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FORMULATION, DEVELOPMENT AND OPTIMIZATION OF CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF MILNACIPRAN HYDROCHLORIDE

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Abstract

Aim: To formulate, develop and optimize Controlled Porosity Osmotic Pump (CPOP) tablets of Milnacipran hydrochloride. **Methodology:** The CPOP tablet contains pore former i.e. water-soluble additive (PEG-8000) in the coating membrane which after coming in contact with water, dissolve, resulting in an in-situ formation of microporous structure. The plasma half-life of Milnacipran hydrochloride ranges from 6 to 8 hours and the dosage regimen is one 50 mg tablet twice a day. Hence, Milnacipran hydrochloride was chosen as a model drug with an aim to develop a controlled release system for 24 hours. The effect of different variables, like, ratio of drug to osmogent, % weight gain and level of pore former in the coating solution on the *In Vitro* drug release is studied using 2^3 factorial design. The effect of pH and agitation on drug release was also carried out. Drug-excipients compatibility was studied by Differential Scanning Calorimetry (DSC). Microporous structure of coating membrane of formulation was determined by Scanning Electron Microscope (SEM). Results: *In Vitro* dissolution studies revealed that drug release rate increased with the amount of osmogent because of increased water uptake, and hence increased driving force for drug release. Drug release was inversely proportional to membrane weight gain: however, directly related to the concentration of pore former in the membrane. **Conclusion:** Optimized formulation (SP7) was found to deliver 99.68 % of drug at a zero order rate in 24 hours.

INTRODUCTION

Oral controlled release systems continue to be the most popular amongst all the drug delivery systems. Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices over the past 2 decades[1,2]. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Theeuwes introduced the elementary osmotic pump (EOP) [3]. The EOP consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice. Various attempts to increase the permeability of the semipermeable coating have been reported, such as incorporating water-soluble pore-forming additives in the coating[4]. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role[5, 6]. Osmotic tablets with an asymmetric membrane coating that can achieve high water fluxes have also been described[7].

Milnacipran hydrochloride is indicated for treatment of major depressive disorder and fibromyalgia [8-11]. Milnacipran hydrochloride is a white crystalline solid with a molecular weight of 282.82 [12]. Milnacipran hydrochloride is having high solubility and high permeability (BCS Class-I) [13].

MATERIAL AND METHODS

Materials

Milnacipran hydrochloride was obtained from Torrent Pharmaceuticals, Bhatt, India. Mannitol obtained from (S.D. Fine Chem. Pvt. Ltd, Boisar), Microcrystalline cellulose-

Avicel PH 102 (FMC Asia – Pacific, Inc. Mumbai, India), PEG-8000 (Astron Research Ltd, Ahmedabad, India), Talc (Apex chemicals, Ahmedabad, India) and Magnesium stearate (Central Drug House (P) Ltd, New Delhi, India). Cellulose acetate with 39.8% acetylene content (CA-398-10NF) was obtained from Eastman Chemical Inc, Kingsport, TN. All other solvents and reagents used were of analytical grade.

Methods

Spectroscopic Analysis of Milnacipran Hydrochloride:

In the present investigation, Milnacipran Hydrochloride has been estimated by UV/Visible Spectrophotometry. The drug release study was carried out using 0.1N HCl as the dissolution medium.

Preparation of Standard Curve:

- For preparation of the stock solution, the drug Milnacipran Hydrochloride (100 mg) was dissolved in 100 ml of 0.1N HCl to obtain a stock solution (1000 µg/ml). 10 ml of solution was taken and further diluted to 100 ml. The obtained solution of Milnacipran hydrochloride (100 µg/ ml) was used as standard stock solution.
- From the stock solution 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 ml were withdrawn and diluted to 100 ml with 0.1N HCl to yield concentration of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml. Absorbance of each solution was measured at 223 nm using Shimadzu 1700 UV/Visible Spectrophotometer.

Formulation of Milnacipran hydrochloride CPOP Tablets

Preliminary studies were carried out to screen best osmogent, pore former, and plasticizer.

In order to investigate the effect of formulation variables on the response variable, and to predict an optimized formulation, a 2^3 factorial design was adopted. List of Independent variables and Dependent variables are mentioned in Table 2.

Selection of levels for independent variables

2 levels selected: High and Low for all three factors, that is summarised in Table 3.

The Drug to Osmogent ratio (X_1), Concentration of pore former (X_2), and %

weight gain (X_3) were selected for different levels were bases on the preliminary work done on the formulation of CPOP tablet of Milnacipran hydrochloride.

Preparation of Core tablet

Core tablets were prepared by direct compression technique. Milnacipran hydrochloride, Mannitol, and MCC avicel pH 102 were sifted together through 40# sieve and blended for 15 minutes. The blend was again passed through 40# and lubricated with Talc and Magnesium stearate (previously Sifted through 60 # sieve) for 5 minute. The blend was compressed into tablets using B-tooling 8.75 mm round, standard concave shaped punches plain on both the sides and corresponding dies. (Cadmach Machines Ltd., India).

Preparation of Coating solution

Cellulose acetate, PEG-8000 and Triethyl citrate was added into the required quantity methanol. Then required quantity of acetone was gradually mixed with the resultant polymeric solution for 80-100 RPM using Remi magnetic stirrer. Finally solution of colour (Ferric oxide red) was mixed with the polymeric solution. At the end, resulting solution passed through 100 # sieve so that if any insoluble particle if remained in the coating solution will be removed. Coating was performed by spray gun (Painter Spray Gun, Model no. PS-3) in a coating pan (Manesty Model no. 354255). Core tablets mixed with equal quantity of dummy tablets. Initially, tablets were preheated by passing hot air through the tablet bed and by rotating at a lower speed of 3 to 4 rpm. Coating process was started with rotation speed of 4 to 5 rpm. The spray rate and atomizing air pressure were 4 to 6 mL/min and 1.75 kg/cm^2, respectively. Inlet and outlet air temperatures were 60°C±10°C and 45°C, respectively. Coated tablets were dried at 50°C for 12 hours and the percentage weight gain of the coating membrane was measured. The detail of composition of each formulation is given in Table 4.

EVALUATION OF MILNACIPRAN HYDROCHLORIDE OF CONTROLLED POROSITY OSMOTIC PUMP (CPOP) TABLET

Evaluation of Lubricated blend

Lubricated blend of all formulation trials were evaluated for Bulk density, Tapped density, and Carr's index and Angle of repose.

Physiochemical evaluation of Milnacipran Hydrochloride CPOP Tablets

All prepared tablets were evaluated for uniformity of weight and drug content, as per I.P. method. Weight variation was determined by weighing 20 tablets of each formulation on digital weighing balance (Reptach, Ahmedabad, India). Tablet diameter of 10 randomly selected tablets was measured by digital vernier caliper. Crushing strength of 10 randomly selected tablets were determined using Dr. Schleuniger tablet hardness tester (Pharmatron 8, Germany). Friability was determined using Roche friabilator (Electrolab, Model EF2, India).

***In Vitro* Drug Release study of Milnacipran Hydrochloride CPOP Tablets**

Dissolution test was performed using a USP type-2 paddle apparatus (Electrolab Dissolution Tester, Model TDT – 08L, India) at 37 ± 0.5° C in 900 ml of 0.1N HCl with a speed of 50 rpm. All dissolution parameters were taken as per OGD recommendation[14]. Samples were withdrawn after predetermined time intervals and Milnacipran hydrochloride content was measured using a UV spectrophotometer (Model UV-1700 Pharmaspec, UV-Visible Spectrophotometer, Shimadzu, Japan) at a wavelength of 223 nm.

Effect of pH

To study the impact of pH and to confirm a consistent performance of the developed formulations independent of pH, *In Vitro* release studies were conducted in media of different pH i.e. 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 phosphate buffer at 37 ± 0.5° C in 900 ml with a speed of 50 rpm. Samples were withdrawn after predetermined time intervals and Milnacipran hydrochloride content was measured using a UV spectrophotometer at a wavelength of 223 nm.

Effect of Agitation Intensity

In order to study the effect of agitation intensity of the release media, release studies were performed using a USP type-2 paddle apparatus at 37^{o} C ± 0.5^{o} C in 900 ml of 0.1N HCl with a speed of 50 rpm, 100 rpm and 150 rpm. Samples were withdrawn after predetermined time intervals and Milnacipran hydrochloride content was measured using a UV spectrophotometer at a wavelength of 223 nm.

Scanning Electron Microscopy

Coating membranes of formulation obtained before and after contact with the dissolution media (0.1N HCl) were examined for their porous morphology by scanning electron microscope (XL30 ESEM TMP+EDAX, Philips, Eindhoven, The Netherlands). Membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination.

Drug-Excipient Interaction Studies

DSC allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift or disappearance of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction[15]. The DSC thermograms of pure drug, core tablets and coated tablets were recorded. The samples were separately sealed in aluminum cells and set in Perkin Elmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Short-term Accelerated stability studies [16]

Short-term accelerated stability study was carried out on optimized formula (SP7). The tablets were stored at 40±2°C/75±5% RH for 30 days. All the tablets were suitably packed in aluminum foil. After the end of which, the *In Vitro* dissolution study and physical characterization of tablets were checked.

RESULTS AND DISCUSSION

The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. Core tablets were prepared by direct compression technique using mannitol as osmogent and MCC as filler showed excellent flowability and good compressibility. Directly compressible core tablets showed acceptable friability and were evaluated for *In Vitro* dissolution. The core tablets were coated by semipermeable membrane-forming polymer i.e. cellulose acetate with PEG 8000 as water soluble pore former and Triethyl citrate as a plasticizer. The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. The

dissolved drug is released through the pores created after leaching of water-soluble additive in the membrane.

Spectrophotometric analysis of Milnacipran hydrochloride

In the present investigation, Milnacipran Hydrochloride has been estimated by UV/Visible Spectrophotometry using 0.1N HCl as the dissolution medium.

Figure 1 showing λmax of Milnacipran hydrochloride in 0.1N HCl at 223 nm. Figure 2 showing standard curve of Milnacipran hydrochloride in 0.1N HCl. Table 2 showing results of the Spectrophotometric Analysis of Milnacipran hydrochloride in 0.1 N HCl at 223 nm

Equation of the regression line from (Figure 2 & Table 1):

Absorbance = (0.028* Concentration) + 0.063

- R^2 =0.99415
- Slope of the Regression Line = 0.028
- Intercept of the Regression Line = 0.0634

Evaluation of Lubricated blends

Lubricated blend of all formulation trials were evaluated for Bulk density, Tapped density, and Carr's index and Angle of repose. Table 5 summarizes blend properties of all formulation trials of Milnacipran hydrochloride CPOP Tablets.

Physiochemical evaluation of Milnacipran Hydrochloride CPOP Tablets

All prepared tablets were evaluated for uniformity of weight and drug content, Tablet diameter, crushing strength and Friability as shown in Table 6.

***In Vitro* Drug Release study of Milnacipran Hydrochloride CPOP Tablets:**

Dissolution test was performed using a USP type-2 paddle apparatus at 37 ± 0.5° C in 900 ml of 0.1N HCl with a speed of 50 rpm. Dissolution of all the trials from SP1 to SP8 is shown in figure 3. *In Vitro* dissolution studies revealed that drug release rate increases as amount of osmogent increases because of increased water uptake due to osmosis mechanism, and hence increased driving force for drug release. Drug release was inversely proportional to membrane weight gain: however, directly related to the concentration of pore former in the membrane. Drug release from batch SP7 was found to be best amongst other trials. Kinetic of drug release was confirmed by Fortran software. Table 7 shows that zero

order model shows best fit for release of Milnacipran hydrochloride from batch SP7 because it shows minimum F value (14.9849) and minimum SSR value (134.8640).

Effect of pH on *In Vitro* dissolution profile:

By performing the dissolution profile of optimize batch (SP7) using a USP type-2 paddle apparatus in 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 phosphate buffer at 37 ± 0.5° C in 900 ml with a speed of 50 rpm, drug release rate was found to be independent of pH of media as shown in figure 4. Drug release pattern from the optimize batch (SP7) was found to be very similar in all above three different pH medium.

Effect of agitation intensity on *In Vitro* dissolution profile:

By performing the dissolution profile of optimize batch (SP7) using a USP type-2 paddle apparatus at 37^{o} C ± 0.5^{o} C in 900 ml of 0.1N HCl with a speed of 50 rpm, 100 rpm and 150 rpm, drug release rate was found to be independent of agitation intensity as shown in figure 5. Drug release pattern from the optimize batch (SP7) was found to be very similar in all three different agitation speed.

Scanning Electron Microscopy

Figure 6 and 7 showed SEM of cellulose acetate membranes of optimized formulation (SP7), obtained before and after dissolution respectively. Membranes obtained before dissolution showed nonporous region. After 24-hours dissolution, the membrane clearly showed pores in the range of 1-50 µm owing to dissolution of PEG-8000. The leaching of PEG-8000 from the membrane leads to formation of pores.

Drug-Excipient Interaction Studies

Figure 8, 9 and 10 showed DSC thermograms of pure API (Milnacipran hydrochloride), core formulation and coated formulation of optimized batch (SP7). No changes in the endotherms were observed as drug exhibited a sharp melting endotherm in the core as well as in coated formulation. So from all the DSC thermograms it was clear those excipients used in the proposed formulation found to be compatible with the drug.

Short-term Accelerated stability studies

Short-term accelerated stability study was carried out at 40±2°C/75±5% RH for 30 days on optimized formula (SP7) and it was found that there was no statistically significant difference in in-vitro drug release before and after stability study. No fracture of coat from any tablet of optimized batch was noticed during and after stability study. The results of the Accelerated stability study are summarized in Table 8.

CONCLUSION

The research work was aimed to formulate CPOP tablets of Milnacipran hydrochloride that deliver a drug at zero order rate for 24 hours. 2^3 full factorial design was employed to optimize the CPOP tablets of Milnacipran hydrochloride by selecting ratio of drug to osmogent, amount of pore former and % weight gain by coating. From the various formulation trials shown in table 4, Batch (SP7) formulated using 1:1.5 drug to Osmogent ratio, 30% w/w of pore former and 4% weight gain, produced 99.68% drug release in 24 hour and found to be satisfactory. CPOP tablets of Batch (SP7) released the drug at zero order rate and found to be independent of the pH of dissolution medium and the agitation intensity. Results of Scanning Electron Microscopy (SEM) confirmed the formation of pores in the membrane after coming in contact with the aqueous environment. Drug-Excipient compatibility study was carried out by DSC and it was found that there is no chemical interaction between the drug and excipients. Short-term accelerated stability studies on the optimized formulation (SP7) indicated that there are no significant changes in drug content and *In Vitro* drug release as well as in the physical appearance of tablet.

In conclusion the present study underlines the importance of formulation and processing variables. By using optimum amount of drug to Osmogent ratio, Concentration of pore former and % weight gain, it is possible to prepare stable and effective CPOP tablets of Milnacipran HCl to provide drug release at zero order for 24 hours.

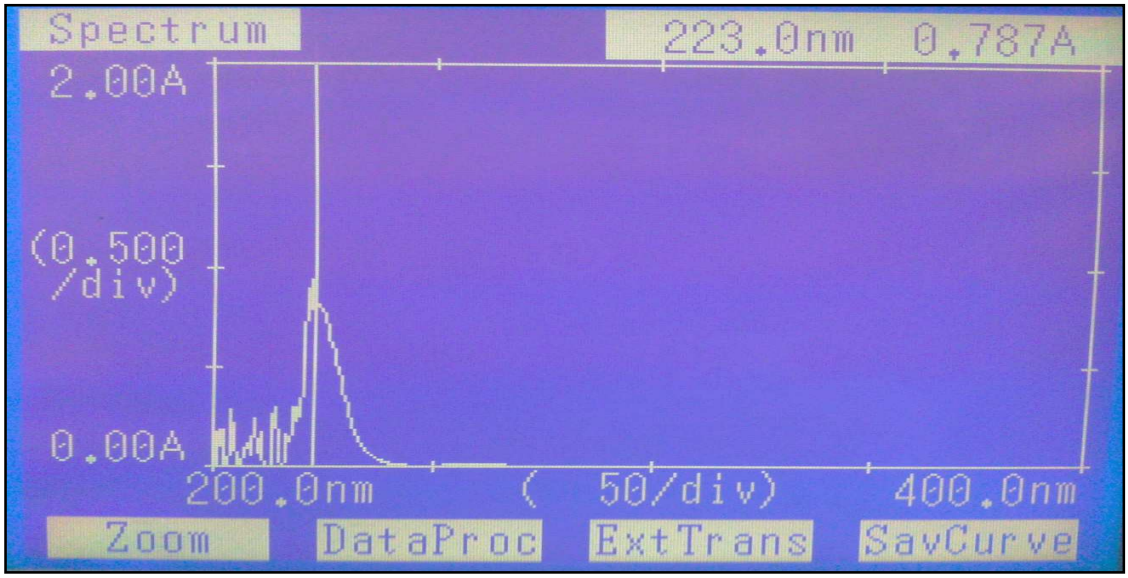

Figure 1 Photographic image showing λmax of Milnacipran hydrochloride in 0.1N HCl at 223nm

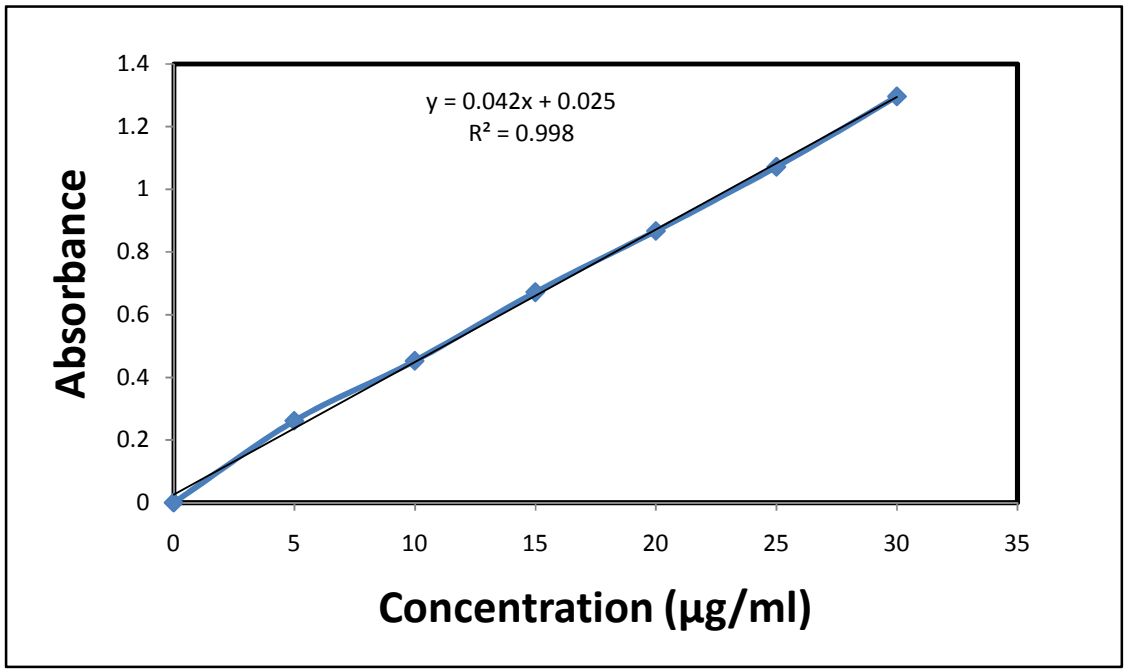

Figure 2 Standard curve of Milnacipran Hydrochloride in 0.1 N HCl at 223 nm

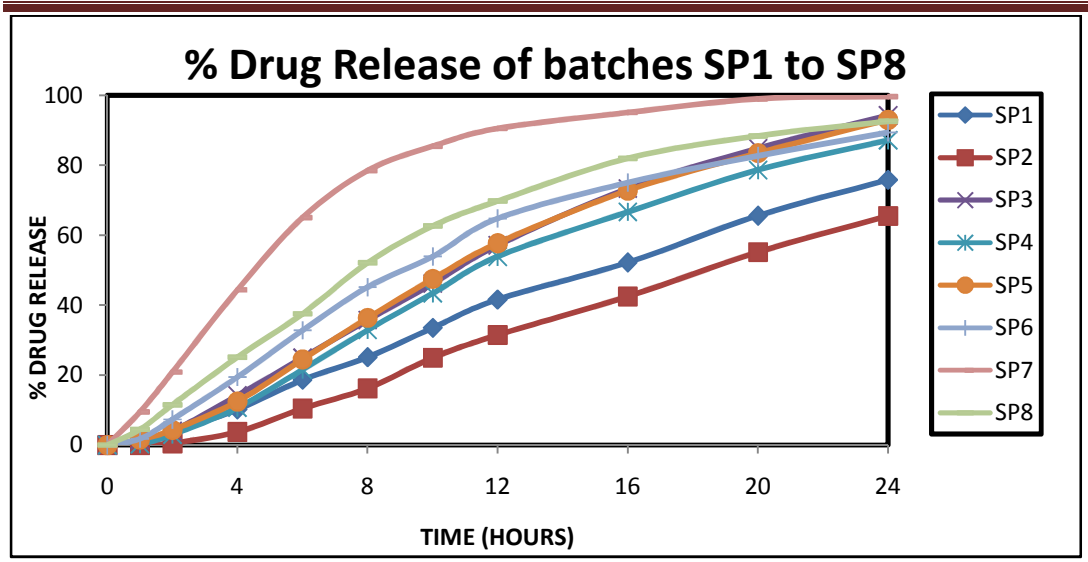

Figure 3 % Drug Release of Trial batches SP1 to SP8

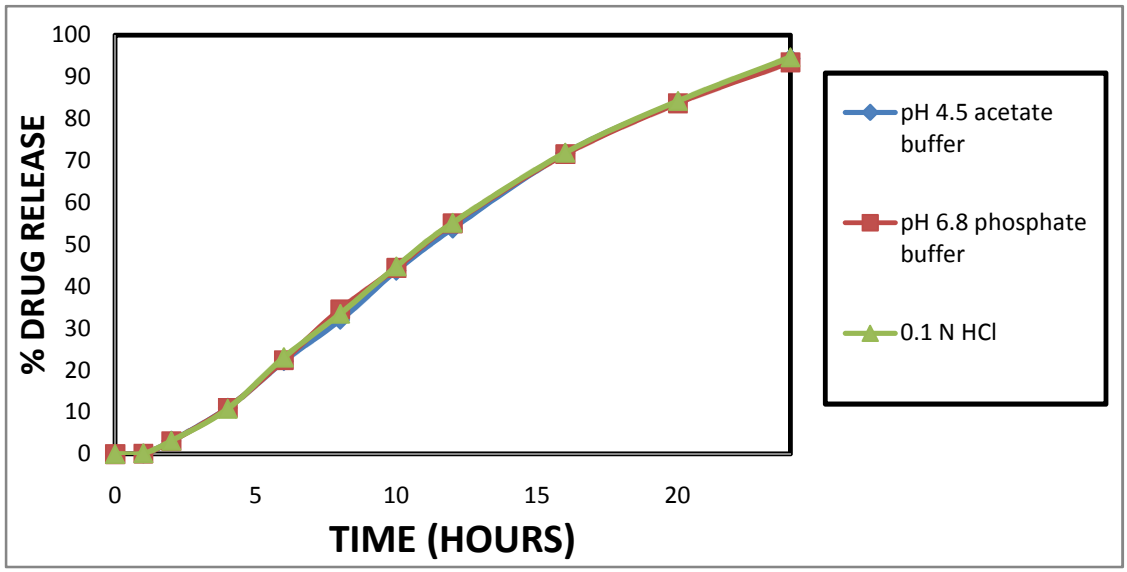

Figure 4 Comparison of *In Vitro* dissolution profile of batch (SP7) in 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 phosphate buffer

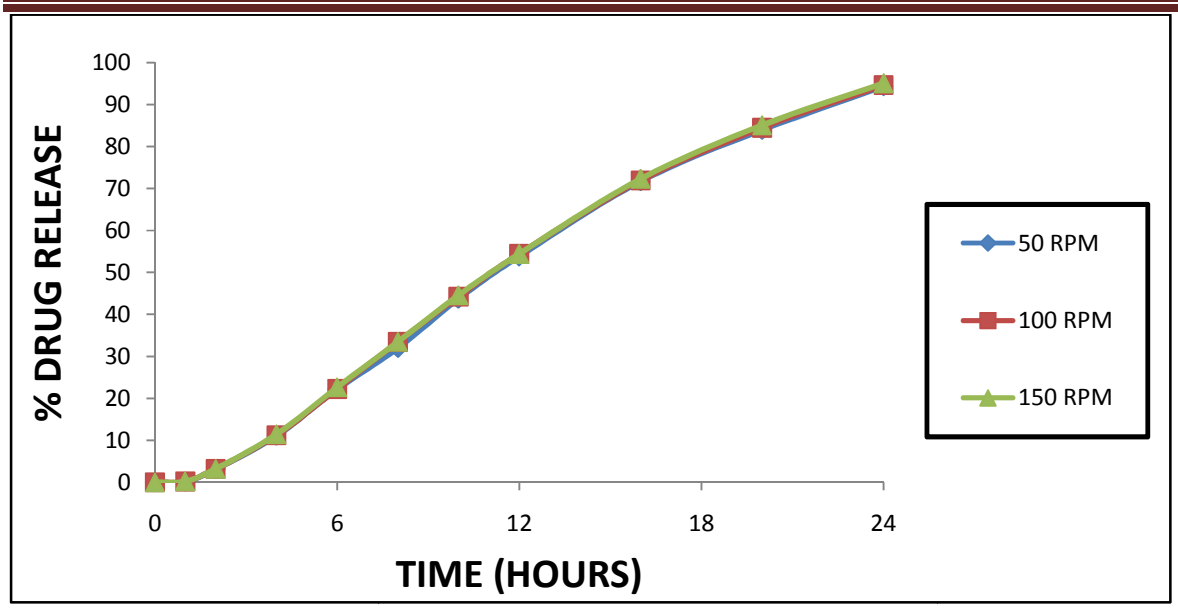

Figure 5 Comparison of *In Vitro* dissolution profile of batch (SP7) at 50 RPM, 100 RPM and 150 RPM (At different agitation speed in 0.1 N HCl)

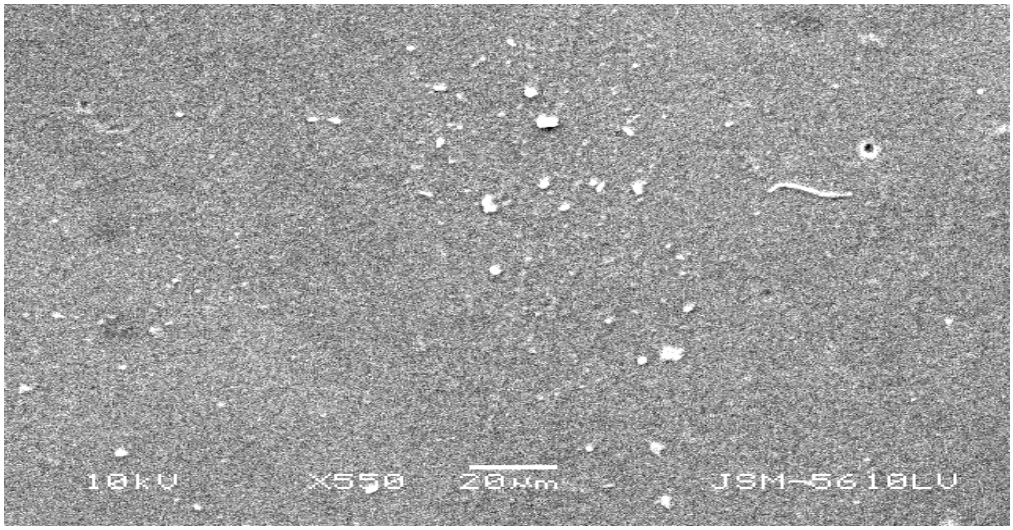

Figure 6 SEM of membrane structure of Batch (SP7) formulation before dissolution studies

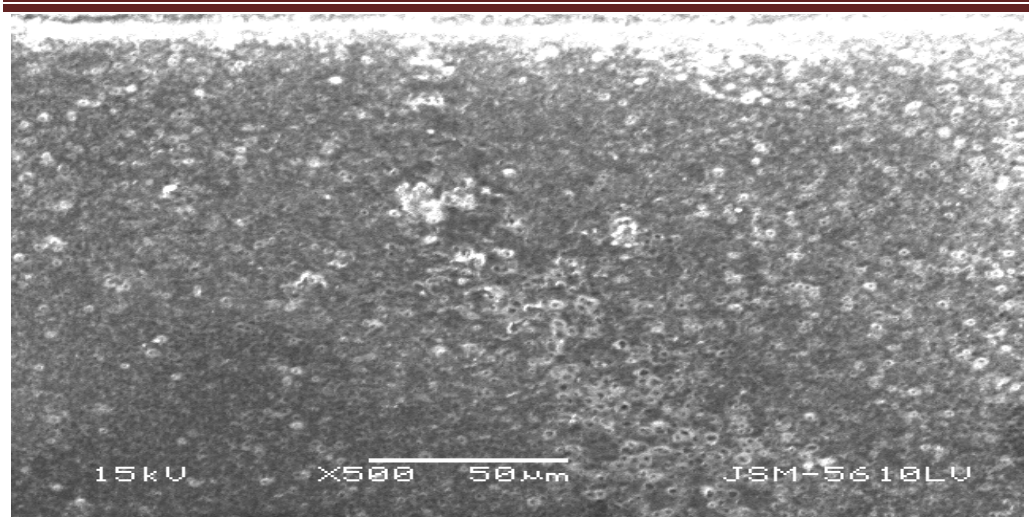

Figure 7 SEM of membrane structure of Batch (SP7) formulation after dissolution studies (after 24 hours)

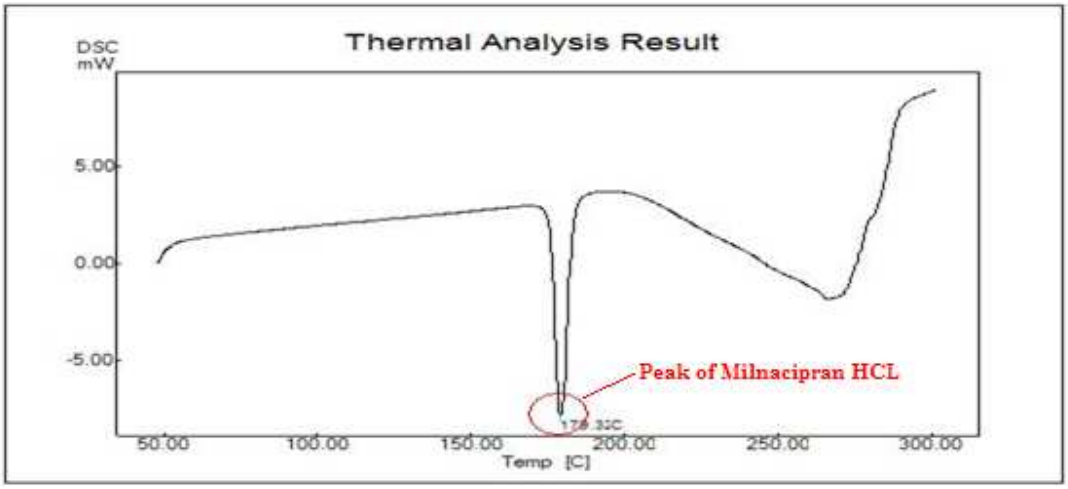

Figure 8 DSC Thermogram of Milnacipran hydrochloride

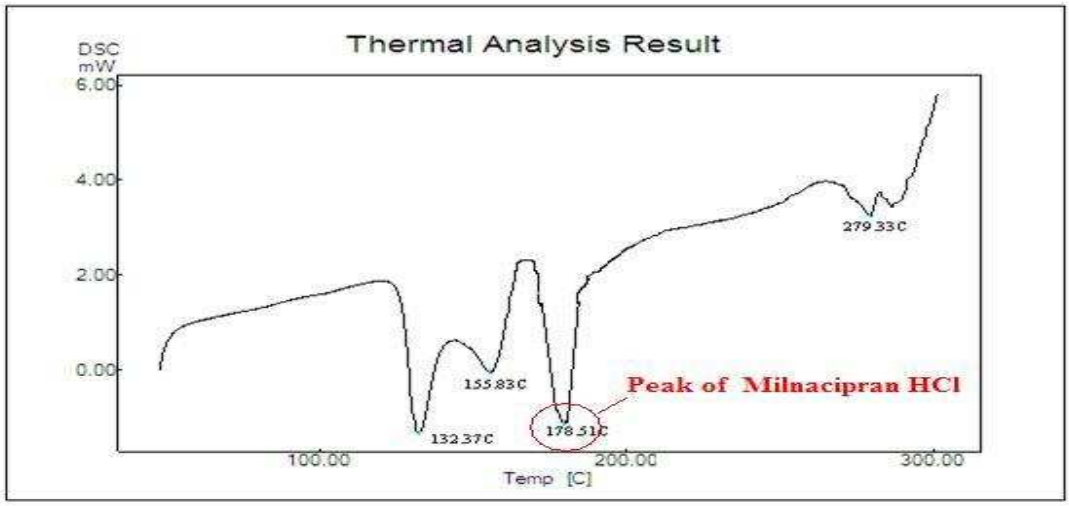

Figure 9 DSC Thermogram of batch (SP7) of Milnacipran hydrochloride Core Tablet

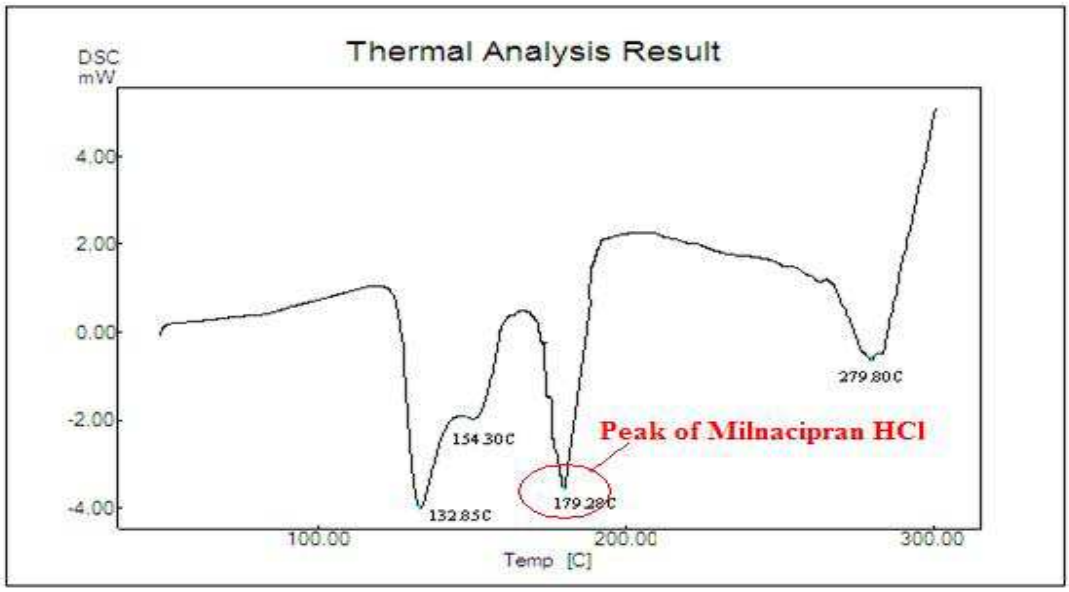

Figure 10 DSC Thermogram of batch (SP7) of Milnacipran hydrochloride CPOP Tablet

Table 1

Results of the Spectrophotometric Analysis of Milnacipran hydrochloride in 0.1 N HCl at 223 nm

Practical λ_{max} : 223 nm

Conc. (µg/ml)	Absorbance Set 1	Set 2	Set 3	Average Absorbance	Standard deviation
0	0.000	0.000	0.000	0.000	0.000
5	0.217	0.207	0.221	0.215	0.007
10	0.395	0.387	0.391	0.391	0.004
15	0.538	0.551	0.541	0.543	0.007
20	0.785	0.789	0.787	0.787	0.002
25	0.871	0.858	0.840	0.856	0.016
30	0.991	1.005	1.010	1.002	0.010
35	1.182	1.140	1.132	1.152	0.027

Summary output

Regression Statistics			
Multiple R	0.997459	Standard Error	0.030566
R Square	0.994925	Slope	0.032
Adjusted R Square	0.994079	Intercept	0.045833
		Observations	08

Equation of the line

Absorbance = Slope * Concentration + Intercept

Absorbance = 0.032 * Concentration + 0.045

Table 2

Independent variables and Dependent variables

2^3 full factorial design			
	Independent variables		Dependent variables
X_1	X_2	X_3	Y
Drug to Osmogent ratio	Concentration of pore former (PEG 8000)	% weight gain	% Drug release in 24 hours

Table 3

Selection of levels for independent variables

Levels	**Low**	**High**
Variables	-1	+1
X_1	1:0.5	1:1.5
X_2	15% w/w	30% w/w
X_3	4%	8%

Table 4

Formulations for preparation of controlled porosity osmotic pump tablet of Milnacipran hydrochloride as per 2^3 full factorial design

EXCIPIENTS		BATCH CODE							
		SP_1	SP_2	SP_3	SP_4	SP_5	SP_6	SP_7	SP_8
Core tablet									
Milnacipran HCl*	mg	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
	%	33.33	33.33	33.33	33.33	33.33	33.33	33.33	33.33
Mannitol	mg	25.00	25.00	25.00	25.00	75.00	75.00	75.00	75.00
	%	16.67	16.67	16.67	16.67	50.00	50.00	50.00	50.00
MCC Avicel pH 102	mg	72.00	72.00	72.00	72.00	22.00	22.00	22.00	22.00
	%	48.00	48.00	48.00	48.00	14.66	14.66	14.66	14.66
Talc	mg	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
	%	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	mg	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
	%	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total weight	mg	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00
	%	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Coating									
Cellulose acetate	%W/V	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
PEG 8000$	%W/W	15.00	15.00	30.00	30.00	15.00	15.00	30.00	30.00
Triethyl citrate$	%V/W	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Acetone: Methanol (80:20)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Ferric oxide red	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
% weight gain	%	4	8	4	8	4	8	4	8

*Actual quantity of Milnacipran HCl is taken based on Assay and water content calculation.

$ Quantity is taken as percentage of Cellulose acetate.

Table 5

Blend properties of various formulation trials of Milnacipran hydrochloride CPOP Tablets

Formulation batches	Bulk Density (g/ml) (± SD)	Tapped Density (g/ml) (± SD)	Compressibility Index (%) (± SD)	Angle of Repose (°) (± SD)
SP1	0.39±0.52	0.46±0.62	15.22±0.78	24.14±0.67
SP2	0.39±0.43	0.47±0.78	17.88±0.33	27.25±0.48
SP3	0.37±0.91	0.46±0.24	18.45±0.64	24.41±0.50
SP4	0.36±0.35	0.42±0.62	14.29±0.80	25.73±0.45
SP5	0.38±0.71	0.48±0.34	20.63±0.77	27.68±0.57
SP6	0.39±0.12	0.45±0.93	15.22±0.42	28.21±0.90
SP7	0.37±0.20	0.41±0.32	12.06±0.71	27.41±0.66
SP8	0.37±0.43	0.46±0.74	19.30±0.49	28.41±0.32

Table 6

Physical evaluation of various formulation trials of Milnacipran hydrochloride CPOP Tablets

Formulation batches	Diameter ± SD	Hardness(N) ± SD	Friability(%) ± SD	Weight Uniformity (mg) ± SD	Uniformity of content ± SD
SP1	8.75 ± 0.10	70 ± 20	0.30 ±0.29	Complies	98.56±0.25
SP2	8.75 ± 0.10	70 ± 20	0.63±0.12	Complies	97.35±0.92
SP3	8.75 ± 0.10	70 ± 20	0.53±0.10	Complies	98.73±0.37
SP4	8.75 ± 0.10	70 ± 20	0.69±0.87	Complies	99.46±0.59
SP5	8.75 ± 0.10	70 ± 20	0.67±0.19	Complies	98.57±0.41
SP6	8.75 ± 0.10	70 ± 20	0.54±0.26	Complies	100.74±0.94
SP7	8.75 ± 0.10	70 ± 20	0.51±0.66	Complies	100.25±0.23
SP8	8.75 ± 0.10	70 ± 20	0.53±0.43	Complies	98.22±0.40

Table 7

Model fitting for kinetics of drug release of Optimized Batch (SP7)

Model	SSR	F-value	R-square	Slope	Intercept
Zero order	**134.8640**	**14.9849**	0.9886	0.0717	-2.4338
First order	2352.2980	261.3664	0.9242	-0.0019	4.9078
Higuchi	979.9918	108.8880	0.9172	2.8124	-20.9669
Hixon-Crowell	501.9519	55.7724	0.9761	0.0020	-0.2380
Korsmeyer	10214.3700	1276.7960	0.9063	1.9068	-5.7616
Weibull	189.0084	23.6261	0.9551	2.2071	-6.4009

Table 8

Accelerated stability results of batch (SP7)

Parameters	Initial	30 days
Appearance of tablets	Red colour tablets	Red colour tablets
Hardness (N) ± SD	70 ± 20	70 ± 20
Uniformity of content ±SD	100.25±0.23	99.89±0.37
% drug release in 24 hours	99.68%	99.42%

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