_{sol-gel}$) for prepared formulas

The normal nasal temperature is within 32-34°C. The effect of percentage of Pluronic F127 on the gelation temperature was studied, where formula F1 with 15% Pluronic F127 had the highest temperature (average 33°C), F2 with 18% Pluronic had average 31°C gelation temperature, whereas F3 containing 20% of Pluronic had the lower temperature (average 27°C) (Table 2). It was demonstrated that the increase of Pluronic F127 concentration resulted in reduction in the sol-gel conversion temperature. This could be due to the solution's polymer network structure solidifying at higher concentrations, being neatly packed and being overcome by a large volume and number of micelles, which then gel at low temperatures [29].

Additionally, adding mucoadhesive agent reduced the transition temperature further. Where F4 (containing 15% Pluronic F127 and 0.5% chitosan) had 32°C transition temperature (lower than F1 containing only 15% Pluronic F127), F5 (containing 18% Pluronic F127 and 0.5% chitosan) had gelation temperature (30°C) lower than F2 (containing 18% Pluronic F127 and 0% chitosan) and F6 (containing 20% Pluronic F127 and 0.5% chitosan) had gelation temperature of 25°C which was lower than F3 (containing 20% Pluronic F127 and without chitosan). This is due to chitosan's higher ability for growing viscosity and for making more comprehensive intermolecular H-bonding to produce a gel structure at low temperature [30, 31]. Accordingly, F1 and F2 showed a gelation temperature (33°C and 32°C, respectively) which is in consistence with nasal cavity temperature (32°C) and the design of in situ preparation which should be in liquid form at room temperature and converted to gel near nasal temperature [32, 33]. Similar results was observed with ondansetron HCl nasal in situ gel [18].

In situ gel pH

All of the in-situ gel formulas (F1-F6) had pH values within the acceptable range designated for nasal formulation. The observed pH values varied from (5.4-5.8), as shown in Table 2. Such acidic pH will aid in the lysosomes' ability to eliminate

bacteria, protecting nasal tissue against microbial infection (while in high alkaline pH will deactivate the nose lysosomes) [34]. The nasal cavity can tolerate formulas with 3-10 pH range [35].

Drug content

Table 2 shows the drug content results of the six prepared formulas. The results of in situ gel formulas Lomustine had high content uniformity [23].

Osmolarity measurement

The osmolarity of the formulas (F1-F6) was calculated (as shown in Table 2) and it was within accepted range of the nasal lining as it can afford wide range of the osmolarity of 85.47–341.88 m Osmol/L. This is indicating that the formulas cannot cause nasal disturbance or irritation [36, 37]. Similar observation was with meloxicam nasal in situ gel [38].

Gelation behaviour

All the in-situ gel formulas were undergone sol-to-gel transition when they got contacted with the medium at 34±1°C due to the presence of Pluronic F127 (gel-forming thermos-responsive polymer). This experiment demonstrated that the gelation process was facilitated by increasing the concentration of Pluronic F127; formula F3 with 20% Pluronic F127 promptly gelled and stood for about 6.75 h, but formula F1 with the lowest concentration of the polymer took longer (about 1.5 min) to gel and quickly dissipated within 2.5 h. Addition of chitosan increasing the gelation time due to increase the formulas viscosity. Formula F4 turned into gel in few seconds faster than F1 (both of the formulas had same concentration of Pluronic F127 of 15% but F4 had 0.5% chitosan) and the gel stayed longer for 4.5 h. Formula F5 turned into gel and it is stood for 6.5 h which was longer than formula F2 which stood for 4 h. Same scenario was with formula F6 stood for 8 h that was longer than formula F3. Similar results was observed with ciprofloxacin in situ gel [39].

Spreadability test

Spreadability is a crucial evaluation test for the in situ gel and explain its ability to be applied and distributed over the nasal mucosa without leaking after delivery and the possibility of formulas distribution with time to check the spreadability of formulas before being transformed to gel. The results showed that the spreadability of gels were within the range of 0.19 to 0.35 cm^2/s. Spreadability of formulas reduced with increasing Pluronic F127 concentration as the spreadability of formula F1 was higher than F2 then F3. The presence of chitosan reduced the spreadability since increased the formulas viscosity and thickness. The spreadibility of formula F4 was lower than F1, formula F5 had lower spreadibility than F2 as well as formula F6 had lower spreadibility than F3 [40]. Moreover, the obtained data from all of the formulas showed suitable spreadability and comparable to similar results observed with darunavir in situ gel [24].

Mucoadhesive force determination

This test is important to ensure that the formulas had acceptable adhesion force and withstand the mucociliary clearance to allow the drug take enough time to permeate nasally. The mucoadhesive force of the formulas should be less than 10,000 $dyne/cm^2$. All the prepared formulas had agreeable force except F6 which had mucoadhesive force more than 10,000 $dyne/cm^2$ and could cause damage for the nose mucosa [41]. The mucoadhesive force of the in situ gel formulas resulted from the hydrogen bond formation between the mucin glycoprotein oligosaccharide chain in nasal mucosa and the formulas polymer [42]. The mucoadhesive force of the formulas (F1-F6) is shown in Table 2, and it was clear that when Pluronic F127 concentration increased (from 15% in F1, 18% in F2 to 20% in F3), the mucoadhesive force of the formulas was significantly ($p \leq 0.05$) increased as more compact lattice structures and higher densities were formed with in situ gel [30]. Formulas (F4-F6; containing constant amount of chitosan) showed that increasing percentage of Pluronic F127 had greater mucoadhesive forces than (F1-F3) and could be attributed to the presence of chitosan that may form more concentrated hydrogen bonds and synergised the effect of pluronic F127 [43]. Where formula F4 had higher mucoadhesive force than F1, formula F5 had higher than formula F2 and formula F6 had higher mucoadhesive force than formula F3. Similar results was observed with loratadine nasal mucoadhesive in situ gel [25].

Table 2. Physicochemical evaluation tests of in situ gel containing Lomustine nanoemulsion.

F-code	pH	Drug content	Osmolarity (mOsmol/L)	$T_{sol-gel}$ (°C)	Spreadability (cm^2/s)	Mucoadhesive Force ($dyne/cm^2$)	Gelation behaviour
F1	5.41±0.1	99.12±1.2	106.03	33	0.35	4965.33±11.3	+
F2	5.61±0.04	99.30±0.9	106.22	31	0.29	6500.67±8.12	++
F3	5.82±0.03	99.50±0.82	106.44	27	0.26	9865.33±3.2	+++
F4	5.53±0.01	99.24±2.11	106.16	32	0.30	5814.67±4.2	++
F5	5.63±0.02	99.19±2.32	106.11	30	0.24	7154±7.11	+++
F6	5.83±0.11	99.53±0.91	106.47	25	0.19	10420.67±22.4	+++

Ex-vivo residence time and drug percentage remaining on tissue

Residence time and drug percentage remaining on the tissue are important to determine the formulae's ability to stand against the normal nasal mucociliary clearance. The residence time for the formulas (F1-F6) was within a range of 30 to 76 min. The percent drug remaining on the mucosa was between 77.35% for F1 and 83.14% for F6, as shown in Table 3. The residence time and percentage of drug remained on the nasal mucosa of the formulas were related directly to the concentration of the gelling polymer where the percentage of Pluronic F127 increased (F3>F2>F1), both Ex-vivo residence time and drug percentage remaining on the tissue significantly ($p \leq 0.05$) increased due to increase the mucoadhesion force, and presence of chitosan in F4-F6 significantly ($p \leq 0.05$) enhanced the residence as well because this polymer increased the mucoadhesion then residence of the polymer and the drug as formula F4 had higher residence time and percent of drug remaining on the tissue than formula F1, formula F5 had higher than F2 and formula F6 showed higher time of residence and percent of drug remaining on the tissue [43, 44].

Table 3. Residence time and drug percentage remaining on the tissue of the prepared mucoadhesive formulas.

F-code	Residence time (min)	%Drug percentage Remaining on the tissue
F1	30±1.5	77.35±1.2
F2	61±2.00	79.23±2.9
F3	66±1.75	81.22±2.81
F4	40±1.33	79.56±0.82
F5	69±3.33	82.11±2.45
F6	76±2.67	83.14±1.55

In vitro Lomustine release

Figure 3 shows the release pattern of the prepared formulas (F1-F6). Formula F1 containing the lowest percent of Pluronic F127 (15%) gave significantly ($p \leq 0.05$) higher percent of drug release (100%) after 120 min. Formulas with higher percent of Pluronic F127 gave significantly ($p \leq 0.05$) delayed release, where formula F2 (18% Pluronic F127) gave 100% drug release after 180 min, and formula F3 (20% Pluronic F127) need 210 min to release its loaded drug. This is due to the decreasing the water channels leading to reinforcement micellar structure [29], that agreed with previous results for indomethacin in situ gel [45].

Formulas containing chitosan (F4-F6) showed significant ($p \leq 0.05$) decrease in Lomustine release, where F6 (containing 0.5% chitosan beside a higher percent of Pluronic F127 of 20%) reached 100% within 300 min. This was due to chitosan crosslinking could slow down the release [46]. Similar results were observed with Orthosiphon Stamineus Extracts in situ gel [47].

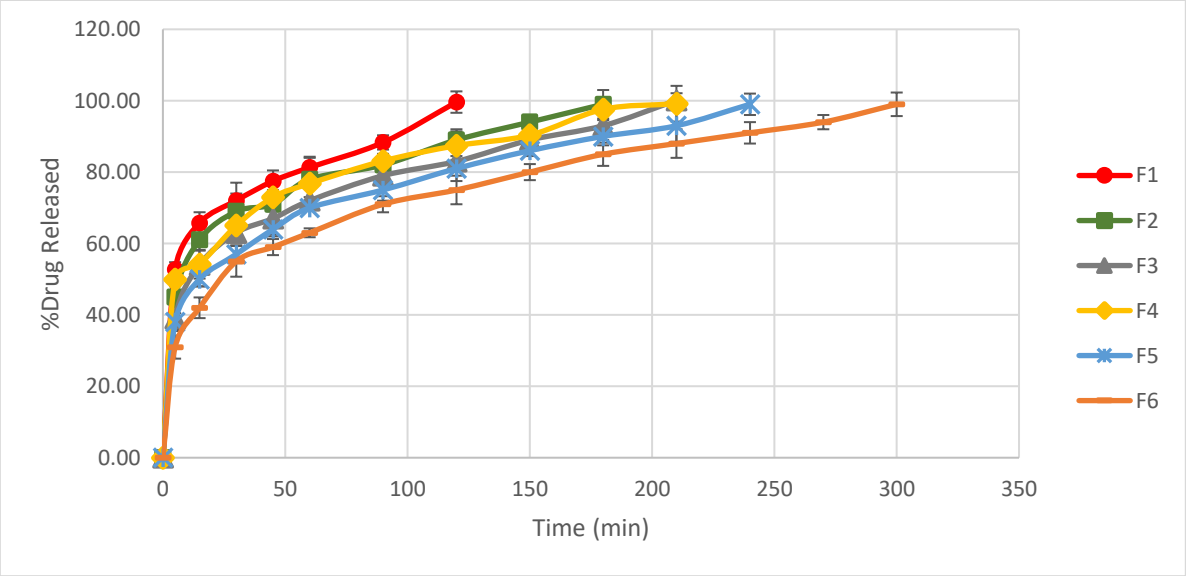

Figure 2. In vitro release of lomustine from the prepared in situ gel in PBS pH 6.4 (mean ± SD) (n=3).

Conclusion

The aforementioned results demonstrated the effect of gelling polymer (Pluronic F127) on the formulated nano-emulsion based mucoadhesive in situ gel of Lomustine for nasal delivery to the brain. The produced in situ gel revealed that increased Pluronic F127 concentration reduced gelation temperature, enhancing the gelation behaviour, reduced spreadability, increased the mucoadhesive force, prolonged residence time and sustained the drug release. The work also revealed that the addition of chitosan with Pluronic F127 (in the optimum formula F4) lead to improve the formula characteristics involving reduction of sol-gel transition temperature (and still compatible with nose temperature), enhanced the gelation behaviour to gel within few seconds and stayed longer, increased the ex-vivo residence time, good percentage of drug remaining on the tissue, and increased the mucoadhesive force. Such formula may be a good potential for the nasal delivery of the drug to give fast onset of action, improving drug targeting to the brain and reduces the systemic side effects associated with oral administration.

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Conflicts of Interest

The authors would like to confirm that there are no conflicts of interest with this publication.

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Ethics Statements

The study did not need ethical approval from an ethics committee.

Author Contribution

The authors contributed to the manuscript equally.

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