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Original Article

Fabrication, optimization and characterization of an osmotic push-pull drug delivery system for paliperidone

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الملخص

أهداف البحث: بالبيبريدون هو عقار نظام تصنيف الصيدلة الحيوية الدرجة الثانية ذو قابلية منخفضة للذوبان ونفاذية عالية. يحتوي على 28 ٪ من التوافر الحيوي عن طريق الفم المطلق ونصف عمر التخلص منه 23 ساعة. من أجل تحقيق إطلاق متحكم به على مدى فترة طويلة من الوقت بجرعة منخفضة وتجنب الحاجة إلى جرعة تحميل، يباع الجهاز اللوحي ثلاثي الطبقات التناضحي الدفع والسحب حاليا في السوق. ومع ذلك، فإن الأجهزة اللوحية ثلاثية الطبقات لها عيوب عديدة مثل العملية المعقدة وتكلفة الإنتاج العالية وصعوبة تحقيق توحيد المحتوى. وبالتالي كان الهدف من هذه الدراسة هو التغلب على الصعوبات المذكورة أعلاه المرتبطة بالريسبيريدون وصياغة قرص ثنائي الطبقة له خصائص دوائية مماثلة لتلك الخاصة بالعقار المرجعي إنفيجا.

طريقة البحث: تم تحضير الأقراص ثنائية الطبقة عن طريق تحسين اللب والغشاء شبه المنفذ. تم تحليل التأثير الإضافي لوقت المعالجة مع حجم وعدد الفتحة على ملف الذوبان للأقراص المعدة. تم استخدام درجتين مختلفتين من أكسيد البولي إيثلين في الطبقة الأساسية وطبقة الدفع كمشكلين للمسام.

النتائج: كانت قيم اختلاف الوزن والقابلية للتلف والصلابة للأقراص المحضرة ضمن حدود الخلاصة. كانت المعلمات المحسنة ثنائية الطبقة للقرص المحضر هي وقت المعالجة 5 ساعات، وطبقة الختم 7٪ وزن/وزن، وغطاء "إي آر" 13% وزن/وزن، وحجم الفوهة 0.6 مم، وعدد الفوهة -02. أظهرت صياغة أخرى للأقراص قيمة "إف 2" تبلغ 75.67 مما يشير إلى أن ملف تعريف الذوبان الخاص بها مشابه للدواء المرجعي إنفيجا.

الاستنتاجات: وهكذا في العمل الحالي، تم إعداد قرص ثنائي الطبقة من الباليبيريدون للتغلب على العيوب المرتبطة بالتركيبة المسوقة بنجاح، مما يوفر مزايا مثل عملية تحضير أبسط، وفعالية من حيث التكلفة، وإعداد أقل استهلاكا للوقت للب القرص.

الكلمات المفتاحية: بالبيبريدون؛ نظام دفع-سحب تناضحي؛ طبقة ثنائية؛ مسام سابقة؛ أوسموجين؛ غشاء شبه نافذ

Abstract

Objectives: Paliperidone is a BCS class II drug with low solubility and high permeability. It has 28% absolute oral bioavailability and an elimination half-life of 23 h. An osmotic push–pull trilayer tablet currently available on the market has achieved controlled release of a low dose over an extended time period, while avoiding the need for a loading dose. However, this trilayer tablet has several disadvantages, such as complicated processing, high production costs and difficulty in achieving uniformity of the contents. Thus, the objective of this study was to overcome the above difficulties associated with paliperidone and to formulate a bilayer tablet with a similar drug profile to that of the reference listed drug Invega®.

Methods: The bilayer tablets were prepared by optimization of the core and semi-permeable membrane. Effects of the curing time, and the size and number of orifices on the prepared tablets' dissolution profile were analyzed. Two different grades of polyethylene oxide were used in the core and push layer as pore formers.

Results: The weight variation, friability and hardness values of the prepared tablets were well within compendium limits. The optimized bilayer parameters for the prepared tablets were curing time, 5 h; seal coat, 7% w/w;

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ER coat, 13% w/w; orifice size, 0.6 mm; and orifice number, 2. Further tablet formulation resulted in an F2 value of 75.67, indicating a dissolution profile similar to that of Invega®.

Conclusion: Bi-layer tablets of paliperidone overcoming the drawbacks of the marketed formulation were successfully prepared, and offer advantages such as a simpler preparation process, cost effectiveness and faster preparation of the tablet core.

Keywords: Bi-layer; Osmogen; Paliperidone; Pore former; Push-pull osmotic system; Semi-permeable membrane

Introduction

Recent efforts have focused on rigorously developing controlled release dosage forms to maintain the plasma levels of drugs within desired ranges. Controlled drug delivery systems offer temporal and/or spatial control of drug release, and have numerous advantages, such as maintaining constant drug levels at sites of action, preventing fluctuations in peak-plasma concentrations, decreasing the required doses and dosing frequencies, minimizing adverse effects and increasing patient compliance.[1]

Osmotically controlled release oral delivery systems are progressively controlled drug delivery formulations. These systems use the osmotic principle, wherein osmosis is defined as the passage of solvent molecules through a semi-permeable membrane, from an area of low solute concentration to an area of high solute concentration. Drug delivery depends on the hydration kinetics of the membrane and core, the membrane permeability, the osmotic pressure of the core formulation and drug solubility. Formulations deliver drugs with zeroth order kinetics under the pressure generated by the swelling of the core at a constant rate.[2] Oral osmotic systems are classified into single chamber (elementary osmotic pump), multiple chamber (expandable and non-expandable membrane) or miscellaneous (controlled porosity, osmotic bursting, effervescent activity based, etc.) systems.[3]

An expandable osmotic pump/push–pull osmotic pump can deliver both poorly water soluble and highly water-soluble drugs at a constant rate. These multi-layer tablets contain one or more drug layers and a push layer (with osmogen) surrounded by a semi-permeable membrane with one or more orifices present on the drug layer side.[4] As the system imbibes surrounding biological fluid into the osmotic pump through the semi-permeable membrane, the osmogen dissolves, thus creating osmotic pressure and pushing the drug outside through the delivery orifice.

Paliperidone (9-hydroxyrisperidone), an active metabolite of risperidone, is a second-generation (atypical) antipsychotic agent, which exerts therapeutic effects primarily through antagonism of D_2 and 5-HT_{2A}, with higher affinity for the latter. Paliperidone is a BCS class II drug with low solubility and high permeability.[5] It has 28% absolute oral bioavailability and an elimination half-life of 23 h.[6] Furthermore, to achieve controlled release of low doses over extended time periods, while avoiding the need for a loading dose, the commercially available formulation Invega® (6 mg) was designed as an osmotic push–pull tri-layer tablet. However, trilayer tablet technology has several drawbacks, as follows: 1. The production process is relatively complicated and requires complex engineering. 2. Tri-layer tablet compression requires a special preparation process with high production costs. Two drug layers with different drug content must be prepared to achieve an initial increase in the release rate and subsequent controlled release, thus making determination of the drug content difficult. 3. For low drug doses, trilayer tablets pose problems in maintaining content uniformity.[6]

This study proposes the design, formulation and optimization of a bilayer osmotic push–pull tablet. The objective of this study was to overcome the above difficulties and drawbacks of tri-layer tablets. The bi-layer formulation is aimed enabling a simpler preparation processes; faster and more cost effective preparation of the tablet core; and a similar drug release profile to that of the reference product.

Materials and Methods

Paliperidone was obtained from MSN laboratories Pvt. Ltd. Lactose monohydrate (Pharmatose 200 M) was used as a diluent as well as an osmogen. Sodium chloride (Merck) served as an osmogen. The polyethylene oxides Polyox™ WSR N-80 and Sentry Polyox WSR 303 (Dow Chemical) were used as pore formers, and the latter was used as a swelling agent in the push layer. Polyvinylpyrrolidone (Povidone K-30; BASF) and butylated hydroxytoluene (Merck) served as binders for wet granulation. Ferric oxide (ROHA) was used as a colorant in the push layer, and stearic acid (BASF) was used for lubrication. Hydroxypropyl cellulose (Klucel LF, Ashland) served as a release retardant in the seal coat, and polyethylene glycol (PEG 6000, CRODA) served as a plasticizer in the seal coat and ER coat. Cellulose acetate served as a semi-permeable membrane and was used for the ER coat. Isopropyl alcohol (SDFCL) and dichloromethane (FINAR) were used as solvents in the binder solution and seal coat. The solvent used in the ER coat was an acetone (FINAR) and water mixture. For the top coat, Instacoat Universal was dissolved in water.[7]

Methods

Optimization of formulation

To optimize the tablet formulation, on the basis of a literature survey, a mixture of different ingredients in varying amounts was used for tablet compression (Table 1).

Preparation of the core

Co-sifting

Drug layer: The dispensed quantity of API was co-sifted with the excipients in a geometric manner. The diluent, lactose monohydrate (Pharmatose 200 M), was divided into three parts. Paliperidone was co-sifted with the first part and

Table 1: Drug and push layer composition, with the role of each excipient in the compressed coated tablet indicated.[29]

Ingredients (mg)	F1	F2	F3	F4	Role
Drug layer					
Paliperidone	6	6	6	6	Anti-psychotic
Lactose monohydrate	28.22	20.22	33.72	20.22	Diluent/filler
Sodium chloride	11.00	11.00	5.50	5.50	Osmotic agent
Polyox WSR N-80	52.00	60.00	52.00	60.00	Rate controlling polymer
Povidone K-30	2.00	2.00	2.00	2.00	Binder
BHT					Anti-oxidant
Isopropyl alcohol	0.025	0.025	0.025	0.025	Solvent
Dichloromethane	q.s.	q.s.	q.s.	q.s.	Solvent
Stearic acid	q.s.	q.s.	q.s.	q.s.	Lubricant
Push layer					
Sentry Polyox WSR 303	55.12	55.12	55.12	55.12	Pore former
Sodium chloride	20	20	20	20	Osmotic agent
Ferric oxide	0.2	0.2	0.2	0.2	Colorant
Povidone K-30	3.9	3.9	3.9	3.9	Binder
BHT	0.025	0.025	0.025	0.025	Anti-oxidant
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	Solvent
Dichloromethane	q.s.	q.s.	q.s.	q.s.	Solvent
Stearic acid	0.75	0.75	0.75	0.75	Lubricant

subsequently with the remaining two parts. Sodium chloride and Polyox WSR N-80 were co-sifted and added to the above mixture.

Push layer: Sentry Polyox WSR 303, sodium chloride and ferric oxide were co-sifted and mixed.

Binder preparation: The dispensed quantities of butylated hydroxy toluene and povidone K-30 were added to isopropyl alcohol and stirred to form a clear solution. Dichloromethane was added to the above solution for both the drug layer and push layer.

Granulation: A paliperidone push–pull osmotic tablet was prepared with the wet granulation method. After sifting, the material was transferred to a rapid mixer granulator for dry mixing, followed by binder addition and kneading. The granulated material was collected through the discharge port.[8]

Drying and milling: The granules were transferred to a fluidized bed dryer bowl for 20 min. Dried granules were passed through #20 ASTM. Retained granules were milled with a Uni-Co-Mill.

Lubrication: On the basis of the practical yield, stearic acid was dispensed, added to the granules, transferred to a double-cone blender and rotated for 3 min at 24 rpm.

Compression: The bilayer tablets were compressed with a 6 mm punch to a thickness of 7.4 mm and weight of 180 mg.[9]

Coating

Seal coat: The dispensed quantity of PEG 6000 was added to dichloromethane under constant stirring. Isopropyl alcohol, followed by Klucel LF (HPC), was added, and stirring continued until a clear solution formed. The solution was sprayed for 2 h. The tablets were dried at 50 °C for 20 min to achieve the target weight gain.

Film coat: To a stainless steel container, the dispensed quantities of acetone, purified water and PEG 6000 were added under constant stirring to obtain a clear solution. To the above solution, cellulose acetate was added and stirred until completely dissolved. Coating was performed for 4 h to achieve the target weight gain, and the tablets were cured for 1 h at 50–55 °C.[10]

Top coat: Instacoat Universal was dissolved in water and sprayed to form a uniform coat.

The bilayer tablets were compressed with a Cadmach (CMD3-16MT, Mumbai, India) instrument, then coated with a Gansons (GAC 380/275, India) coating machine.

In-process quality control of the tablet blend

The flow properties of dried granules were estimated before compression into tablets.

i. Bulk density: Bulk density was determined by placing the powder in a measuring cylinder and measuring the volume and weight of the total powder. Bulk density was determined with a tab density tester (LAB India, India, model-TD 1025).[11]

$$bulk\ density = \frac{M}{V}$$

where M = weight of the test sample
V = unsettled apparent volume

ii. Tapped density: The tapped density is a limited density attained after "tapping down," usually in a device that lifts and drops a volumetric measuring cylinder containing the powder from a fixed distance. Tapped density was determined with a tab density tester (LAB India, India, model-TD 1025).[11]

$$tapped\ density = \frac{M}{Vf}$$

where
M = weight of the test sample
Vf = final tapped volume

iii. Hausner's ratio: This indirect index indicates the flowability of a powder, and flow indicates the flowability of a powder, and is defined as the ratio of tapped density to bulk density. Hausner's ratio was calculated as[11]:

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

iv. Compressibility index: This index is a measure of the property of powder compressibility. The packing ability of the drug was evaluated from the change in volume due to rearrangement of packing during tapping. The compressibility index was defined as Carr's index/compressibility index and was calculated as follows.[11]

$$Carr's\ index\ (\%) = \frac{(tapped\ density - bulk\ density)}{tapped\ density} \times 100$$

Evaluation of compressed coated tablets

Tablets were evaluated for weight variation, thickness, diameter, hardness and friability after compression.

i. Weight variation test: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of the 20 tablets was calculated. The observations were compared with USP Pharmacopoeial limits for weight variation.[12]
ii. Uniformity of thickness: Ten tablets were selected at random from the final formulation batch, and their thickness was measured individually with Vernier calipers (Mitutoyo, Japan; model-CD-6ASX). Thickness was expressed in millimeters, and the average was calculated.
iii. Diameter: Ten tablets were selected at random from the final formulation batch, and their diameters were measured individually with Vernier calipers (Mitutoyo, Japan; model-CD-6ASX) in millimeters, and the average was calculated.
iv. Hardness test: Tablets were randomly selected from the final batch, and their hardness was measured with a hardness tester (LAB India, India; Model-TH 1050 M) in Newtons (N).[13]
v. Friability: The friability of the tablets was determined with a Roche Friabilator (LAB India, India; Model-FT 1020) instrument and expressed as a percentage. Ten tablets were initially weighed and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 min, and the tablets were weighed again. The friability was then calculated with the following formula.[13]

$$\text{friability}(\%) = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

vi. *In vitro* dissolution: In the development of a generic drug product, comparison of the dissolution profile with that of the reference listed drug (RLD) is important for quality control. The dissolution profile was evaluated with a USP type II apparatus with simulated gastric fluid pH 1.0 (pepsin, and NaCl 0.2% w/v in 0.0825 N HCl) as the medium and a paddle speed of 50 rpm. The study was performed for 24 h in 500 mL medium with time points of 1, 2, 4, 6, 8, 12, and 24 h. All samples were analyzed with a symmetry C18 column, 100 Å, 5 µm, 3.9 mm × 150 mm on an HPLC (e2695, Waters Milford, MA) system with a 275 nm detector. The mobile phase consisted of acetonitrile:ammonium acetate buffer, pH 4.0 (50:50 v/v), at a flow rate of 0.8 mL/min. Similarity and difference factors were calculated for comparison of dissolution profiles of the test product and innovator product.[14]

On the basis of the results of the above tests, tablet composition was optimized, and further optimization was performed as described below. Mathematical modeling of the dissolution data was performed to assess the best fit for zeroth order, first order and Korsemeyer Peppas models, according to R^2 values.[15]

Optimization of curing time

On the basis of the dissolution profiles of the prepared tablets, F1 was found to be optimized, and further studies were performed. Three different time points were selected as curing times for the F1 batch (Table 2).[16]

Table 2: Effects of curing time and ER % weight gain on the prepared tablets (n = 3, mean ± SD).

Batch No.	Parameter
Curing time (hrs)	
F5	0
F6	03
F7	05
ER % weight gain	
F8	11 ± 1.23%
F9	13 ± 1.08%
F10	15 ± 1.64%

Optimization of extended-release percentage weight gain

A trial for lesser percentage weight gain of the ER coat was performed according to the decreased percentage drug release after curing of tablets for 5 h.

Optimization of orifice size and number

Two different orifice sizes and numbers were studied to observe any deviations from the innovator formulation. Single and double drilled tablets with 0.6 mm and 0.8 mm orifices were manufactured.[17] The laser drilling was performed with an R & D laser from Ackley Machine Corporation, USA.

Content uniformity

Ten tablets from the optimized batch of paliperidone were randomly selected, and the paliperidone content of each tablet was estimated individually, per compendium standards.

Stability studies

The optimized batch was subjected to stability study evaluation. The optimized tablet batch was stored at two conditions, 25 °C/60% RH and 40 °C/75% RH, for 1 month. The samples' physical and chemical parameters were evaluated. The similarity factor (F2) for both conditions with respect to the initial (0 month) drug release profile was calculated for comparison.[18]

Results and discussion

In-process quality control

Flow properties of the tablet blend, such as bulk density, tapped density, Carr's index and Hausner's ratio, are important for manufacturing and may affect the physical properties of the tablet, such as thickness, hardness, weight variation and content uniformity[19] (Table 3). The flow properties of the drug layer blend were fair, because the values were in the range of 16–21, whereas the values for the push layer blend were in the range of 12–16. Thus, the push layer tablet blend had good flow properties. Of note, the drug layer blend had lactose monohydrate Pharmatose® M200 grade,

Table 3: Estimation of flow properties and loss on drying of the prepared tablet blend (n = 3, mean ± SD).

Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Loss on drying (%)
Drug layer					
F1	0.5126 ± 0.065	0.6280 ± 0.091	16.94 ± 1.95	1.2039 ± 0.245	0.3 ± 0.02
F2	0.4923 ± 0.057	0.6077 ± 0.045	15.90 ± 2.03	1.1945 ± 0.142	0.5 ± 0.015
F3	0.5211 ± 0.021	0.6292 ± 0.076	16.88 ± 1.78	1.2110 ± 0.321	0.3 ± 0.035
F4	0.5045 ± 0.072	0.6112 ± 0.057	16.92 ± 1.67	1.2061 ± 0.721	0.3 ± 0.072
Push layer					
F1	0.5284 ± 0.067	0.6066 ± 0.089	12.90 ± 2.11	1.1481 ± 0.624	0.2 ± 0.072
F2	0.5214 ± 0.084	0.6102 ± 0.091	13.56 ± 1.64	1.1428 ± 0.413	0.4 ± 0.02
F3	0.5198 ± 0.059	0.6219 ± 0.082	11.98 ± 1.82	1.1399 ± 0.276	0.5 ± 0.034
F4	0.5238 ± 0.076	0.6098 ± 0.076	12.42 ± 1.73	1.1467 ± 0.371	0.2 ± 0.71

which is intended for wet or dry granulation. Lactose M−200 intended for granulation has been reported to generally have small particles, with a median particle size of 70 µm.[20] Owing to its small particle size, M200 has been found to have poor flowability. Thus, the presence of lactose monohydrate in the drug layer blend hampered the overall flowability with respect to that of its push layer counterpart.

Physical evaluation of compressed coated tablets

Weight variation: To ensure dosage uniformity, each unit should contain a narrow range of active substance according to the label claim. We performed weight variation tests[13] in which 20 tablets were selected at random and weighed individually. The observed individual weights of tablets for all batches were found to be within the limits, i.e., 7.5%.

Diameter and thickness: These parameters were evaluated to ensure the uniformity of each unit. The average diameter of the prepared tablets was found to be 6 ± 0.2 mm, and the thickness was found to be 7.5 ± 0.2 mm. The results obtained were found to comply with the limits.

Hardness: Hardness was tested during the entire compression process to adjust the pressure during the process and maintain uniform hardness.[13] In this study, hardness was tested with a Monsanto hardness tester. The hardness of the prepared tablets was found to be 155.5 ± 10.21 g/cm^2.

Friability: The friability test measures tablets' physical strength. For all batches, the friability was found to be 0.8 ± 0.2%, which is within the compendium limit, i.e., NMT 1%.

In vitro *dissolution study*

Optimization of the core

Four batches were planned, on the basis of the literature, for core optimization. As depicted in Table 1, the F2 batch had a higher concentration of Polyox N-80, whereas in F4, NaCl, i.e., the osmogen, had a lower concentration. However, both these formulations exhibited a lag phase due to high polymer and low osmogen concentrations (Figure 1A). Thus, with respect to the innovator drug release profiles, the F1 batch had the drug release pattern closest to that of the reference product.[21,22] The F1 batch was considered to be optimized and was used for further finetuning of the parameters.

Optimization of curing time

Among the three time points (0, 3 h and 5 h), 5 h of curing resulted in controlled release of the drug from tablets over 24 h (Figure 1B). On the basis of the results for curing time, optimization of ER coat percentage weight gain was performed.

Optimization of ER coat percentage weight gain

With an optimized curing time, the percentage weight for the ER coat decreased from 18% w/w to 11% w/w for F8, 13% w/w for F9 and 15% w/w for F10 respectively (Figure 1C). On the basis of drug release, 13% w/w ER coat was considered optimized.[23]

Optimization of orifice size and number

Single drill and double drill orifices on the drug layer side of 0.6 mm and 0.8 mm each were evaluated. These parameters did not significantly affect the percentage drug release (Figure 1D and E). To comply with the reference product, a double drill orifice of 0.6 mm was made in the optimized formulation.[24] The optimized parameters for tablet preparation were as follows: curing time, 5 h; seal coat, 7% w/w; ER coat, 13% w/w; orifice size, 0.6 mm; and orifice number, 2.

Content uniformity

The prepared tablets of paliperidone were subjected to content uniformity testing. Among all randomly selected tablets (n = 10), each tablet had a paliperidone content in the range of 85−115% of the average content (101.6 ± 2.24% w/w), thus suggesting that the tablets complied with the compendium standards.

In vitro *dissolution of the test product*

In the development of a generic drug product, comparison of the dissolution profile with that of the RLD is an important quality control tool. The innovator tablets had a percentage cumulative drug release (% CR) as follows: 1 h, 1% CR, 50 RSD; 2 h, 1% CR, 0 RSD; 4 h, 4%, 22.5 RSD; 6 h, 10% CR, 10 RSD; 8 h, 18% CR, 6.67 RSD; 12 h, 38% CR, 8.95 RSD; and 24 h, 99% CR, 1.82 RSD. Our objective was to mimic the RLD drug release pattern. One simple method for comparison of dissolution profiles is the model independent similarity factor (F2). This factor has been recommended by many regulatory authorities as a means of demonstrating similarity between two drug products. This

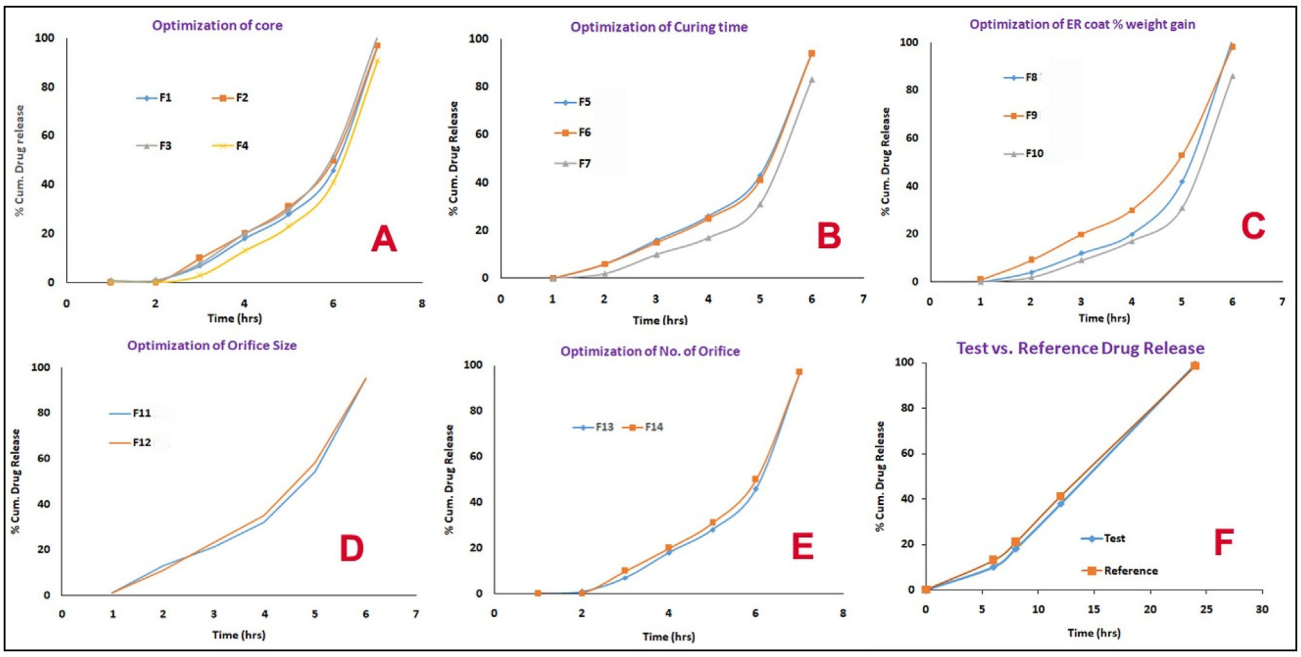

Figure 1: A) Optimization of the core with varying polymer and osmogen concentrations. B) Optimization of the curing time, i.e., 0, 3 or 5 h. C) Optimization of ER coat percentage weight gain. D) Optimization of orifice size. E) Optimization of orifice number. F) Drug release profiles of the test formulation versus the reference drug.

approach is favored because it is relatively easy to use, given that the F2 value is easy to calculate, and a clear acceptance criterion for profile similarity (i.e., F2≥50) has been established.[25] The similarity factor F2 of the test sample compared with the RLD was found to be 75.67. Thus the F2 value of test formulation was within the acceptance criterion of 50–100 suggesting that the dissolution profile of the test formulation was similar to that of the RLD (Figure 1F). Figure 2a shows the formulated tablets with a push layer (colored) and drug layer, and Figure 2b shows the orifices created on the tablets to match the innovator tablet. Moreover, we performed model fitting for the dissolution data to investigate the best fit model. The prepared tablets followed zeroth order kinetics with an R^2 value of 0.997, thus suggesting that the amount of drug released was independent of the initial concentration of paliperidone.

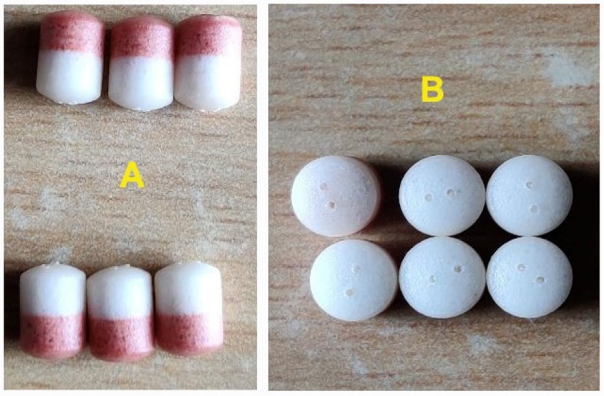

Figure 2: Photographs of prepared tablets A) with the drug layer and push layer (colored). B) Two orifices created on the tablet, similarly to the innovator tablets.

The results are in agreement with findings in the literature: oral osmotic tablets are well known examples representing zeroth order drug release.[26]

Comparative evaluation of the prepared tablets versus the RLD

As described above, we successfully developed bilayer tablets of paliperidone with a drug release profile mimicking that of the RLD, which is a trilayer tablet (Figure 3). The innovator tablet thickness was 11.3 ± 1.42 mm, the diameter was 5.24 ± 0.76 mm, and the average weight was 267.3 ± 4.13 mg. The bilayer tablet with two laser drills, similarly to the innovator tablet, had an average weight of 225.61 ± 3.21 mg, a thickness of 7.5 ± 3.21 and a diameter of 6 ± 0.2 mm. Thus, in terms of weight and thickness, the prepared tablets were superior to the RLD in terms of ease of packaging and transport. Moreover, the final tablets had a hardness of 155.5 ± 10.21 g/cm^2 and a friability of 0.8 ± 0.2%. Stability studies were performed on the final optimized batch of tablets.

Stability studies

The optimized batch was loaded for stability testing, and physical and chemical parameters were evaluated.[18]

Water content: The determination of water content is an important aspect for moisture sensitive formulations and hygroscopic drugs. Ensuring that a formulation remains stable over a given period of time is important. The water content was determined with the Karl Fischer method, and the results are described in Table 4.

The water content after 1 month was found to be 2.4 ± 0.18% and 2.6 ± 0.34% at 25 °C/60% RH and 40 °C/75% RH, respectively; whereas the initial value was 3 ± 0.23%. Therefore, we concluded that the HDPE containers used provided a good barrier, and the formulation remained stable.

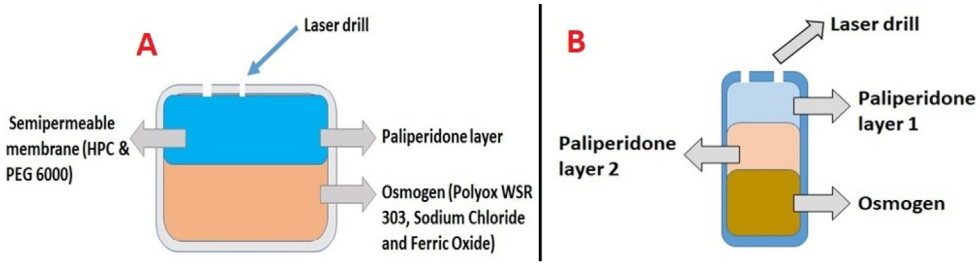

Figure 3: Schematic representation of the A) prepared bilayer tablet and B) innovator Invega®.

Table 4: Evaluation of the physical and chemical stability of optimized tablets under accelerated conditions (n = 3; mean ± SD).

Parameters	Initial	Accelerated condition	
		25 °C/60% RH	40 °C/75% RH
Physical parameters			
Appearance	Beige color	Beige color	Beige color
Thickness (mm)	7.5 ± 0.2	7.5 ± 0.2	7.5 ± 0.2
Weight (mg)	225.61 ± 3.21	225.61 ± 2.13	225.61 ± 2.34
Chemical parameters			
Water content (%)	3 ± 0.23	2.4 ± 0.18	2.6 ± 0.34
Assay (%)	101.6 ± 2.24	100.7 ± 1.924	101 ± 1.13

Assays

For stability samples, a 5% change with respect to the initial value denotes a significant change (ICH Q1A).[27] The assay result for 25 °C/60% RH was 100.7 ± 1.924%, and that for 40 °C/75% RH was 101 ± 1.13%. The results are in line with those from the initial assay, i.e., 101.6 ± 2.24%.

In vitro *dissolution study*

The dissolution profiles of the prepared tablets recorded at 25 °C/60% RH and 40 °C/75% RH after 1 month were compared with the initial (0 month) drug release profile (Figure 4).[28] The similarity factor of 25 °C/60% RH v/s initial was found to be 61.75 ± 2.13, and that of 40 °C/75% RH with respect to the initial value was 64.78 ± 1.94, which was statistically insignificant ($P > 0.05$). After 1 month, the samples were found to be stable under both conditions.

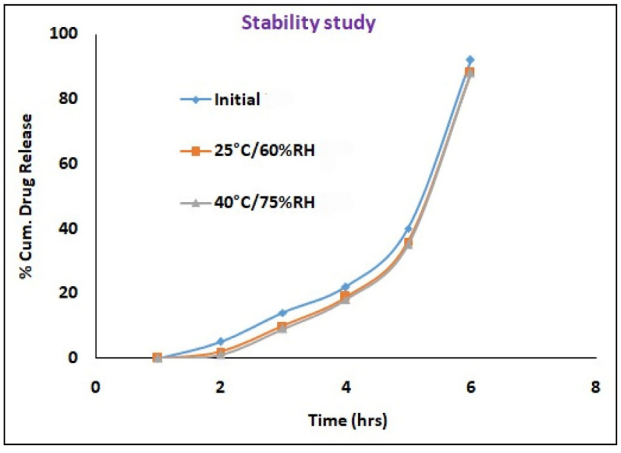

Figure 4: Comparison of the dissolution profiles of optimized tablets stored at 25 °C/60% RH and 40 °C/75% RH after 1 month with the initial drug release profile.

Conclusion

The three main components of formulation—diluent (lactose monohydrate), osmogen (sodium chloride) and polymer (Polyox WSR N-80)—were optimized, and the results of the F1 batch were closest to those of the innovator formulation. The most effective curing time was found to be 5 h, which resulted in better control of drug release, and a 13% w/w ER coat was considered optimal. The prepared bilayer tablets showed a drug release profile similar to that of the innovator formulation, as reflected by the similarity factor (F2 value). Herein, bilayer tablets of paliperidone overcoming the drawbacks associated with the marketed formulation were successfully prepared; these tablets offer advantages such as a simpler preparation process, cost effectiveness and faster preparation of the tablet core.

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Conflict of interest

The authors report no conflicts of interest.

Ethical approval

The work did not involve use of human volunteers or animals for testing of the formulated tablets.

Authors' contributions

SN and AA performed the experimental work and characterization of prepared formulations as described in the main text. KRM reviewed the written draft of the manuscript, and SP conceptualized the idea and wrote the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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