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Research Article

Preparation and Evaluation of Paliperidone Thermal Muco-Adhesive in Situ Gel as a Nasal to Brain Delivery System

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Abstract

Background: Paliperidone PAL is a second-generation (atypical) antipsychotic medication widely used in the treatment of schizophrenia disorders. It is practically insoluble in water (class II) and has a first-pass metabolism, with oral bioavailability of about 28%. ***Objective:*** To optimize and evaluate PAL in a nanothermal residence gel as an intranasal in situ gel formula near or at the site of the nasal-brain delivery system. ***Methods***: The previously prepared nanosuspension formula of PAL was introduced into the creation of in-situ gel formulas using Poloxamer 407 (18–20%w/v), hydroxypropyl methylcellulose HPMC K4 (0.5–1%w/v), and hyaluronic acid (0.5–1%w/v). The selected prepared formula was subjected to different *in vitro* evaluation studies. ***Results***: The previously prepared nanosuspension formula of PAL, which enhanced its dissolution rate using Soluplus® as a stabilizer, was incorporated into mucoadhesive thermal sensitive gel formulas, using poloxamer 407 as a thermal gelling agent and different concentrations of mucoadhesive polymers. The formula NIG, which contains 20% w/w poloxamer 407 and 1%w/w HPMC K4, exhibited favorable and accepted Characteristics, including the ideal gelation temperature of 33°C and drug content of 99.96%, gel strength of 55.0 seconds, spreadability of 5.2cm, and 98.0% in vitro cumulative drug release extended for 6 hours in simulated nasal fluid (SNF) at pH 6.5 maintained at 34°C. ***Conclusions***: The current mucoadhesive in situ gel PAL formula is a promising nasal-to-brain formula that can be used for the management of psychotic disorders drug therapy in the future.

Keywords: In situ gels, Paliperidone, Poloxamer 407, Thermo-sensitive polymers.

تحضير وتقييم مادة هلام انفي حراري حساس كنظام توصيل من الأنف إلى الدماغ

الخلاصة

الخلفية: بالبيريدون دواء مضاد للذهان من الجيل الثاني (غير نمطي) يستخدم على نطاق واسع في علاج اضطرابات الفصام. وهو عمليا غير قابل للذوبان في الماء (الفئة الثانية)، وله استقلاب أولي، مع توافر حيوي عن طريق الفم حوالي 28٪ .**الهدف:** تحسين وتقييم بالبيبريدون كتركيبة هلامية موضعية داخل الأنف بالقرب من أو في موقع نظام توصيل الأنف إلى الدماغ .**الطرائق:** تم إدخال صيغة التعليق النانوي المُعدة مسبقًا لـبالبيبريدون في إنشاء صيغ هلامية في الموقع باستخدام بولوكسامير 18-20%وزن/حجم، وهيدروكسي بروبيل ميثيل سلولوز HPMC K4 0.5-1% وزن/حجم، وحمض الهيالورونيك (0.5-1% وزن/حجم). تم إخضاع الصيغة المعدة المختارة لدراسة تقييمية مختلفة في المختبر.**النتائج:** تم دمج صيغة التعليق النانوي المعدة مسبقًا لـ بالبيبريدون، والتي عززت معدل الذوبان باستخدام سوليبلس كمثبت، في صيغ هلامية حساسة للحرارة لاصقة مخاطية، باستخدام بولوكسامير 407 كعامل تبلور حراري وتركيزات مختلفة من البوليمرات اللاصقة المخاطية. أظهرت النتائج أن الصيغة NIG التي تحتوي على وزن 20% بولوكسامير 407 ووزن 1 % من الهيدروكسي بروبيل مثل سيليلوز أظهرت خصائص مفضلة ومقبولة، بما في ذلك درجة حرارة التجلن المثالية البالغة 33 درجة مئوية ومحتوى الدواء 99.96%، وقوة الهلام 55.0 ثانية. ، قدرة الانتشار 0.14 سم، و 98.0٪ في المختبر إطلاق الدواء التراكمي ممتد لمدة 6 ساعات في السائل الأنفي المحاكي pH 6.5 عند درجة حرارة 34 درجة مئوية. **الاستنتاجات**: إن صيغة بالبيبريدون من الجل المخاطي الموضعي الحالي هي صيغة واعدة لتوصيل الدواء من الأنف إلى الدماغ ويمكن استخدامها للعلاج الدوائي للاضطرابات الذهانية في المستقبل.

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INTRODUCTION

Intranasal administration is a recognized method for delivering active pharmaceutical ingredients, achieving either local or systemic effects. Its significance is increasing due to the unique anatomical connection it has with the brain [1]. The olfactory and trigeminal nerves, situated in the olfactory and respiratory regions, respectively, facilitate the absorption of drugs from the nose to the brain, targeting the central nervous system (CNS) [2]. Consequently, direct access to the brain enables drugs to skip the first-pass effect and circumvent the blood-brain barrier; this will lead to enhanced bioavailability, greater accumulation in the central nervous system, and a more rapid onset of action. These properties are crucial for managing acute seizure episodes [3]. Nanosuspensions (NS) present an important opportunity for nose-to-brain drug delivery by enhancing the absorption and bioavailability of various poorly soluble drugs through intranasal administration. Nanosuspensions

are defined as dispersions of drug nanoparticles in appropriate polymers and/or surfactants, with particle sizes typically less than 1 µm, predominantly ranging from 200 to 500 nm [4]. Due to their small particle size and extensive surface area, nanostructures have advantages in augmenting the solubility and dissolution rate of poorly soluble pharmaceuticals [5]. Nevertheless, liquid suspensions experience brief retention durations in the nasal cavity owing to swift mucociliary clearance. This issue can be addressed through the application of intelligent stimuli-responsive systems [6]. The in situ gelling formulation is one of the most often employed procedures among these systems. Following intranasal administration, induced by physiological parameters (temperature, ion concentration, and water content), the solution converts into a gel, facilitating a more precise dosage delivery [7]. These in situ gels have a number of benefits, including a simple manufacturing procedure and great permeability of therapeutic agents, and they have been found to increase the nasal retention period, which in turn improves the drug delivery efficiency [8]. Paliperidone (PAL) is an antipsychotic drug used in schizophrenia. It belongs to the class of benzisoxazole derivatives and is the primary active metabolite of risperidone. Paliperidone acts primarily through antagonizing dopamine D2 and serotonin 5-HT2A receptors in the brain, leading to its therapeutic effects in managing psychotic symptoms [9]. PAL (Figure 1) has an MWt of 426 g/mole, is practically insoluble in water (30 mg/L), is class II, and has a log p of 2.39.

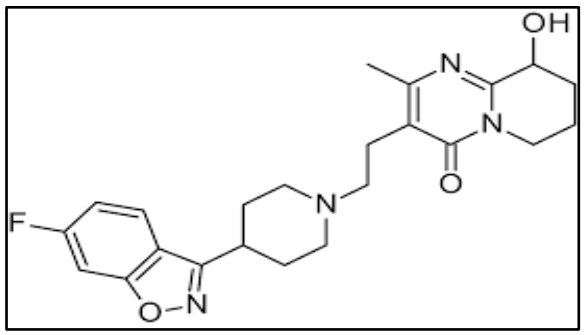

Figure 1: Chemical structure of paliperidone (PAL).

The pharmacokinetic properties of paliperidone include its relatively long half-life of t½ 23 hours, with oral bioavailability of 28% [10]. Nanosuspensions incorporated within an in situ gel represent a compelling approach for the nose-to-brain administration of poorly soluble pharmaceuticals, leveraging the benefits of both nanosuspensions and in situ gels. The formulation of PAL as a nasal nanosuspension utilizing nanotechnology addresses the primary barrier to drug delivery, mucociliary clearance. This is achieved by incorporating a temperature-sensitive polymer, such as poloxamer 407, to enhance the poor oral bioavailability of PAL in tablet form and to facilitate in-situ gelling properties [11]. This study aims to optimize and evaluate PAL in a nanothermal residence gel as an intranasal in situ gel formula near or at the site of the nasal-brain delivery system.

METHODS

Materials

PAL powder was purchased from Heowns Biochem Technologies, LLC, in Tianjin, China. Hangzhou Hyper Chemicals Limited of Zhejiang, China, provided Soluplus®, HPMC KM4, and hyaluronic acid. Poloxamer 407 was obtained as a generous gift from BASF. Benzalkonium chloride was obtained as a generous gift from Al-Hayat, Iraq. HIMEDIA (Mumbai, India) provided the dialysis membrane 70. All remaining chemicals and solvents were of analytical reagent-grade quality.

Preparation of intranasal mucoadhesive nano-in situ gel

The paliperidone nanosuspension was prepared using the anti-solvent precipitation technique. 6 mg of PAL were dissolved in 2 ml of ethanol, representing a solvent system. The anti-solvent system comprises 10 ml of distilled water and 18 mg of Soluplus as a stabilizer. The organic phase was slowly added dropwise through a needle attached to a plastic syringe and directly into a water solution at room temperature [12,13]. The cold fashion for in situ gel preparation was utilized in order to accomplish the preparation of the intranasal mucoadhesive NIG [14]. To obtain a clear solution, mucoadhesive polymer(s) (HPMC K4 and hyaluronic acid) were added to the NS formula that had been prepared. After that, the solution was stored in the refrigerator and cooled to a temperature of four degrees Celsius. After that, poloxamer 407, which is a thermos-responsive polymer, was added to the cold dispersion at concentrations of 18% and 20% by weight. Additionally, benzalkonium chloride was added as a preservative, and the mixture was stirred continuously at a speed of 500 revolutions per minute for a period of two hours [15]. This solution was stored in the refrigerator at a temperature of 4 degrees Celsius for an entire night. NIG1-NIG8 were the eight ING formulations that were created (Table 1).

Table 1: Composition of the PAL NIG formulas

Ingredient	NIG 1	NIG2	NIG 3	NIG 4	NIG 5	NIG 6	NIG 7	NIG 8
PAL (mg)	6	6	6	6	6	6	6	6
Soluplus® (mg)	18	18	18	18	18	18	18	18
Poloxamer 407 (%w/v)	18	18	18	18	20	20	20	20
HPMC K4 (%w/w)	0.5	1	-		0.5	1	-	-
Hyaluronic acid (%w/w)	-	-	0.5	1	-	-	0.5	1
Benzalkonium chloride (%w/w)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Evaluation of NIG Formulas

The pH of nasal formulation is crucial for the prevention of the growth of pathogenic bacteria, as well as the maintenance of normal physiological ciliary movement and prevention of nasal mucosal irritation [16]. The digital calibrated pH meter was employed to assess the apparent pH of all formulated NIG solutions (NIG1-NIG8) at ambient temperature 25°C. A 5 ml sample was placed in a 10 ml beaker. Precisely 1.0 ml of the formula equivalent to 3 mg/mL PAL from selected NIG formulas was diluted to 10 ml with SNF. Each one ml of this solution was diluted again to 10 ml with SNF. Finally, absorbance was determined at maximum absorption wavelength using a UV spectrophotometer [17]. Two milliliters of the refrigerated NIG formulae NIG1-NIG8 were placed in a 10 ml test tube, which has a diameter of 1.0 cm, and sealed with parafilm. The tube was kept in a water bath at a temperature of approximately 15 °C. The water bath temperature was incrementally increased by 1°C, with a 10-minute equilibrium period following each increment, until gelation was observed, at which stage the preparation remained stable when the test tube was tilted at 90º. [18]. The spreadability of the suggested IG formulations was assessed by depositing about 0.5 g of the IG formula, post-complete gelation, at the center of a glass plate (square area = 400 cm²). A second glass plate of identical dimensions was employed to cover the glass plate carrying the NIG formula. The initial diameter of the NIG was specified. A 0.5 kg scale weight was carefully positioned on the upper side of the plate for one minute, resulting in the NIG expanding between the plates. The ultimate diameter was recorded following the removal of the weight, and the spreadability was assessed in centimeters [19]. A 5 g sample of the NIG was placed in a 10 ml cylinder and immersed in a water bath for the gelation of the formulations. A mass of 3.5 grams was positioned on the surface of the NIG. The gel strength was assessed by the duration needed for the mass to penetrate 0.5 cm into the gel [20]. The viscosities of the formulated NIG samples (NIG1-NIG8) were assessed using a viscometer (NDJ-5S, China) and recorded after a duration of 30 seconds. Three sets of measurements were made using spindle number 4 and shearing speeds of 6, 12, 30, and 60 rpm at the gelation temperature of each NIG formula [11].

In vitro drug release study

PAL release investigations were conducted on a dialysis membrane with a molecular weight cut-off of 8000-14000 Da. The rotating paddle dissolution apparatus type II was used to test how well all eight formulated NIG samples released drugs in vitro. The sealed dialysis bag containing 6 mg of PAL was submerged in a dissolving medium of 300 ml of SNF (pH 6.4) at a rotation speed of 50 rpm. The medium temperature was preconditioned and sustained at 34±0.5°C. Five-milliliter aliquots were extracted at specified time intervals (15, 30, 60, 90, 120, 180, 240, 300, and 360 minutes) and promptly substituted with a new dissolving medium. The drug concentration in the retracted sample was quantified spectrophotometrically at 237 nm with a UV/Vis spectrophotometer [21].

Statistical analysis

The results obtained from the experiments are presented as the mean of three replicated samples and ± standard deviation (SD). These findings were analyzed using a one-way analysis of variance (ANOVA), and statistical significance was set at $p < 0.05$.

RESULTS

Table 2 shows that all of the NIG formulas had pH values between 5.0 and 5.9. These values are in line with the range given for intranasal formulas (4.5 to 6.5), and they are compatible with pH of the nasal mucosa [22].

Table 2: Different properties of paliperidone PAL as mucoadhesive nasal in situ gel formulas

Formula No.	pH	Drug content (%)	Gelation Temp (ºC)	Gel strength (Sec)	Spread ability (cm)
NIG 1	5.83±0.20	99.86±0.1	37±0.2	42±0.2	6.8±0.3
NIG 2	5.96±0.15	99.31±0.06	36±0.36	40±0.8	6.5±0.24
NIG 3	5.66± 0.05	99.56±0.07	37±0.16	45±3.2	6.3±0.21
NIG 4	5.56± 0.05	98.86±0.1	36±0.21	49±1.6	5.9±0.18
NIG 5	5.42±0.15	100.5±0.02	34±0.16	51±2.3	5.6±0.22
NIG 6	5.73±0.25	99.96±0.1	33±0.06	55±3.5	5.2±0.14
NIG 7	5.56± 0.05	99.936±0.01	36±0.41	56±0.6	5.4±0.31
NIG 8	5.51±0.25	99.27±0.05	36±0.32	58±1.5	5.1±0.11

Moreover, the drug content of all formulas (NIG1-NIG8) revealed over 98.86% that are agreed with the requirements of USP. Meanwhile, the gelation temperature of formulations NIG1–NIG8 was found to be in the range of 33±0.06 to 37±0.16°C. Increasing the concentration of Poloxamer 407 from 18% w/w to 20% w/w significantly decreased the gelation temperature ($p < 0.05$). This was clear in formulations (NIG1-NIG4) as compared to formulations (NIG5-NIG8) containing 18 and 20% P407, respectively. The gel strengths of the formulations ranged from 40.0±0.8 to 58±1.5 sec, and the spreadability of the formulas ranged from 5.1±0.11 to 6.8±0.3 cm in terms of viscosity values for NIG formulas before and after the gelation temperature of each formula. A formulation should ideally have a low viscosity when administered to the nasal cavity; nevertheless, following administration, it should have enough viscosity to remain at the site of application. The viscosity of formulations both in solution and gel states is illustrated in Figures 2 and 3.

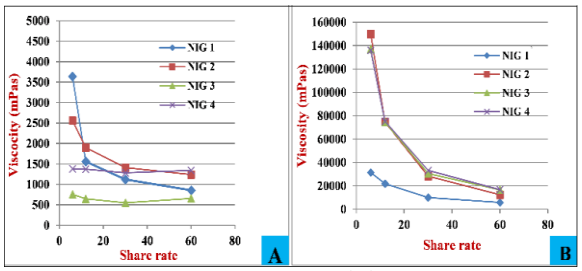

Figure 2: Rheological evaluation: of formulas NIG (1-4) in presence of 18%w\w poloxamer (A) before gelation and (B) after gelation.

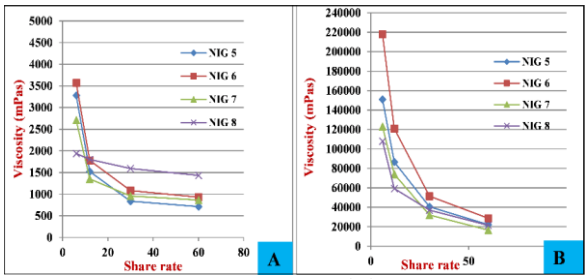

Figure 3: Rheological evaluation: of formulas NIG (5-8) in presence of 20%w\w poloxamer (A) before gelation and (B) after gelation.

Figures 4 and 5 display the PAL release profiles for the NIG1–NIG8 formulas. The NIG formulas with 18% poloxamer-407 (NIG1, NIG2, NIG3, and NIG4) demonstrated a higher percentage of release after 5 hours compared to the NIG formulas with 20% poloxamer-407 (NIG5, NIG6, NIG7, and NIG8), which showed a higher percentage of release after 6 hours.

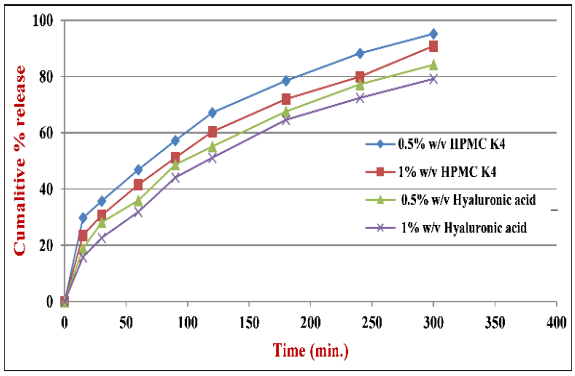

Figure 4: Effect of muco-adhesive polymers concentrations on cumulative percent PAL released profile in presence of 18%w\w poloxamer 407 in SNF pH 6.5 at 34±1°C.

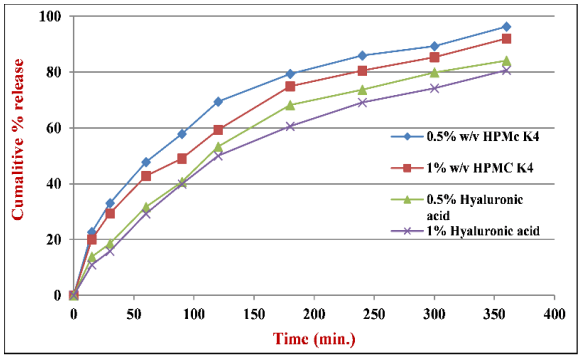

Figure 5: Effect of muco-adhesive polymers concentrations on cumulative percent PAL released profile in presence of 20%w\w poloxamer 407 in SNF pH 6.5 at 34±1°C.

DISCUSSION

Thoroughly evaluating formulation aspects is crucial, as none of the components should irritate the nasal mucosa. The pH of the formulation should closely match that of the nasal mucosa, ranging from 5.0 to 6.5. Additionally, the formulation should be isotonic to slightly hypertonic to prevent any feelings of discomfort or toxicity in the nasal epithelium to avoid enhancing mucociliary clearance [22]. The pH for every formula in the present was determined and found to be within the suitable range for the nasal passages, between 5.0 and 5.9 [23]. The medication content was determined for all manufactured in situ gel formulations. The acceptable range of medication content is above 85%, according to BP 2023 pharmacopeia, indicating that all the formulations exceeded the permissible amount. The drug content concentration is directly proportional to the polymer concentration. However, when the polymer concentration is very high, the drug concentration is slightly lower than the previous concentration [24]. The gelation temperature of formulations (ING1-ING8) was found to be in the range of 33±0.06 to 37±0.16°C. Increasing the concentration of P407 from 18% to 20% significantly decreased the gelation temperature (p<0.05). The reduction in gelation temperature of in situ gel formulations with an increase in the concentration of P 407 can be elucidated by a higher proportion of polypropylene oxide (PPO) units, leading to dehydration and the formation of a greater number of micelles at a lower temperature, facilitating easier gelation [25]. The addition of other formula ingredients will affect the gelation temperature. The impact of additives on the gelation temperature was found to depend on their nature and concentration of the additives used, HPMC K4M or HA. The concentration of mucoadhesive polymer HPMC used increased from 0.5 to 1% w/v, while for HA, the concentration was 0.5% and 1% w/v and produced a gradual decrease in the gelation temperature of the corresponding intranasal IG. For the same concentration of the mucoadhesive polymer HA, formulas with lower gelation temperature than the HPMC K4M were produced since HA has higher viscosity. The reduction in gelation temperature caused by HA and HPMC K4M can be attributed to their capacity to interact with the polyoxyethylene chain found in poloxamer molecules. This will promote dehydration, resulting in heightened complexity of adjacent molecules and extensive intermolecular hydrogen bonding, ultimately leading to gelation at lower temperatures [26]. Gel strength was influenced by the concentrations of thermosensitive and mucoadhesive polymers. Table 2 presents the data regarding gel strength. With an increase in polymer concentration, there was a corresponding increase in gel strength. Among the polymers examined, HA exhibited greater gel strength than HPMC K4M. The increase in gel strength may be attributed to hydrogen bonding interactions between Poloxamer and mucoadhesive polymers in the intranasal IG

[27,28]. Also, the results revealed that as the concentration of the poloxamer and mucoadhesive polymer increased, the viscosity of the solution increased, and the readability decreased. The spreadability of mucosal semisolid preparation is related to the hardness or firmness, rate, and time of shear produced upon smearing and the temperature of the target site as well as the viscosity of the formulation. All the prepared formulations gave acceptable spreadability (2.5-7 cm), and these results agreed with reported data [29]. All the preparations showed relatively low viscosity at low temperature, while there was a significant increase in viscosity at the point of gelation temperature. However, increasing the gelation temperature at gelation temperature results in a well-defined gel form; therefore, the viscosities are higher. Increasing the concentration of poloxamer increased the viscosity of formulations both in solution and in gel state. This can be attributed to the rise in both the number and size of micelles, which increased the micelle count per unit volume and led to a greater number of cross-links among adjacent micelles [30]. Moreover, increasing the concentration of mucoadhesive increased the viscosity of formulations. Such an effect can be related to the increasing crosslinking of the polymers and is consistent with those observations reported in earlier studies [31]. As shown in Figures 2 and 3, viscosities decreased as the shear rate increased. All gel formulations exhibited non-Newtonian flow and shear-thinning properties. Shear-thinning features are considered advantageous for thermosensitive hydrogels destined for nasal administration since they will increase the spreadability of the gels and their ability to remain at the site of application [32]. The cumulative drug release profiles from different nasal drug delivery (NIG1, NIG2, NIG3, and NIG4) are shown in Figure 4. The cumulative PAL release from all the formulations after 5 hours. The formulation comprising 18% w/v P 407 exhibited the highest drug release of 99.88% after 5 hours. And the formulation comprising 20% w/v P 407 exhibited the highest drug release of 99.88% after 5 hours. On comparing the drug release profiles, it is evident that the release of PAL was reduced with an increasing concentration of poloxamer as well as the concentration of mucoadhesive polymer. This behavior may be attributed to the decreased number and dimensions of channels in the micellar structure at higher poloxamer and creating a higher viscosity gel network with mucoadhesive polymer, trapping the drug and hindering its release [33].

Conclusion

In terms of gelation temperature, drug concentration, viscosity, and mucoadhesive strength, formulation NIG 6 (poloxamer 407: 20% and HPMC K4: 1%) was shown to be acceptable. The results indicate that the suggested formulation is suitable for nasal delivery, with a good retention period and a controlled drug release effect.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

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

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