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Original Article

Application of 3^2 Factorial D-Optimal Design in Formulation of Porous Osmotic Pump Tablets of Ropinirole; An Anti-Parkinson's Agent

Anoop Narayanan V*[1], Praveena George[2], Dhamelia Akshay L[2]
[1]Department of Pharmaceutics, NGSM Institute of Pharmaceutical sciences. NITTE University, Paneer, Mangalore - 575018, INDIA
[2]Department of Pharmaceutics, Shree Devi College of Pharmacy, Airport Road, Kenjar, Mangalore, Karnataka, INDIA.

ABSTRACT

Objective: In the present study, our objective was to develop porous osmotic pump tablets of an anti-Parkinson's agent, ropinirole. It also aimed to demonstrate the applicability of factorial designs and there by a statistical optimization in developing a controlled drug releasing device. **Methods:** A 3^2 factorial D-optimal study design was adopted to identify an optimized formulation. Tablets were prepared by direct compression using varying amounts of microcrystalline cellulose (MCC) and sodium chloride, followed by coating with semipermeable membrane of cellulose acetate (CA) containing polyethylene glycol (PEG) 400 as a pore former. The plasticity of the membranes was adjusted using castor oil. All the formulations were evaluated for various physical parameters including *in vitro* drug release and the effect of osmogent and pore former were also studied. Drug release kinetics studies such as zero order, first order and Korsmeyer Peppas were carried out and compared. ANOVA in drug release of all the formulations were determined. Formulations were optimized by using numerical optimization technique to achieve a controlled zero order release of ropinirole for 12 hours. **Results:** Drug release from the optimized formulation containing 20%w/w of PEG, without osmogent was not significantly affected by change in pH or agitation of the dissolution medium. The mechanism of drug release was further confirmed by studying the effect of osmotic pressure on drug release. **Conclusion:** The porous osmotic pump tablets of ropinirole can provide prolonged, controlled and GI environment-independent drug release. A software based optimization is helpful and reliable in developing porous osmotic pump tablets.

Key words: Osmotic pump, Ropinirole, Controlled release, Factorial design, D-optimal design, Optimization.

Correspondence:

Dr Anoop Narayanan V,

Department of Pharmaceutics, NGSM Institute of Pharmaceutical sciences. NITTE University, Paneer, Mangalore - 575018 INDIA.

Mob: +91-9902823433

E-mail: anoopvn84@gmail.com

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INTRODUCTION

The degeneration of cells producing dopamine with a subsequent reduction in dopamine levels in basal ganglia results in a common pathological condition called Parkinson's disease (PD).[1] A specific non-ergoline dopamine D2 receptor agonist, ropinirole is often employed in the treatment of PD worldwide.[2] Repeated oral administration of long acting dopamine agonist ropinirole is known to cause fluctuating plasma levels leading to low levels of diskinesia. Controlled release formulations of ropinirole were found to be resulting in prolonged reversal of motor deficit with reduced diskinesia, smooth plasma concentration-time levels and better tolerability.[3-6] Because of their numerous advantages, osmotic pump tablets may be the best drug delivery system which can offer prolonged well controlled delivery of ropinirole.

Among all the osmotic systems, porous osmotic pump tablets (POPT) may be the easier version to manufacture as they require lesser technologies, but deliver greater results with better reproducibility. The system contains a core tablet coated with a semi permeable membrane containing pore forming materials which leach out on exposure to an aqueous medium. Imbibition of water occurs across the membrane, due to the osmotic gradient created by the osmogent or the drug itself. After dissolution inside the core, drug is released through the pores generated.[7] Oral POPT are known to deliver the drug independent of pH of the surroundings with high degree of predictability and *in vitro-in vivo* correlation.[8]

Though researchers could achieve controlled delivery of various drugs irrespective of water solubility; a suitable drug would be the one with moderate aqueous solubility.[9,10] Ropinirole, being moderately soluble drug is expected to be a suitable candidate for POPT.[11] Ropinirole shows a plasma half life about 6 hours, with very high bioavailability. The therapeutic dose varies from 2-9 mg daily. The present study aimed to formulate POPT containing sodium chloride as osmogent and CA with polyethylene glycol (PEG) as semipermeable coating membrane, which was adopted a D-optimal 3^2 factorial design.

D-optimal designs are known to be model independent and hence a staright way of optimization based on a set of criterion chosen and the sutable model that can fit. These designs reduce the costs of experimentation as the statistical model can be estimated with a fewer runs of the experiment.[12] As there are two major factors namely the amout of osmogent as well as pore former, which significally affects the suitability of an osmotic pump, we used a 3^2 factorial design in the experiment. The effect of factors was evaluated at 3 different levels resulting in 9 drug excipent combinations.[13]

MATERIALS AND METHODS

Materials used

Ropinirole was a gift from Cadila Health Care Limited, Ahemdabad, India. Microcrysatlline cellulose, sodium chloride and magnesium stearate were purchased from Central Drug House (P) Limited, New Delhi, India. Poly ethylene glycol was procured from Merck Specialities (P) Limited,

Mumbai, India. All the other chemicals used were of analytical or reagent grade, purchased locally in Mangalore, India.

Softwares

A 3^2 full factorial batches were performed by multiple regression analysis using Microsoft excel. To evaluate the contribution of each factor with different levels to the response, the two way analysis of variance (ANOVA) was performed using the Design Expert 8.0.5.2 version software, State Ease Inc, Minneapolis, USA.[14]

Drug - excipient compatibility studies

Compatibility of Ropinirole with formulation excipients were evaluated by combined Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) analysis.

Differential scanning calorimetry (DSC)

Physical mixtures of excipients with and without ropinirole and pure ropinirole samples were subjected to DSC studies using Shimadzu DSC-60 thermal analyser and the thermograms were recorded. The analysis was performed in an atmosphere of nitrogen (flow rate 50ml/min) in order to eliminate any oxidative and pyrolytic effects, at a standard heating rate of 10 °C/min over a temperature range of 50°C-340°C.

Fourier transform infrared spectroscopy (FTIR)

Above mixtures as subjected for DSC were analysed by FTIR spectroscopy between wave number 600-4000 cm^{-1} using FTIR 4100 type A. Jasco International co. Ltd, Japan. This could eliminate the chances of any chemical interactions possible.

Flow property study of precompression mix

The angle of repose, bulk density, porosity and compressibility index are determined by standard laboratory procedures.

Preparation of core tablets

Nine batches of core tablets were prepared by direct compression based on 3^2 factorial designs. Accurately weighed ingredients were passed through #60 sieves and were blended in a mortar with a pestle for 10 min to obtain uniform mixing. (Table 1). This blended powder was lubricated with magnesium stearate and compressed in to tablets with 6 mm standard concave punch on a Cadmach 16 station rotatry tablet machine.

Coating of tablets

The tablets were coated by dip coating in a mixture of CA, PEG 400 and Castor oil in acetone.[15,18]

Characterization of tablets

Weight, thickness and diameter

The average weight of ten randomly selected tablets and standard deviation of them were calculated.

Thickness and diameter of the core tablets were measured by using screw gauge. Ten tablets from each batch were randomly selected and used. Thickness and diameter is expressed in millimeters.

Hardness and friability

Hardness of randomly selected tablets was tested using monsanto hardness tester. Friability of tablets was tested using a Roche friabilator (25rpm for 4 min) for six accurately weighed tablets.

Content uniformity

Ropinirole from the tablets were extracted using phosphate buffer pH 6.8 solution. Absorbance of resulting solution was measured at 250 nm by using UV Visible Spectrophotometer. Amount of drug present was determined using calibration curve method.

Membrane morphology of porous osmotic pump tablets

Scanning electron microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope. Membranes were dried at 45°C for 12 h and stored between sheets of wax paper in a dessicator until examination. The membranes were coated under an argon atmosphere and observed with a scanning electron microscope.[16]

Determination of ANOVA

The analysis of variance of the POPT were determined using commercially available software Design-Expert software (Stat-Ease Inc, Minneapolis, USA) by considering the response of 4, 8, 12 h *in vitro* drug release, R^2 value and n value.

Characterization of optimized formulation

Effect of pH

The optimized formulation of matrix and POPT were tested for the effect of pH on drug release. The dissolution studies were carried out for best formulation in 0.1N HCl, 6.8 pH phosphate buffers and 7.4 pH phosphate buffer in 50 rpm and 37 ± 0.5°C using USP dissolution test apparatus (type I) and compared.[15]

Effect of agitation intensity

The dissolution studies were carried out for best formulation by maintaining different rotation speed of 50, 100, 150 rpm and at 37 ± 0.5°C in 6.8 pH phosphate buffer for 8 h using USP dissolution test apparatus (type I).[15]

Effect of osmotic pressure

To confirm the major mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to 37 ± 1°C), mannitol was added in 500 ml phosphate buffer of pH 6.8. Release studies were performed using USP-I dissolution apparatus (50 rpm). To avoid any interference in the analysis by mannitol, the samples were analyzed to determine the residual amount remaining in each formulation. At the end of 8^{th} hour, formulations were withdrawn from each vessel, cut open and the contents were dissolved in sufficient volume of phosphate buffer. Accuracy of this method was checked in phosphate buffer, where results after direct measurement of drug in to the release media were similar to the results of residual drug analysis method. The osmotic pressure of the medium was determined using Van't Hoff and Morse equation.

$$\pi V = nRT$$

Where, π – Osmotic pressure, V- Volume of the solution in liter, n- Number of moles of solute. T- Absolute temperature, R- Gas constant which is equal to 0.082 litatm/mol deg.[15,17]

Drug Release kinetics

In general, the release of drug from an osmotic system depends on many factors like osmotic pressure, pore size, coating thickness etc. In order to describe the kinetics of drug release from controlled release formulation, various mathematical equations have been proposed namely, zero order rate and first order. To authenticate the release model, dissolution data can further be analyzed by KorsmeyerPeppas equation.

Stability studies

The optimized formulation was subjected to accelerated stability studies as per ICH guidelines. The formulation was sealed in an aluminum foil and stored at 30 ± 2°C, 65 ± 5% RH and at 40 ± 2°C, 75 ± 5% RH for 2

Table 1: Composition of porous osmotic pump tablets

Ingredients/Tablet	OP1 (mg)	OP2 (mg)	OP3 (mg)	OP4 (mg)	OP5 (mg)	OP6 (mg)	OP7 (mg)	OP8 (mg)	OP9 (mg)
Core tablets									
Ropinirole	2	2	2	2	2	2	2	2	2
MCC	116.8	116.8	116.8	110.8	110.8	110.8	104.8	104.8	104.8
NaCl	----	----	----	6	6	6	12	12	12
Mg.stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Coating composition (%w/w)									
Celluloseacetate	70%	60%	50%	70%	60%	50%	70%	60%	50%
PEG 400	10%	20%	30%	10%	20%	30%	10%	20%	30%
Castor oil	20%	20%	20%	20%	20%	20%	20%	20%	20%

Table 2: Summary of drug release kinetics of formulations

Formulation Code	Zero order		First order		Korsmeyer Peppas	
	Ko	R^2	K	R^2	N	R^2
OP1	4.11	0.987	-0.076	0.938	0.81	0.954
OP2*	4.67	0.991	-0.106	0.936	0.83	0.986
OP3	6.47	0.976	-0.147	0.978	0.79	0.993
OP4	9.81	0.917	-0.387	0.973	0.94	0.933
OP5	9.84	0.866	-0.389	0.961	0.59	0.938
OP6	12.36	0.931	-0.448	0.935	0.62	0.981
OP7	9.52	0.949	-0.362	0.994	0.88	0.966
OP8	12.36	0.865	-0.432	0.988	0.49	0.973
OP9	14.07	0.892	-0.523	0.986	0.79	0.879

Table 3: Summary of ANOVA table for porous osmotic pump tablets from D - Optimal design

Source	d.f	Sum square	Mean square	F value	p value
OP release at 4 h					
A	2	2080.01	1040.01	13.65	0.0141
B	2	346.86	173.43	2.72	0.1603
Model	8	2733.98	341.75	5.64	0.0464
OP release at 8 h					
A	2	780.26	390.13	15.42	0.0127
B	2	526.16	263.08	10.40	0.0128
Model	4	1102.09	275.52	10.89	0.0237
OP release at 12 h					
A	1	0.0	20.48	17.24	0.0237
B	1	20.48	20.48	12.54	0.0224
Model	0	20.48	20.48	12.98	0.0347
R2					
A	2	1	0.010	6.32	0.0536
B	2	1	4.86	0.30	0.6077
Model	8	3	3.755	2.31	0.1931
n value					
A	2	0.016	0.012	0.46	0.5281
B	2	0.088	1.031	1.15	0.3325
Model	8	0.18	0.015	0.55	0.6716

Table 4: Comparison of experimented and predicted values of optimized formulation

Optimized formula OP2*	Dependable variables				
	Drug release at 4 h	Drug release at 8 h	Drug release at 12 h	R^2 value	Release Exponent
Predicted	33.33	66.66	99.99	Maximize	0.89
Experimental	32.07	69.99	95.1	0.991	0.832

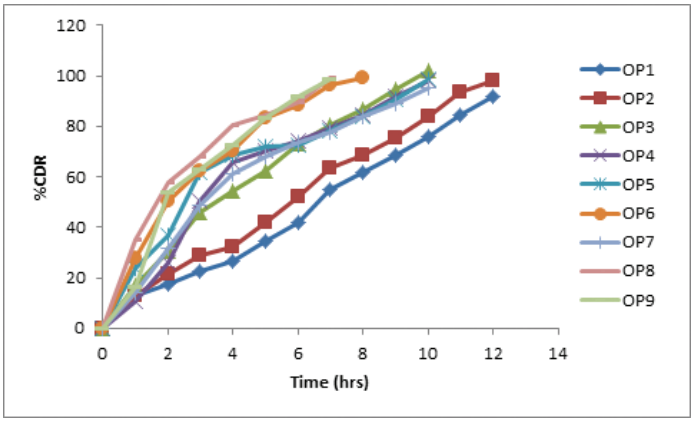

Figure 1: *In vitro* release profile of osmotic pump tablet batches.

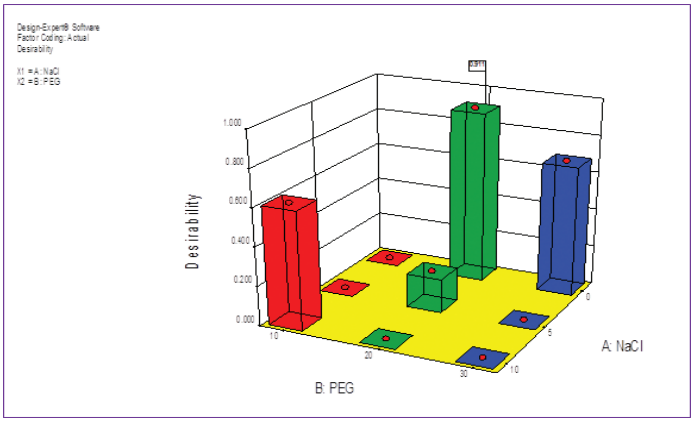

Figure 2: 3D surface plot showing the desirability of the formulations.

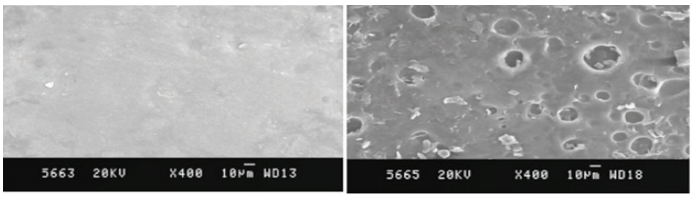

Figure 3: SEM photographs of coating membrane of OP2 before and after dissolution.

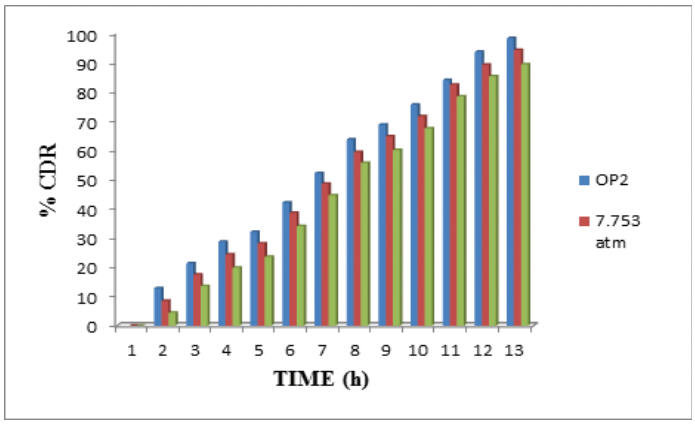

Figure 4 : Effect of osmotic pressure of the release media on drug release from OP2.

months. Tablets were periodically removed and evaluated for physical characteristics and *in vitro* drug release.[15]

RESULTS

Drug excipient compatibility studies

As shown in Figure 1, all spectra showed peaks at 1312 to1313, 1241 to 1242 cm^{-1}. Stretching vibrations were obseved in regions of 1717 to1722 cm^{-1} wavelength regions. Aromatic and Aliphatic C-H vibrations were obesrved at 3003 to 3075 cm^{-1} as well as 2936 to 2940 cm^{-1}.

The DSC thermogram of the drug and that with excipients showed a distict edotherm at 243°C. An endothermic peak at 200 was observed in the thermogram of excipients alone.

Powder flow properties

For POPT angle of repose ranged from 25.5 to 29.7°, bulk density ranged from 0.352 to 0.375 g/cm^3, % compressibility ranged from 11.82 to 12.54%.

Formulation of osmotic pump tablets

Resultant core tablets were round in shape appeared uniform in size. The coated tablets retained their shape and exhibited a smooth surface, masking the core tablets.

Characterization of tablets

Weight, thickness and diameter

Weight variation test of tablets indicated no significant difference in the weight of the invidual tablet from the average value.

Thickness and diameter of all the tablets were found to be in the range of 3.0±0.02 to 3.41±0.012 mm and 6.2±0.014 to 6.3±0.013 mm respectively.

Hardness and friability

Hardness of the prepared tablets was found in the range of 6.3±0.013 to 6.5±0.46 kg/cm^2. Friability of all the tablets was found below 1%.

Uniformity of drug content

The percentage drug content of all the batches of ropinirole tablets was in the range of 97.52±0.91and 98.18±0.51.

In vitro drug release

The linearity of drug release varied remarkably with each formulation during the 12 hours study. OP8 and OP9 formulations completed the drug relase in 8 hours while the other formuations except OP1 and OP2 could sustain till 10 hours. More linear and sustained dug release was observed with OP1 and OP2 formuations. OP1 released 91.9% of ropinirole in 12 hours while OP2 released 98.3% of the same (Figure 1).

Study of mechanism of drug release

Formulations without osmogent exhibited a zero order drug release with a regression co-efficient ranging from 0.978 to 0.991. Zero order models showed best linearity for OP2 formulations, with a regression co-efficient 0.991. The zero order plots for other formulations had regression coeffient in the range of 0.971 to 0.865. First order plots for formulations showed regression coefficients ranging from 0.935 to 0.994, where OP7 was fitting the best among all the other formulations. Table 2 show the summary of drug release kinetics of formulations. The value of 'N' in Korsmeyer Peppas graphs are as represented in the table.

Statistical optimization of formulations

In vitro drug release at every 4 hours

Total amount of Ropinirole released from all formulations varied from 26.31 to 80.45 % in 4 hours. Increased rate of drug release was observed after 4 h with increase of the concentration of osmogentt and pore former. Table 4 represents the observed response values compared to that of predicted values. Total amount of Ropinirole released from all formulations at 8th hour ranged from 61.8 to 98.94. After 12 hours 91.9 to 98.3% of the drug was released. The effect of A and B were further elucidated with the help of 3D surface plot.

Effect of formulation variable on R^2

The linear model was found to be not significant for release exponent with the model F-value 2.31 and p value 0.607.

Effect of formulation variable on release exponent

The linear model was found to be not significant for release exponent with the model F-value 0.55 and p value 0.33. The effects of factors were explained with help of the response surface plot too. The 'n' value of optimized formula was found to be 0.83 which further evaluated for release mechanism.

ANOVA

In POPT the result of ANOVA demostrate all the independent variables (Factors) were found to be significant for response R1, R2, R3, but not significant for response R4 and R5 (Table 3). The linear model was found to be significant for all responses except R4 and R5.

Characterization of optimal formulation

Membrane morphology for porous osmotic pump tablets

Scanning electron microscopy (SEM) studies revealed the membrane morphology of OP2*. Membranes obtained before dissolution clearly showed non porous region. After 12 h dissolution, they clearly showed pores formed in range of 1 to 10 μm (Figure 3)

Effect of pH

When formulation OP2 was subjected to *in vitro* release studies in buffers with different pH, no significant difference in the release profiles were seen compared to that in phosphate buffer pH 6.8.

Effect of agitation intensity on drug release

The release profile of Ropinirole from OP2 at various agitational intensites, were comparable without any significant difference.

Effect of Osmotic Pressure

The drug release rate decreased with an increase in osmotic pressure of the media; however, the lag time was prolonged. The drug release profiles with varying osmotic pressure are shown in Figure 4.

*Stability studies for most satisfactory formulation OP2**

During the 2 months storage of formulation OP2, values of all parameters like hardness, diameter, thickness, % drug content, friability were checked and found to be almost similar to the initial values.

DISCUSSION

Drug excipient compatibility studies

Ropinirole showed chatacteristic tertiary and secondary C-N stretching vibrations at 1312.32, & 1241.93 cm^{-1}. C=O stretch was obseved in 1717 cm^{-1} wavelength regions. Aromatic & Aliphatic C-H vibrations were obesrved at 3003& 2938 cm^{-1}. Above charecteristic peaks were retained in spectra with or without shift in regions in the mixtures of drug with various excipients like CA, MCC and sodium chloride indicating the chemical compatibility.

Further insight on the compatibility of ropinirole with excipients was achieved by differential scaning calorimetry. Thermograms of drug with excipients showed a distict edotherm at 243°C which is the melting point of the drug. No significant change in the endotherm of the drug was observed in coated porous osmotic pump tablets, ruling out any possibility of physicochemical interactions of formulation components.

Powder flow properties

The flowability of the polymers was found to be good according to the flow properties evaluated. The values for angle of repose, bulk density and compressibility were in acceptable limits.

Formulation of osmotic pump tablets

The porous osmotic pump was designed as a tablet core coated with a rate controlling membrane. Tablet core consists of drug along with osmogent, and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble pore-forming additives. The semipermeable membrane forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. 3^2 factorial design was applied for the formulation development. Porous osmotic pump tablets of Ropinirole were prepared by direct compression technique using MCC as diluent, sodium chloride as osmogent. After compression, the core tablets were coated with CA as semipermeable membrane with a pore former PEG 400 mixed with castor oil as plasticizer.

Characterization of tablets

Because of the good flow properties of the compression mix, tablets exhibited uniformity in weight which may further render adequate hardness and uniform drug content to the tablets. Core tables of similar thickness and hardness of the tablets were obtained on compression. Hardness of 6 kg/cm^2 or above is sufficient for keeping the tablet non fragile during further processing like coating and packing. On assay

tablets showed sufficient uniformity in the drug content, which further justify the method of powder mixing was accurate.

In vitro drug release

The concentration of osmogent increased the osmotic pressure created inside the tablet as the core compartment imbibes more aqueous fluids from the surrounding environment across the membrane. The imbibed fluid may dissolve the drug so that the drug release takes place. As the pore former concentration increased the greater numbers of pores were formed or the pore size increased, causing an easy leaching of drug from the formulation. Very high concentrations of the pore former as well as osmogent found to cause the release of the drug by diffusion manner. The cumulative drug release (CDR) was faster from the formulation with increased PEG concentration. Higher concentration of PEG with increased amount of osmogent resulted in higher release rate which could not sustain for 12 h.

Study of mechanism of drug release

Drug diffusion through the outside layer of the matrix follows various mechanisms such as Fickian release or case-I mechanism, Non- Fickian or anomalous transport, Zero order release or case- II mechanism.[8,18-20] In such cases, the drug release follows square root of time relationship (Higuchi) as fitted to various kinetic models like First order, Zero order and Koresmeyer Peppas. In Korsmeyer-Pappas semi-emperical model the value of 'n' identifies the release mechanism of drug. $0.45 \leq n$ corresponds to a Fickians diffusion mechanism, $0.45 < n \leq 0.89$ to Non-Fickians transport, and n = 0.89 to Case II (relaxational) transport and $n > 0.89$ to Super Case II transport. The CDR from the formulations with 5% and 10% NaCl were best fitted in first order kinetics than zero order. This showed the dependence of NaCl concentration on drug release. A decrease in the rate of drug release was observed for these formulations after 4-5 h of dissolution study. This may indicates the complete leaching of NaCl from the tablets. Formulations without osmogent showed a zero order release with a regression co-efficient ranging from 0.978 to 0.991. Zero order models show best linearity for OP2 with a regression co-efficient 0.991.

Statistical optimization of formulations

In vitro drug release at every 4 hours

The effect of both osmogentt (A) and pore former (B) can be explained by mathematical equation in terms of coded factors:

R1 = R1 = +59.09 + 16.85 × A[1] - 4.57 × A[2] + 7.51× B[1] - 0.67 × B[2] - 4.12× A[1]B[1]+ 2.52× A[2]B[1] - 3.67× A[1]B[2] - 0.20 × A[2]B[2]

The linear model is selected for this response with Model F-value 5.64 and p value is 0.046, indicate the model is significant. The Equation shows both factors A and B have significant positive effect on the response.

Increased rate of drug release was observed after 8 h with increase of the concentration of osmogent and pore former (positive effect). The effect of A and B can be explained by mathematical equation in terms of coded factors:

R2 = + 86.31+12.49×A[1] -1.32× A[2]+10.97×B[1]+1.25×B[2]

The linear model is selected for this response with Model F-value 10.29 and p value is 0.023 indicate the model is significant**.**

At 12th hour rate of drug release was found increased with an increase of the concentration of osmogent and pore former. The effect of formulatino variables can be explained by mathematical equation in terms of coded factors:

R3= +95.10

The linear model is selected for this response with Model F-value 12.98 and p value is 0.0346 indicate the model is significant.

Effect of formulation variable on R^2

In this response the release exponent with the model F-value 2.31 and p value 0.607, factors A and B were found to be not significant. So, the model equation is as follows:

R4 = +0.93-0.041×A[1]+0.013×A[2] - 9.000E-003 × B[1] + 0.012 × B[2]- 0.012 × A[1]B[1] - 8.000E - 003 × A[2]B[1] + 0.011 × A[1]B[2] - 3.889E - 003 × A[2]B[2]

The linear model is selected for this response with Model F-value 2.31 and p value is 0.19 indicate the model is not significant.

Effect of formulation variable on release exponent

In this response, factor A and B was found to be not significant. So, the model equation is as follows:

R5 = +0.75-0.044×A[1]+0.016×A[2]-0.072×B[1]+0.056×B[2]-0.015 × A[1]B[1] + 0.044 × A[2]B[1] + 0.062 × A[1]B[2] - 3.611E - 003 × A[2] B[2]

From the 'n' value of optimized formulation; 0.83 indicates the mechanism of drug release is non Fickian.

ANOVA

The result of ANOVA demostrate all the independent variables (formulation factors) were found to be significant for response R1, R2, R3, but not significant for response R4 and R5. The linear models were significant for all responses except R4 and R5. So, above result indicate that both the factor (osmogent and pore former) play an important role in the formulation of porous osmotic pump tablet containing Ropinirole. These factors can directly control the drug release from the osmotic pump tablets.[21]

Optimized formulation

A 3^2 full factorial design was employed to systematically study the effect of osmotic agent (X1) and osmopolymer concentration (X2) on drug release at 540 min (%Y540). In the numerical optimization techniques, the desirability approch was used to generate the optimum settings for the formulation (Figure 2). For the optimized formulation, the drug release at 4, 8, 12 hours, release exponent (n) were kept in target and R^2 value kept maximize. It was concluded that the formulation OP2 is the most satisfactory formulation. A good releationship between the experimental and predicted values (Table 4) confirmed the practicability and validity of the model.

Characterization of optimal formulation

Membrane morphology for porous osmotic pump tablets

SEM images of the coating film before dissolution found to be non porous. After 12 h dissolution, they revealed the pores formed in range of 1 to 10 µm owing to dissolution of PEG 400 acting as a pore former. The leaching of PEG 400 from the membrane leads to formation of pores, and thus the release of drug takes place. When the pore former concentration increases the pore size or the number of pore formed also increases. The pore size or number of pore formed is proportional to the drug release.

Effect of pH

An osmotically controlled release system delivers its contents independent of external variables. There was no remarkable difference in the *in vitro* drug release of OP2 formulations when performed in various buffers of pH 1.2, 6.8 and 7.4. Hence, the fluid in different parts of the GI tract may scarcely affect drug release pattern from the osmotic system.

Effect of agitation intensity on drug release

The release profile of Ropinirole from the optimized formulation OP2 was independent of the agitational intensity of the release media. Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body.

Effect of Osmotic Pressure

The effect of osmotic pressure on the optimized formulation was studied in media of different osmotic pressure. The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. It is evident from the results, that the drug release from the formulation decreased as the osmotic pressure of the media increased. This finding confirms that the mechanism of drug release is by the osmotic pressure built in the tablet followed by liquid imbibition.

*Stability studies for most satisfactory formulation OP2**

Up on evaluation of OP2 tablets that are stored at accelerated stability conditions for 2 months, values of parameters like hardness, diameter, thickness, % drug content, friability remained almost similar to their initial values. The drug dissolution and diffusion profile were similar to the initial profile. There was no significant changes in any quality attributes and as well as in the physical appearance. Hence it can be deemed that formulation can be stable even in normal storage conditions.

CONCLUSION

Porous osmotic pump tablets of ropinirole coated with cellulose acetate semipermeable membrane had developed and the effect of different formulation variables were studied to optimize release profile.

The desired zero order release profile was obtained by optimizing amount of osmotic agent, and osmopolymer. From the *in vitro* drug release study, it was inferred that drug release increased with the amount of osmotic agent and osmopolymer. The osmotic system (batch OP2) containing 1116.8 mg of MCC without an osmogent was found to be optimum fomulation. The drug release from the developed formulations was independent of pH and agitational intensity. The formulation was found to be stable in accelerated condition.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

POPT: Porous osmotic pump tablets; **PEG:** Polyethylene glycol; **CA:** Cellulose acetate; **FTIR:** Fourier Transform Infrared; **DSC:** Differential Scanning Calorimetry; **MCC:** Microcrystalline Cellulose; **SEM:** Scanning Electron Microscopy; **CDR:** Cumulative drug release.

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