



Research Article

DEVELOPMENT OF CONTROLLED RELEASE FORMULATION OF PALONOSETRON HYDROCHLORIDE USING NOVEL PARENTERAL DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this study was to formulate and evaluate Parenteral Controlled Release Formulation of an antiemetic drug using the technology of in situ forming gel, based on temperature change mechanism in order to reduce the frequency of dosing and increase patient compliance in the long term treatment of Chemotherapy induced nausea and vomiting. Formulation was optimized, prepared, filled aseptically, sterilized and evaluated for prerequisites of Parenterals and other parameters like gelation temperature, gel strength, viscosity, drug content, in vitro and in vivo studies and stability studies. It was prepared using cold method and optimized by 3³ factorial design, comprising of drug, Pluronic F127, HPMC K 100M, PEG 400, was found to be clear, colorless, isotonic, sterile, pH as 6.2-6.5, viscosity of 1400cps, syringeable through 21 gauge needle, forming a stable in-situ gel at body temperature having gel strength of 16.47gm/cm showing a controlled release of 96.0 % in Simulated Body fluid at 120hrs following Korsmeyer-peppas model. The in vivo pharmacokinetics showed increase in t_{max} and AUC. Histopathological analysis showed no signs of inflammation or necrosis or any other cellular changes. The sterile formulation packed in amber colored ampoule was found to be stable with most suitable storage condition at the refrigerator temperature. Thus, a biocompatible, stable parenteral formulation was developed which can be an alternative and convenient approach to the patients that require frequent parenteral administration, reducing the frequency of dosing and ultimately increasing patient compliance and comfort.

Keywords: Palonosetron HCL, In situ gel, Pluronic F127, Gel strength

INTRODUCTION

Palonosetron hydrochloride an antiemetic and antinauseant agent is a serotonin (5- hydroxytryptamine or 5-HT) receptor antagonist is which exerts its effect by interacting with the 5-HT₃ receptors as an antagonist used in chemotherapy induced nausea and vomiting. A single dose of 250 µg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy given 30 minutes prior to start of Chemotherapy. The drug has to be repeatedly administered as a single day injection for 5 days over the course of Chemotherapy and also further to prevent the nausea and vomiting incidences associated.¹⁻³

Frequent injections leads to patient discomfort, pain and patient noncompliance. These problems can be overcome by administering, controlled release drug delivery systems which can reduce total number of injections throughout the effective treatment and improve patient compliance. Parenteral controlled release drug delivery systems include novel technology as *in situ* forming implants which use smart polymers that release the drug in controlled manner by undergoing sol-gel transition once administered due to stimuli like, temperature change.⁴⁻⁷

Thus the overall aim was to formulate a parenteral controlled drug delivery of Palonosetron Hydrochloride using the technology of *in situ* forming implant based on temperature change stimuli as a once a day injection to be administered at the start of

chemotherapy to achieve a release over a 5 day time period with an aim to improve patient compliance and reduce dosing frequency in chemotherapy induced nausea and vomiting.

MATERIALS AND METHOD

Palonosetron HCL was obtained as a gift sample from Emcure Pharmaceuticals Pune. PluronicF127 was provided by Ana lab fine chemical, Mumbai. Hydroxy propyl methyl cellulose K 100 M (HPMC K 100M) was provided by Chemica-biochemic-reagents, Otto chemie, Pvt. Ltd.

OPTIMIZATION

A response surface statistical experimental design was used to optimize the effect of different independent factors on response. The responses were investigated using a Box-Behnken statistical experimental design using Design-expert software® 9.0.4 (Stat-Ease, Inc., USA)

This design was based on a 3³ factorial design, three replicates of the central run, leading to 13 sets of experiments, enabling each experimental response to be optimized. Different batches were prepared with different independent variables at different levels and responses. The criterion for selection of optimum formulations was based on the gelation at body temperature and highest gel strength to remain stable for prolonged period of time i.e. for 5 days.

The quality of the fitted model was expressed by the coefficient of determination R^2 , and its statistical significance was checked by an F-test (analysis of variance) at the 5% significance level. The statistical significance of the regression coefficients was determined by using the t-test (only significant coefficients with p-value < 0.05 are included). The optimum processing conditions were obtained by using graphical and numerical analysis based on the criteria of the desirability function and the response surface.⁸

PREPARATION OF FORMULATION

The formulation was prepared by using cold method. Drug 0.06% was dissolved in water followed by addition of thermosensitive polymer Pluronic F127, stirred and kept in refrigerator at 4°C for 24 hrs to dissolve completely and form a clear solution. The other excipients like copolymer HPMC K100M, temperature modifier PEG 400 and tonicity adjusting agent NaCl were added to this solution and stirred continuously to dissolve to give complete clear viscous solution which was filled aseptically in amber glass ampoules 2ml and sterilized by autoclaving at 121°C at 15 psi for 20 min and stored at room temperature.^{11,12,13,32}

EVALUATION OF FORMULATION

Appearance & pH

The optimized formulation was visually checked for its appearance and pH. The pH of the sol form was measured using standardized digital pH meter (Deluxe pH meter 101/EI) at room temperature by taking adequate volume in a 10 ml beaker.⁴

Gelation Temperature

Gelation temperature was determined by modification of Miller and Doravan technique. A 2 ml aliquot of gel was transferred to test tubes immersed in a water bath at 40°C and sealed with aluminum foil. The temperature of water circulation bath was increased with increments of 10° and left to equilibrate for 5 min. at each new setting. The samples were examined for gelation which was said to have occurred when the meniscus would no longer move upon tilting through 90°. ^{11, 12, 13}

Gel strength

Gel strength was determined by Surimi test using Texture Analyzer (Texture Pro CT V1.4). Formulation (20 ml) was placed in 25 ml beaker and gelled using heating plate at 37°C. The probe (TA 3/100) was allowed to traverse the gel up to 1 cm at a speed of 1mm/s. The load reading was taken in g/cm for gel strength.¹⁸

Viscosity

Viscosity was measured on Brookfield viscometer using RV (spindle no. 21) and T-type helipath spindle (spindle no. S21). Rheological behavior was analyzed by subjecting the sample at temperature ambient temperature and 37°C and variable shear stress.²¹

Osmolality

The samples were subjected to osmolality test using an Osmometer (Model 3250, Version 2.4).⁴

Syringiability

Syringiability of the formulations at room temperature was assured using 21 to 26 G needles. Formulation was withdrawn into identical 5 ml plastic syringes placed with 21 to 26 gauge needles to a constant volume (1 ml). The solutions which were easily passed from a particular syringe were termed as pass and the ones which were difficult to pass were termed as fail.⁴

Drug content estimation

0.25 ml of the test formulation was diluted with excess of methanol and evaporated to dryness. The residue was diluted up to 100 ml with mobile phase to get a stock solution of 100µg/ml. From this stock solution, a solution of 40µg/ml was prepared and analyzed by HPLC. The concentration of the drug present in formulation was computed from the calibration curve using the equation $y=mx+c$.²⁴

Sterility Testing

Sterility testing was carried out as per the IP 2014. The formulation was incubated for not less than 14 days at 30-35°C in the alternate fluid thioglycolate medium to find the growth of bacteria & at 20°C-25°C in Soya bean casein digest medium to find the growth of fungi in formulation. The test was performed using positive and negative controls.²⁶

In-vitro Drug Release Studies

In vitro release studies of Palonosetron HCL from thermo-responsive in situ gel forming system were performed at 37°C using membrane less dissolution method i.e orbital shaking incubator at 30rpm. 2ml of formulation was added into the 2ml of simulated body fluid (pH-7.4) which was preheated at 37°C and 1 ml of dissolution medium was withdrawn after predetermined time intervals at 1,24,48,72,96,120 hrs and replaced with fresh medium to maintain sink conditions. Aliquots withdrawn were suitably diluted and analyzed using UV spectrophotometer at 280nm. ^{27, 31}

Pharmacokinetic analysis

In vivo release profile of Controlled and immediate release formulation of Palonosetron HCL

Six male rats, weighing 210–250 g, were divided in three study groups (n=2). Control group received a subcutaneous injection of sterile water for injection (SWFI); the second and third group received 0.5 ml Palonosetron HCL *In situ* gel formulation (6 mg/250 g body weight) and 0.5ml of immediate release formulation, subcutaneously at the back of the neck respectively. The blood samples were collected from tail vein at 1, 24,48,72,96 and 120 h for controlled release and 1, 3,5,7,8 h for immediate release after injection. The blood serum was separated and assayed for Palonosetron HCL content by HPLC. AUC from time zero to the last day of sampling (AUC); maximum blood concentration (C_{max}), time to the maximum concentration (T_{max}), and plasma drug concentration were evaluated, and graphs were plotted.²⁷

Histopathological analysis

Formulation treatment and control rats were killed at a scheduled time, carefully cut open the skin at the injection site, together with the surrounding tissue. To evaluate the biocompatibility of the in situ-forming gel, the injection site was observed, and the surrounding tissue was harvested for histopathological analysis.

The harvested tissues were preserved in 10% formalin followed by paraffin embedding. Sections were cut to 0.6μ thickness and stained with Standard hematoxylin eosin solution. The stained sections were checked for tissue necrosis or inflammation or any changes in cellular arrangement.²⁸

Accelerated Stability study

Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines. A sufficient quantity of formulations were kept at room temperature i.e. at 25°C ± 2°C/60% ± 5% RH, refrigerator i.e. at 5°C ± 3°C and accelerated conditions (40°C ± 5°C/75% ± 5% RH) for 1, 3, 6 month. After 1, 3, 6 month samples were evaluated for appearance, pH, clarity, gelation temperature, % drug content and *in vitro* drug release.^{29,30}

RESULTS

Optimization

Based on responses for gelation temperature and gel strength batch F13 was selected as an optimized batch comprising of PF127 20%, HPMC K100M 2.5% and PEG 400 2% with gelation temperature at 37°C and gel strength 16.47g/cm.

Gelation Temperature = $+1.63*A - 0.37*B - 0.25*C + 0.25*AB - 16*AC - 0.50*BC - 3.38*A^2 - 0.87*B^2 - 1.62*C^2$

Where, A is concentration of Pluronic F127, B is the concentration of HPMCK100M and C is the concentration of PEG400.

Gel Strength = $+16.47*A + 0.03*B - 0.03*C - 0.03*AB - 0.16*AC - 0.03*BC + 0.30*A^2 - 0.021*B^2 - 0.014*C^2$

Where, A is concentration of Pluronic F127, B is the concentration of HPMCK100M and C is the concentration of PEG400.

Appearance and pH

All the formulations were clear and colorless. The pH of the all the formulations was found to be between 6.2-6.5.

Gelation temperature

Gelation temperature of optimized batch was found to be 37°C.

Gel strength

Gel strength of optimized formulation was found to be 16.47gm/cm.

Viscosity

Viscosity of optimized formulation was found to be 1400cP.

Osmolality

The Osmolality of the sample was found to be 310mOsmol/L

Syringeability

The optimized formulation passed through needle gauze no.21

Drug content

The percentage drug content in the formulation was calculated and found to be 95.66%, indicating insignificant loss of drug during the formulation.

Sterility testing

No turbidity was observed after 14 days. It passes the sterility test. The formulation was found to be free from bacteria and fungi and hence suitable for parenteral and administration. Thus the sterility of the formulation may be attributed to aseptic process of preparation and filling the container and autoclaving at 121°C at 15 psi for 20 min.

In vitro Release study

The optimized formulation showed controlled release of 96.0 % in Simulated Body fluid at 120hrs. Drug release follows Korsmeyer –peppas model with R² value 0.9803.

Pharmacokinetic analysis

In vivo release profile of Controlled and immediate release formulation of Palonosetron HCL

The pharmacokinetic parameters and release profiles for Controlled and immediate release formulation were studied and compared.

Histopathological analysis

The study showed no significant difference in tissue arrangement and fat between control and test group. The skin section showed no signs of inflammation or necrosis or any other cellular changes and found similar constitution as that of control.

Accelerated stability study

From stability studies it was observed that the formulation of Palonosetron HCL was stable at selected storage conditions with most suitable storage condition at the refrigerator temperature. It shows no change in appearance, clarity, pH, gelation temperature, gel strength with negligible changes in % drug content and *in vitro* drug release profile.

DISCUSSION

Optimization

Design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. The Box- Behnken Design is an independent quadratic design which does not contain an embedded factorial or fractional factorial design. 3-D response surface plot were used to plot relationship between variables and responses. The objective of formulation was to achieve gelation at body temperature once injected in Simulated Body Fluid and retaining the formed gel and have sufficient strength and slowly releasing the drug over the time period of 5 days. From the Box Behnken experimental design with Response, Batch F13 followed all the predetermined parameters of gelation temperature and gel strength. From the Response surface plot and graphs of gelation temperature it is observed that as the concentration of Pluronic F127 increases the temperature of gelation decreases. Thermosensitive polymer Pluronic F127 contains POE-PPO-POE triblock copolymer. As the temperature increases dehydration of PPO block causes formation of micelle and hydration of PEO block leads to form gel. But as the concentration of Pluronic F127 increases, solution becomes more viscous and gelation temperature decreases. So as to achieve gelatinous body temperature, and make the solution viscous so that it can be easily injected, temperature modifier PEG400 needed to be added. PEG and Pluronic shows similarity in PE moiety. PEG 400 causes modification in process of micelle formation which ultimately results in modification of gelation temperature. Thus combination of Pluronic F127 20% and PEG 400 2% showed gelation at 37°C. Pluronic F127 alone cannot retain the formed gel and does not impart sufficient gel strength to maintain the *insitu* formed gel over a period of 5 days. So HPMCK100Ma copolymer was added to achieve sufficient gel strength so as to maintain stability of the *insitu* formed gel for prolonged time period. From the Response surface plot and graphs it is observed that as the concentration of HPMCK100M increases gel strength increases. Although HPMCK100M and Pluronic F127 differ in chemical structures, both have hydrophobic regions in their chains. It is reported that solvation

of hydrophilic chains (POE moiety) of Pluronic PF 127 at high temperature in water promotes interaction between hydrophobic moieties of HPMCK100M and Pluronic F127. Beyond 2.5% concentration of HPMC the solution becomes highly viscous and the interaction between the moieties decreases leading to decrease in gel strength. Thus combination of Pluronic F127 and HPMC imparts desired gel strength to the *in situ* formed gel. Thus the combination of thermosensitive polymer, copolymer and temperature modifier is optimized so as to form a sol of adequate syringeable viscosity, achieving gelation at body temperature and possessing sufficient gel strength and stability to maintain over prolonged period releasing the drug slowly.^{8-10,14-17,20-22}

Appearance and pH

Terminal sterilization with autoclaving had no effect on physical and chemical properties of the formulation. The pH values were found to be in the range tolerated by the subcutaneous tissue. Moreover, the drug was found to be most stable in this pH range.⁴

Gelation temperature

Pluronic F127 is POE-PPO-POE triblock copolymer. As the temperature increases dehydration of PPO block causes formation of micelle and hydration of PEO block leads to form gel. As the concentration of Pluronic F127 increase, gelation temperature decreases. Thus concentration of Pluronic F127 was optimized to attain gelation at body temperature. Generally phase transition depends upon the PEO: PPO ratio. As the temperature increases, dehydration of the PPO leads to formation of a micelle core while hydration of the PEO causes it to expand and form a hydrogel. So as the concentration of Pluronic F127 increases the gelation temperature decreases. During preliminary trials different formulations were prepared to achieve temperature range between 30-37° since if gelation temperature was below 30°, it will form gel at room temperature which ultimately leads to patient in compliance and problems regarding administration of dosage form. So as the concentration of Pluronic F127 increases, it dehydrates the micelle structure which leads to lowering of gelation temperature. So to increase gelation temperature, PEG400 was added, which possess same hydrophobic portion which interfere with micelle association of Pluronic F127 and causes entanglement, which ultimately leads to increase in gelation temperature.^{15,17,18}

Gel strength

Pluronic F127 undergo phase transition from sol-gel at body temperature but it does not possess sufficient gel strength to withstand various body shear forces and remain stable for prolonged period. So to achieve desired gel strength to remain stable over prolonged time period a copolymer HPMC K100M was added. Solvation of hydrophilic chains (POE moiety) of Pluronic F127 at high temperature in water promotes interaction between hydrophobic moieties of HPMCK100M and Pluronic F127 and thus imparting strength to the formed gel.^{16,22}

Viscosity

The viscosity of formulation was sufficient to impart the Syringeability to sol and maintain stability of the gel *in situ*. The viscosity of the formulation could be attributed to the polymer and copolymer used.

Osmolality

The formulation was found to be isotonic with the physiological fluids. The normal physiologic osmolality range is approximately 280-320 mOsmol/L. Thus formulation follows prerequisite of parenterals.

Syringeability

Syringeability is the ability or ease by which a formulation can be dispensed out of a syringe. The needle gauge No. selected is suitable for subcutaneous administration.

Sterility testing

The sterility of the formulation may be attributed to aseptic process of preparation and filling the container and autoclaving at 121°C at 15 psi for 20 min.

In vitro Release study

The objective was to achieve a controlled release over a period of 5 days. The optimized formulation achieves the predetermined release profile. Both Pluronic F127 and HPMC K 100M forms the matrix for drug entrapment and then slow release through it. Dissolution of polymer includes absorption or adsorption of water in one or more accessible place, rupture of polymer-polymer linkage with simultaneous forming water-polymer linkage, separation of polymeric chain, swelling and finally dispersion of polymeric chain in dissolution medium. Pluronic F127 and HPMCK100M were used to regulate the drug release in controlled manner for longer period from *in situ* gel formulation. The combination of HPMC with one or more ionic, non ionic or insoluble polymers in the formulation may provide additional functionalities which improve the release mechanism. In HPMCK100M polymer, because of low content of methoxy groups, hydrate quickly which justifies its application in the controlled release matrices.

Pharmacokinetic analysis

It was seen from the figures and table that the plasma concentration profile of the drug after administration of *in situ* forming gel showed controlled drug release in the systemic circulation for 120 hours. The increase in time (t_{max}) to reach C_{max} and increase in AUC for controlled release formulation in plasma after subcutaneous administration, as compared to immediate release injection may be attributed to the slow diffusion of the drug from the polymeric matrix. The higher AUC and lower C_{max} indicate prolonged duration of action for 5 days which reduces frequency of dosing and ultimately increases patient compliance and comfort.

Histopathological analysis

Subcutaneous tissue consists of loose connective tissue and fat beneath the dermis. Histological evaluation of SC tissue was carried out using hematoxylin eosin stain. The formulation was found to be biocompatible with no abnormality detected. The biocompatibility could be attributed to the use of biocompatible polymers and other excipients within their approved limits. Moreover, the pH and osmolality of the formulation within the desired ranges did not trigger any immunological response. Mild increase in collagen fibers in control group indicated initiation of healing of the disrupted tissue at the site of injection. Absence of collagen fibers in test formulation indicated complete healing of the damaged tissue at the injection site.

Table 1: Levels for the Box Behnken Design

Independent factors	Unit	Symbol	Levels	
			High	Low
PluronicF127	%	A	21	19
HPMC K100M	%	B	2.5	1.5
PEG 400	%	C	1.5	2.5

Table 2: Box Behnken experimental design with Factors

Batch no	Factors		
	PF 127	HPMC K100M	PEG400
F1	19	1.5	2
F2	21	1.5	2
F3	19	3.5	2
F4	21	3.5	2
F5	19	2.5	1.5
F6	21	2.5	1.5
F7	19	2.5	2.5
F8	21	2.5	2.5
F9	20	1.5	1.5
F10	20	3.5	1.5
F11	20	1.5	2.5
F12	20	3.5	2.5
F13	20	2.5	2

Table 3: Box Behnken experimental design with Response

Batch no	Response	
	Gelation temp (°C)	Gel strength (gm/cm)
F1	32	15.87
F2	35	17.62
F3	30	15.88
F4	34	17.62
F5	31	15.85
F6	34	17.65
F7	30	15.86
F8	33	17.66
F9	34	16.43
F10	35	16.41
F11	35	16.42
F12	34	16.40
F13	37	16.47

Table 4: ANOVA test result

SOURCE	ABSORBANCE		
	F-value	P-value	R-square
Quadratic model	3092.51	0.0001	0.997

Table 5: Syringeability of optimized formulation

Needle gauge no.	Outcome
21	Pass
22	Fail
24	Fail
26	Fail

Table 6: Pharmacokinetic parameters

Parameters	Controlled Release Formulation	Immediate Release Formulation
C _{max}	25.63ng	40.57ng
T _{max}	72hr	15min
K _{ale}	0.2326	2.2799
AUC ₀₋₁₂₀ (Prolonged R)	1402.615	129.0115
AUC ₀₋₃₀ (IR)		
AUC _{0-∞}	78.92206	12.15012

Table 7a: Evaluation of Stability samples at Room temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\%$)

	Appearance/clarity	pH	Gel temperature $^{\circ}\text{C}$	Gel Strength (g/cm)	Drug Content (%)	In vitro drug release (%)
1 month	Transparent, clear	6.2	37	15.60	95.78	96
3 month	Transparent, clear	6.2	37	14.8	92.67	95
6 month	Transparent, clear	6.0	36.8	14.0	89.67	95

Table 7b: Evaluation of Stability samples at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$

	Appearance/clarity	pH	Gel temperature $^{\circ}\text{C}$	Gel Strength (g/cm)	Drug Content (%)	In vitro drug release (%)
1 month	Transparent, clear	6.2	37	15.25	94.87	95
3 month	Transparent, clear	6.0	36.5	15.0	91.59	93
6 month	Transparent, clear	6.0	36	14.5	90.21	91

Table 7c: At Refrigerator ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$)

	Appearance/clarity	pH	Gel temperature $^{\circ}\text{C}$	Gel Strength (g/cm)	Drug Content (%)	In vitro drug release (%)
1 month	Transparent, clear	6.2	37	15.65	95.32	95
3 month	Transperant, clear	6.2	37	15.0	91.87	94
6 month	Transparent, clear	6.0	37	14.3	90.43	93

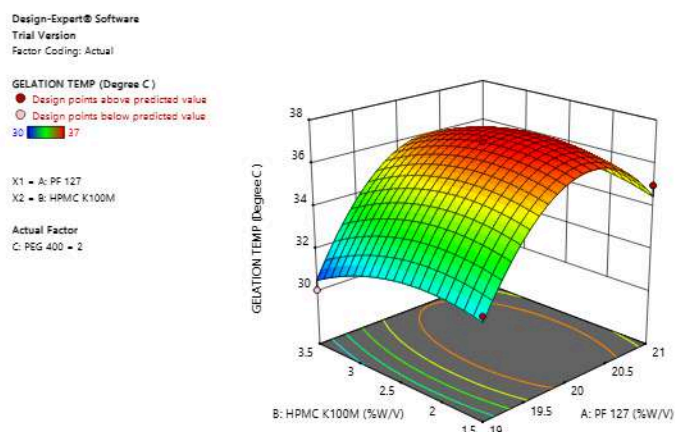


Fig.1 Response surface plot of gelation temperature

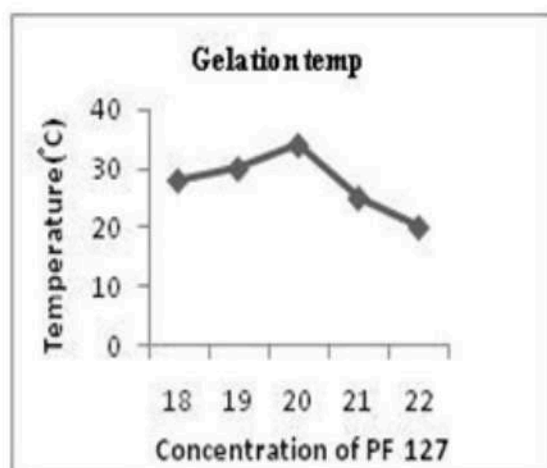


Fig.1a Effect of concentration of PF127 on gelation temperature

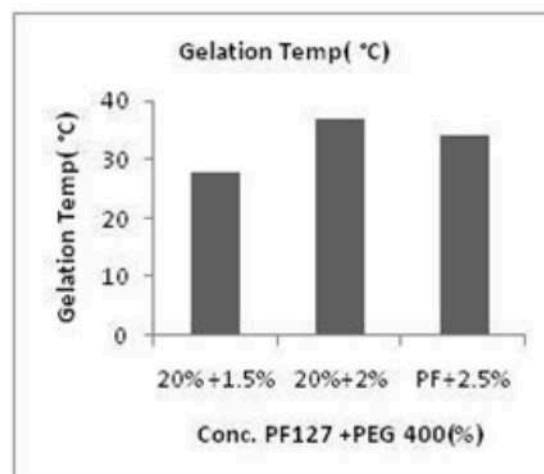


Fig.1bEffect of combination of PF127and PEG400 on gelation temperature

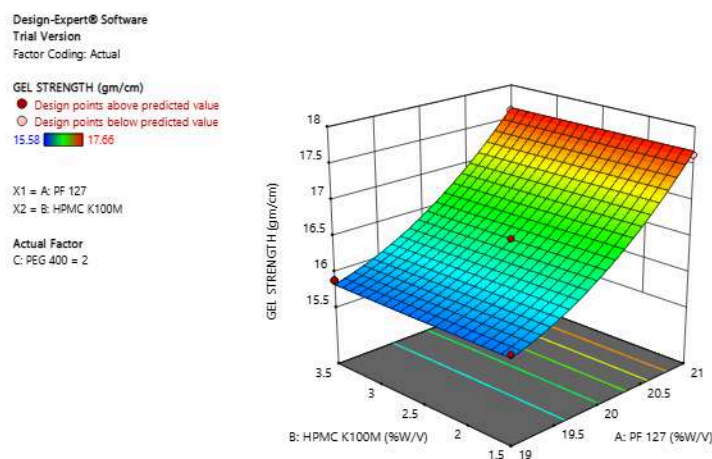


Fig.2 Response surface plot of gel strength

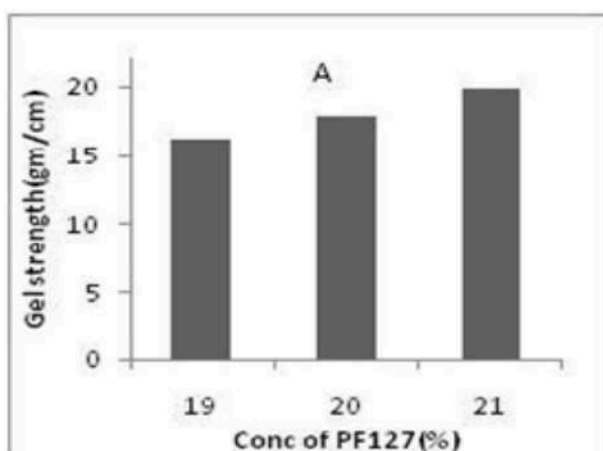


Fig.2a Effect of PF127 (20%) on gel strength

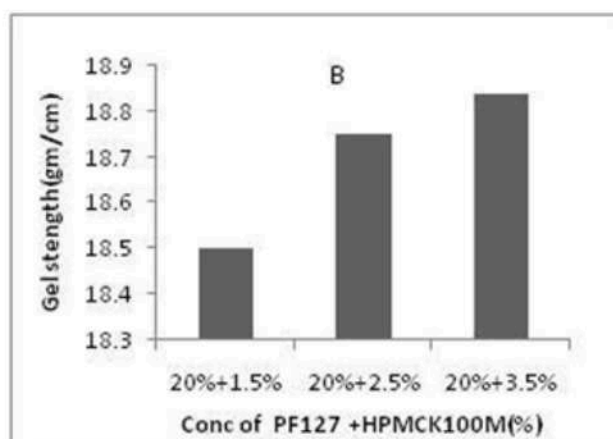


Fig.2b EffectPF127 (20%) + HPMCK100M on gel stre

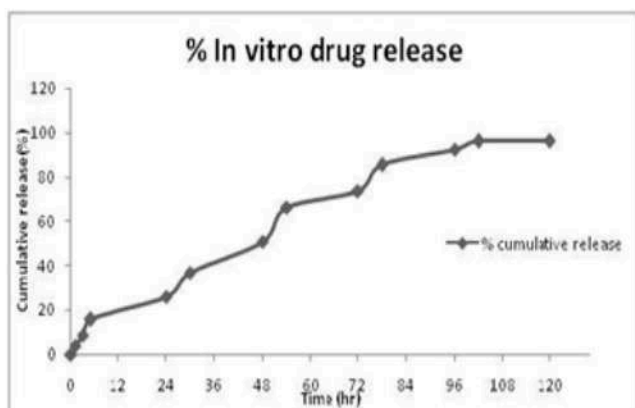


Fig.3 In vitro drug release

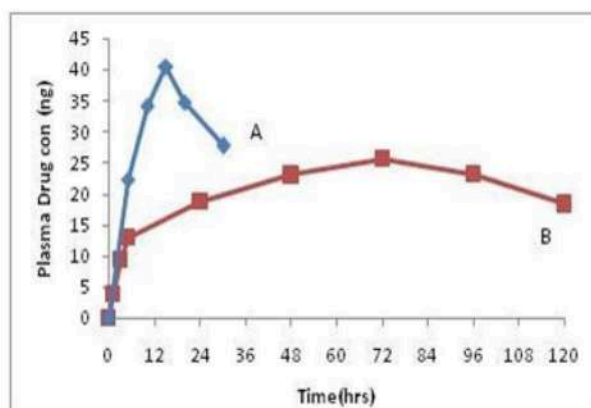
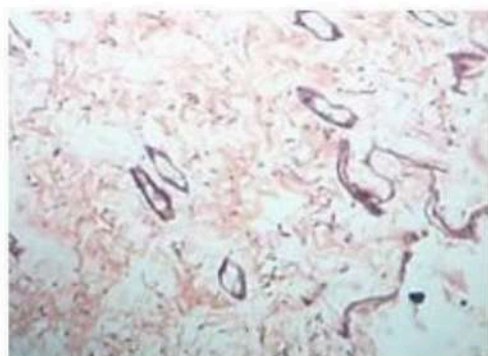
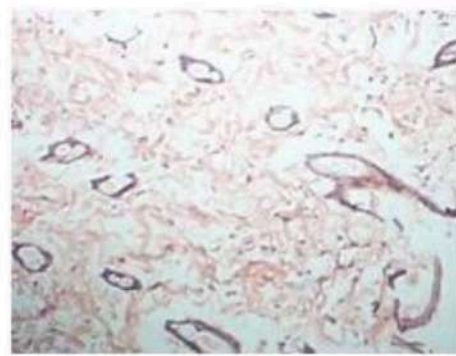


Fig.4 A) *In vivo* drug release profile from immediate release formulation Fig.4 B) *In vivo* drug release from controlled release formulation



A) Control



B) Sample

Fig.5 Optical photographs of subcutaneous tissue

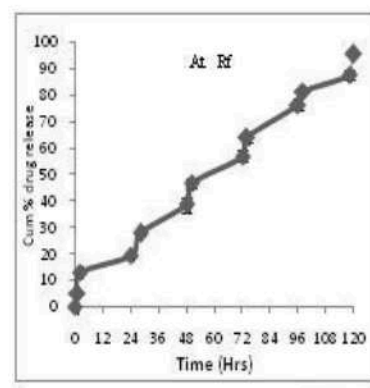
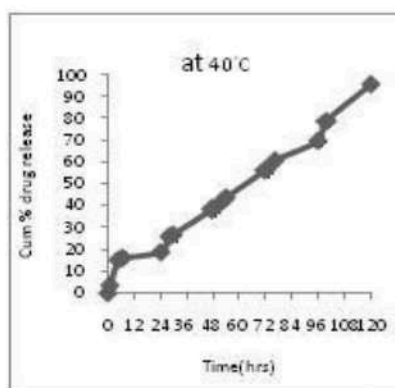
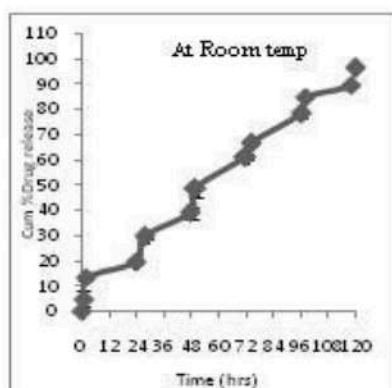


Fig.6 a Drug release after 1 month

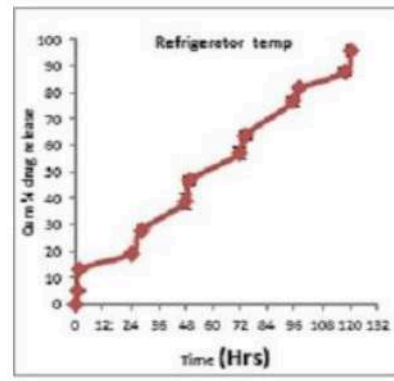
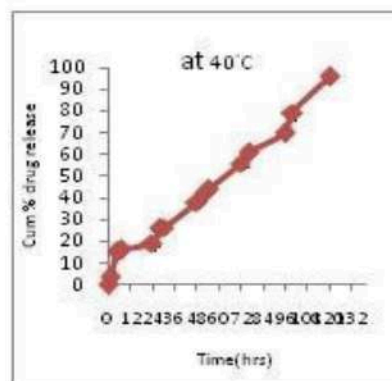
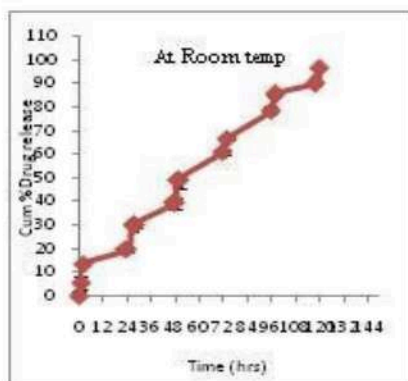


Fig.6 b Drug release after 3 month

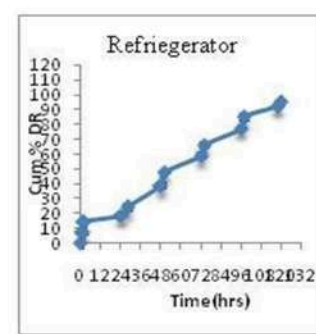
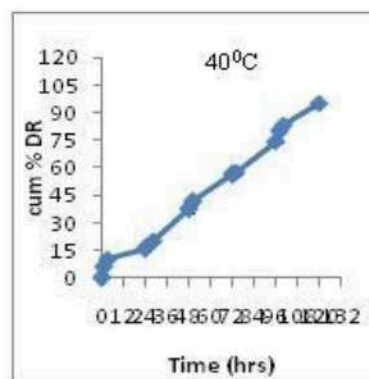
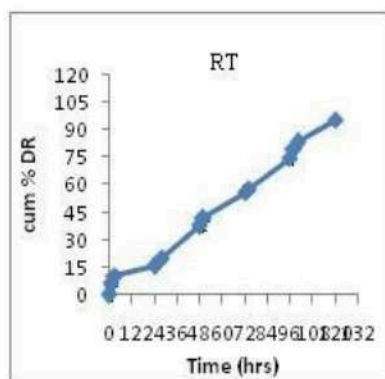


Fig.6 c Drug release after 6 month

Fig.6 In vitro drug release Evaluation of Stability Samples at Room temperature, 40°C $\pm$ 2°C/75% RH $\pm$ 5% RH and at Refrigerator for 1, 3 and 6 Months

Accelerated stability study

Thus the formulation packed in amber colored ampoule sterilized by autoclaving proves to be stable.

CONCLUSION

A novel stable temperature triggered *in situ* gelling parenteral drug delivery was successfully formulated by using thermosensitive polymer Pluronic F-127 along with copolymer HPMC K100M and PEG 400. Formulation of Palonosetron HCL as an *in situ* gelling parenteral drug delivery system is an alternative to the conventional formulations owing to its ability to Control drug release over the long time period. Thus such drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous in terms of compliance and as well to improve the quality of the therapy. Thus length of treatment with reduced dosing frequency and increased patient compliance experiencing long term treatment. The formulation involves less complicated fabrication and easy administration. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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