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Research Article

Controlled Release Matrix Formulation of Paliperidone in Concurrence with Regulatory Requirements

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ABSTRACT

Paliperidone is the 9-hydroxy metabolite (9-hydroxy) of risperidone and is a psychotropic drug of the atypical antipsychotic family. Paliperidone has the racemates (+)- and (-)-paliperidone. It is a dopamine D2 antagonist with serotonergic 5-HT2A antagonistic action that acts centrally. ALZA OROS® osmotic medication release technology is used to create Invega ER tablets. It is a tri-layer longitudinally compressed tablet based on a sophisticated osmotic delivery method that is meant to administer the paliperidone in a defined way over 24 hours. This research aims to create a generic controlled-release single-layer matrix tablet of paliperidone. Different combinations of Polyox and hypromellose in the core were used, followed by coating, to assist/build a stable and strong formulation. All strengths have similar *in-vitro* dissolution profiles. Freeze formulation was assessed for nitrosamine risk assessment as well as challenge for alcohol dose dumping study. Paliperidone is a basic compound with a pKa1 of 8.2 (piperidine moiety) and a pKa2 of 2.6 (pyrimidine moiety). As a result, a substantial portion of the molecule is ionized at physiological pH. It is relatively insoluble in water (0.003 g/100 mL water at pH 7.4). The solubility decreases at higher pH (0.001 g/100 mL at pH 12.9) and significantly increases at lower pH (3 g/100 mL at pH 5.3). The partition coefficient octanol/water (log P) is 2.39. Hence, discriminating media was identified as pH 2.75 buffer. The Higuchi model was used for expressing the *in-vitro* release profile through matrix composition. Formulation withstands 0–40% alcoholic conditions under *in-vitro* release tests. It is easy to formulate, stable and cost-effective. The manufacturing process involves dry blending followed by compression and coating so there will be the least chemical interaction of an active substance with other excipients. Hence, there is a negligible possibility to generate nitrosamine impurity in the formulation. The formulation is classified as rugged against dose dumping.

Introduction

Paliperidone, is water insoluble antipsychotic drug belongs to BCS Class II drug[1] is widely used in clinical management of schizophrenia, bipolar disorder, and irritability in children.[2] Novel formulations of osmotic-based drug delivery systems for antipsychotic drugs have become popular because of convenience in dosage, reduced side effects, and improved efficacy. Better therapeutic outcomes were exhibited by the OROS-based extended-release tablet of 9-hydroxyrisperidone (an active metabolite of risperidone) commercially known as paliperidone,[3] Invega®. However, the semi-permeable membrane in osmotic pumps should be 200 to 300 mm thick to withstand pressure within the device.[4] These thick coatings lower the water permeation rate, particularly for moderate and poorly soluble drugs. Hence, these thick coating devices are suitable for highly water-soluble drugs. Other side, thin coating enhances the permeability, there is a risk of film defects due to poor performance in the coating process. The critical step is the size of the orifice through which the drug is delivered, which directly impacts the drug delivery system's performance. There might be a risk of dose dumping, resulting in a greater concentration of the drug in the blood than required with potential for toxicity.[5]

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Manufacturing of osmotic tablets is a complex as well as multi-unit operation.

Polymer-based hydrophilic matrices have attracted considerable attention in recent years as controlled-release devices for the delivery of drugs.[6] Polyethylene oxide (POLYOX®) has been commonly used in the formulation of controlled release monolithic matrix, owing to their solubility in water, availability in a range of molecular weight and viscosity grades, FDA acceptance, and unique swelling/erosion characteristics which can be utilized in modulating drug release profiles.[7] The swelling rate and erosion of POLYOX®-based matrix tablet[8] are affected by numerous other parameters such as different molecular weights, the structure of the device appears, drug solubility/loading, and the incorporation of HPMC. It's easy to manufacture, cost-effective and safe in use. Hydroxypropyl methylcellulose (HPMC, hydrophilic) has been a popular release-retarding polymer in simple matrix tablets.[9, 10] Blending of HPMC with Polyox has been recommended for the alteration of its functionalities. In this study, single layer matrix formulation of paliperidone has been prepared and evaluated against osmotic based marketed product Invega®.[11] To get the *in-vivo* bioequivalent formulation, dissolution discriminating media has been identified.[12] The effect of commonly imbibed alcohol concentrations was evaluated on drug release performance of the formulation. Alcohol concentrations of up to 40% (wt./wt.) were used, equivalent to those present in undiluted spirits such as whisky and vodka.[13]

It will be applicable in pharmaceutical industries due to major parameters such as cost-effectiveness, robustness, no dose dumping effect and easy to manufacture. These are candid parameters in pharmaceutical industries. In the past, no such study observed where single-layer matrix formulation developed have been developed against OROS.

Materials and Methods

paliperidone was received from SUN Pharma, Vadodara as a gift sample. Various grades of Polyox and hypromellose were gratefully provided as gift samples by Colorcon Asia Ltd. India. OROS Invega® tablets of 6 mg paliperidone were used as a reference tablet for *in-vitro* studies. HPLC grade acetonitrile and methanol (Merck, Germany) were purchased from the authorized dealer in the local market. Other chemicals used were of analytical grade.

Evaluation Parameters

Preparation of tablets

Two different prototype formulations F1 and F2 were prepared by blending different grades of Polyox and Hypromellose in various proportions. A definitive screen design was applied to choose the proper grade of polymer in the appropriate combination. Based on preliminary experiments, out of 13 runs, first 4 runs were carried out as shown in Table 1.

Table 1: Trial batches of prototype F1 and F2 formulation

	Trial 1	*Trial 2*	*Trial 3*	*Trial 4*
HPMC K100 LVCR	35%	17.5%	-	17.5%
Polyox WSR N80NF	-	17.5%	17.5%	-
Polyox WSR 301 NF	-	-	-	17.5%
HPMC K4M Premium	-	-	17.5%	-

Based on core tablet dissolution data, which combination would be more effective in controlling the release in modified SGF media was identified. Further, two prototypes have been prepared. Prototype F1 blend constituted of Polyox WSR N 80 NF and hypromellose K4M whereas Prototype F2 blend constituted of Polyox WSR301 – NF and Hypromellose K100LVCR Table 2. The polymeric blends were thoroughly mixed with pre-set fixed amount of paliperidone and lactose anhydrous, followed by lubrication with magnesium stearate. Geometrical mixing was done to address the content uniformity concerns in both prototype formulations as drug content in core tablet was approx. 3.0% w/w. The powder blend was compressed using 8.00 mm round, standard concave punch. Formulation parameters such as Polyox molecular weight; Polyox to Hypromellose ratio have major influence on drug release properties.[14] In both prototype formulations, hypromellose concentration was evaluated from 12.5 to 22.5%, whereas Polyox was evaluated from 17.5 to 32.5% irrespective of grade.

Further, a functional coat of ethyl cellulose and hypromellose in ratio of 60:40 was optimized for different weight gain in Prototype 1 whereas methacrylic acid copolymer[15] (Acryleze) as a functional coat was optimized at different weight gain level in Prototype 2 formulation. Each tablet contains 6 mg of paliperidone and 7 to 8% w/w functional coating.

Physicochemical evaluation of powder mixture and tablets

The powder mixture was evaluated for flow and compressibility characteristics.[16] The angle of repose (AR) of the powder mixture was determined using a fixed funnel, while the compressibility index (CI), and Hausner's ratio (HR) were determined with a 100 mL cylinder in accordance with United States Pharmacopoeia XXX (USP XXX). The friability of the tablets was determined with a friability tester (Electrolab, India), while the hardness and physical dimensions of the tablets were determined with a Dr. Schleuniger hardness tester. Weight variation was determined as mentioned in USP XXX. Drug release studies were conducted in 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825 N HCl at thermostatically controlled temperatures of 37 ± 0.5°C using a type II paddle dissolution apparatus (Electrolab, India) run at 100 rpm.

Table 2: Prototype 1and 2 final formulation compositions

S. No	*Ingredients*	*Prototype F1*	*Prototype F2*
		%w/w	*%w/w*
1	Paliperidone USP	2.86	2.86
2	Lactose anhydrous	39.04	46.19
3	Polyox WSR N80	30.95	-
4	Polyox WSR 301 NF	-	23.81
5	HPMC K100 P LVCR	-	16.67
6	HPMC (Methocel K4M)	16.67	-
7	Magnesium Stearate	0.95	0.95
Functional Coating/Seal Coating			
8	Ethyl cellulose (Ethocel)	2.45	-
9	HPMC (Methocel E3 LV HPMC)	1.63	-
10	Tri ethyl citrate	0.61	-
11	Talc	1.02	-
12	Opadry yellow (Hypromellose and Macrogol)	3.81	-
13	Acryl Eze Pink Powder 93O54222 (Methacrylic acid copolymer)	-	9.52
Weight of Coated Tablets =		210.00	210.00

The samples withdrawn were replaced with similar dissolution media. Percent drug release was analysed after 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours using HPLC method. The drug release data were fitted to the usual kinetic models, including zero-order, first-order, Higuchi's square root of time, and Hixon Crowell's cube root of time to determine the release rate (K) and coefficient of determination (R2).[17] Korsemeyer–Peppas's equation was applied to determine the linearity of the drug release curves (coefficient of determination, R2) and release exponent (n) with the following equation:

Korsemeyer Pappas's equation; $Q_t/Q_\infty = kt^n$ (1)

where Q_t is the percent drug release at time t; Q_∞ the percent drug release after infinite time, usually taken as 100; Q_t/Q_∞ is the fraction of drug released at time t; and k in Korsemeyer's model is a release constant incorporating the structural and geometric characteristics of the system; n is the release exponent, indicative of the drug release mechanism. Release profiles of prototype 1 and prototype 2 formulations, determined in dissolution media of modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825 N HCl, were also compared using the model-independent approach of similarity factor f_2 as a determinant parameter.

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}W_t\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

where n is the number of data points collected, R_t and T_t are the percent drug dissolved at each time point for the reference and test tablets, respectively, and W_t is an optional weight factor. Further, extended drug release was designed in a manner that drug release is well controlled. The concomitant intake of alcoholic beverages together with oral controlled-release formulations poses a serious safety concern since alcohol has the potential to alter the release rate controlling mechanism of the dosage form, which may result in an uncontrolled and immediate drug release. Thus, the Food and Drug Administration (FDA) recommends that *in-vitro* drug release studies of controlled-release dosage forms be conducted in up to 40% of ethanolic media.[18] This was accomplished by entrapping the drug in a matrix that contains a suitable polymer that regulates drug release and prevents dose dumping.[19]

The release of paliperidone from matrix tablets was performed according to the USPII paddle method using a dissolution apparatus. The tablets were added into 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825N HCl] at 37 ± 0.5°C and with a paddle speed of 50 rpm. Each sample (10 mL) was withdrawn at defined time intervals, and the same volume of dissolution medium was compensated. Samples were filtered using a 0.45 µm PVDF filter and were assayed for paliperidone by HPLC. HPLC system equipped with UV detector. Paliperidone was analysed using a C18 (150 x 4.6 mm), 5 µm or equivalent. The mobile phase consisted of buffer and methanol in the ratio of 85:15% v/v and was pumped at a flow rate of 1.5 mL/min. The detection wavelength was 275 nm.

Paliperidone is a weakly alkaline drug with a pH-dependent solubility, the dissolution rate increases with decreasing pH, test formulation prototypes dissolve fastest in dissolution medium of pH 1.0, with the slowest rate when the pH was 6.8.

Drug release was observed faster when Hypromellose K100 LVCR was used alone (Trial 1) or in combination with Polyox WSR NF 80 (Trial 2). However, in the presence of high viscosity Polyox WSR 301, control release of drug was observed. Comparative drug release profile of all combinations has shown in Fig. 1 and Table 3. It could conclude that main retardation is due to hypromellose. Further, trials were carried out with high-viscosity hypromellose and low-viscosity of Polyox and vice-versa. The tablets could completely release the drug when the media pH was 1, however, prototype 1 (contain Polyox WSR

Table 3: Initial screening design drug release was observed in modified SGF, pH 1.0

S. No	*Trials*	*2 hours*	*4 hours*	*8 hours*	*12 hours*
1	Trial 1	50.1	98.7	-	-
2	Trial 2	92.0	97.5	-	-
3	Trial 3	35.1	63.0	85.1	92.0
4	Trial 4	61.0	79.7	83.8	95.2

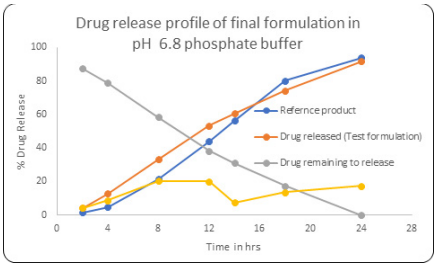

Fig. 1: Drug release of Prototype 2 (final formulation) drug release in pH 6.8 phosphate buffer

N80 and HPMC K4M) formulation only released less than 70% after 24 hours when the media pH was 6.8 whereas prototype 2 formulation (contain Polyox WSR 301 NF and HPMC K100 P LVCR) drug release is similar to the reference formulation. The commercial Invega® are osmotic pump tablets and thus show no pH dependency. In prototype 2 test formulation, due to enteric coating, pH dependency of the drug has been balanced.

Further, dissolution discrimination media has been identified. Based on pKa value of paliperidone (8.2 for piperidine moiety and 2.6 for pyrimidine moiety), dissolution has been carried out in pH 2.75 buffer. It was identified that pH 2.75 buffer is more discriminatory in nature. Prototype 1 has faster drug release to reference drug product whereas Prototype 2 has similarity factor (F2 Value) 60 in discriminatory media. Drug release at 4, 8, 12 and 24 hours was carried out in discriminatory media as a response to evaluate the best fit for bioequivalence study.

The tablets were evaluated for dissolution media uptake and understand the wetting nature of polymer (Water uptake study).[20] Tests were conducted using the dissolution apparatus, the samples were placed in 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825N HCl] at 37 ± 0.5°C and the paddle stirred at 50 rpm. At various time points, the tablets were withdrawn from the medium and the excess liquid was removed and then weighed. Samples were dried at 60°C until a constant weight was reached. Six different tablets were measured at each time point, and fresh tablets were used at each individual time point. The percentage of the removing mass (RM) was used for calculation erosion as an indicator. The water absorption (WA) was used to explain the process of water uptake and expansion as weight of the tablets increased due to the absorbed liquid.

RM and WA were calculated according to the following formula:

$$RM\ (\%) = (w_o - w_r / w_o) \times 100$$
$$WA\ (\%) = (w_t - w_r / w_r) \times 100$$

where W_0 is the original weight of the dry tablet; W_r is the weight of the remaining dried tablet after entering the media at time t; W_t is the weight of tablet without water on the surface at time t before drying.

While n value (the release exponent) as response variables were calculated from experimental data for Qt/Q_∞ 0.6 using Korsmeyer-Peppas Equation to investigate the effect of factor on the drug release kinetics and mechanism:

$$Q_t / Q_\infty \text{ ------- } kt^n = \log Q_t / Q_\infty \text{ ------- } = \log k + n \log t$$

where Q_t/Q_∞ is the fraction of the drug release at time t, k is the release constant, and n is the release exponent indicating the mechanism of drug release. Considering the cylindrical shape of the tablets, $0.89<n<1.0$ indicates the zero-order drug release kinetics, while $0.45<n<0.89$ shows anomalous release kinetics.[21]

There was no dose dumping observed in the ethanolic solution. The drug (Paliperidone) is having highest solubility in 0.1 N HCl. The addition of ethanol in water or 0.1 N HCl will reduce the solubility.[22] So, there is very least possibility of dose dumping. Further, it depends on the matrix system and product design so *in-vitro*, optimized formulation was examined in 0.1 N HCl with 40% V/V alcohol considering the worst condition. Drug release of final formulation composition in 0.1 N HCl with 40 % v/v alcohol has shown in Fig. 2.

The effect of polymer concentration and how it impacts drug release was also evaluated as part of optimization trials. When Polyox WSR 301 is completely replaced with Hypromellose concentration, the drug is completely released in 12 hours. So, the optimum concentration of polymer combinations requires controlling the drug release and matching the release profile with the reference drug product.

Bio-waivers are used when multiple strengths are in development[23] to obtain a Biowaiver is very important with respect to industry because of the substantial savings in resources and time. The aim is to develop the BCS-based biowaiver approach as reflected by the US FDA, the EMA and the Health CANADA regarding eligibility and requirements for testing. The criteria include both proportionality of formulations as well as comparative dissolution profiles. Differences in the proportion of excipients are considered to be minor when the differences in amounts for excipients of particular functions are within the limits. The rate and extent of absorption is controlled by dissolution as a formulation factor and solubility and permeability as drug substance parameters. If the predefined criteria for these factors are met, a biowaiver can be granted. Product containing similar amount of the same excipients as the test product, sameness of the manufacturing method and quality of the test product. The drug content or potency difference between the test and comparator products should be less than 5% w/w. In conclusion, bio-waivers have opportunities when science- and risk-based approaches are used to develop products. Polyox and HPMC are hydrophilic polymers and significantly provide desire-controlled release profiles in optimum concentrations. Drug releasing rate can be further

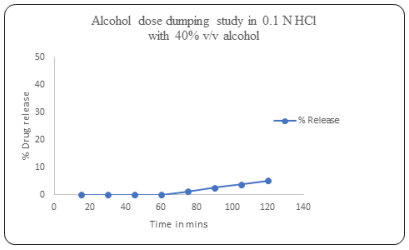

Fig. 2: Drug release of Prototype 2 (final formulation) in 0.1 N HCl with 40% v/v alcohol

suppressed as the viscosity of the polymer is increased. The release rate is mainly dependent on the viscosity of HPMC grade. In case of Prototype 1 formulation, drug release is incomplete in pH 6.8 phosphate buffer. It's due to high viscosity of polymers (HPMCK4M has a viscosity of approx. 4000 cp and Polyox WSR N80 having a viscosity of 65 to 115 cp) whereas complete drug release observed from prototype 2 formulation (HPMCK100 P LVCR having viscosity 100 cp and Polyox WSR 300NF is having viscosity 1650 to 5500 cp). In this case, the release rate was found to be significantly influenced by the viscosity grade of HPMC. This can be explained by the higher viscosity grade of HPMC requiring more water to reach a hydration state of the core layer. As the water permeability decreased with increasing viscosity of materials, this resulted in lower erosion and drug release speeds. The results showed that the most suitable release rate, with complete dissolution at 24 hours, was achieved when using HPMC-K100LVCR and Polyox WSR 301 NF as the materials.

The formulation of extended-release drug delivery by single-layer approach successfully achieved required dissolution (of reference drug product) in modified SGF media. Further, discriminatory media has been identified to optimize the final formulation dissolution. Based on drug pKa, acidic media pH 2.75 has been selected as dissolution discriminatory media. The hypromellose K100 P LVCR blend and Polyox WSR 301 NF successfully prepared the paliperidone CR tablets. The controlled-release test formulation tablet of optimized concentration would be bioequivalent to reference drug product INVEGA® tablets.[24] It is cost-effective and easy to manufacture. Bioequivalence studies for a generic product intended for the EU and the USA need to be performed against both reference products. For many products in the EU, one single-dose fasted study is sufficient, while prolonged-release dosage forms often require three BE studies (single-dose fasted and fed and multiple dose). For the USA, as stated before, immediate as well as modified-release dosage forms often require two studies (single-dose fasted and fed) while multiple-dose is usually not required. In case of paliperidone, bioequivalence strength would be 6 mg, additional strengths 3 and 9 mg was developed and its similarity factor was evaluated against 6 mg strength of the optimized formulation. Both 3 and 9 mg strength have a similarity factor more than 50 in modified SGF media (recommended dissolution media) as well as pH 2.75 buffer.

Ethanol is less polar compared to pure water, which is reflected by the differences in the dielectric constants (25 and 80 for ethanol and water at 20 C, respectively). If ethanol is added to water, a decrease in the dielectric constant in relation to pure water occurs. Polyethylene oxide (PEO) is a non-ionic homopolymer of ethylene oxide. PEO is soluble in water due to hydration of the ether oxygen and insoluble in alcohol.[25] Drug release from the PEO matrix is controlled by erosion of the matrix and diffusion of the drug through the swollen hydrogel layer at the tablet surface.[26]

Final formulation was evaluated for Nitrosamine risk assessment.[27] The nitrosamine crisis first erupted in July 2018, when the FDA announced voluntary recall of several drugs containing Valsartan: a medicine used to treat high blood pressure and heart failure. Due to an unreported change in synthesis of Valsartan, the potentially cancer-causing chemical *N*-nitroso dimethylamine (or NDMA) was detected in the marketed drug product. Regulatory agencies such as the EMA, Health Canada and US FDA are now requiring *N*-nitrosamine risk assessments to be performed on all marketed pharmaceuticals. The first step in a nitrosamine risk assessment is to identify sources of potential risk. This may relate to amine functionality which has been identified within the active substance(s), finished product(s) or formed throughout the manufacturing process. Paliperidone extended-release tablets excipients composition reviewed w.r.t. to IPEC Europe Questionnaire (Questionnaire for excipients Nitrosamines Risk Evaluation) and received a statement from the excipient manufacturer and it does not contain nitrous acid, secondary/tertiary amine source and reusable/recovery of solvents/nitrogen-containing solvents during the manufacturing process. Hence the possibility of formation of nitrosamine impurities are unlikely.[28-31]

The evaluation is solely based on the information/ assessment received from the vendors for inactive ingredients/excipients used in the paliperidone extended-release formulation manufacturing process. The interaction of Paliperidone API, excipient functional groups and manufacturing process conditions does not generate nitrosamines impurities. Hence the possibility for the formation of N-Nitrosamine impurities like NDMA, NDEA, NEIPA, NDIPA, NDBA, NMBA and any other N-Nitrosamines impurities in the finished product of paliperidone extended-release formulation are unlikely.

Putting in a nutshell *in-vitro* drug release of test formulation (matrix based) is comparable to the reference drug product (Invega). It has also been assessed using discriminatory dissolution media. The matrix formulation process is inexpensive and simple to produce. To design a robust and alcohol-resistant dosage form, it is vital to systematically analyze the physicochemical key factors, including solubility, wettability, swellability and mechanical

properties of the API, the excipients and the properties of the final dosage form, including hardness, swelling and drug release characteristics. Nitrosamine risk assessment has also been performed on the final formulation. In a nutshell, it is a single-layer matrix formulation that is equivalent to the reference medication product's osmotic-based drug delivery method. Transferring the dossier of a generic oral human medicinal product from the USA to the EU or vice versa seems at first glance like an easy, quick, and low-cost opportunity that should be taken. However, as in most cases things are not as easy as they seem.

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