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Novel multi granules controlled release tablets of milnacipran: Design with simplex lattice, *in vitro* characterization and pharmacokinetic predictions

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ABSTRACT

Aim: Milnacipran is well used drug for the treatment of depression and fibromyalgia. Its short elimination half-life, frequent dosing and associated side effects cause lack of patient compliance and discontinuation of present therapy. To overcome such problems, the aim of the present study was to design a novel multi granules based controlled release (CR) formulation with simplex lattice technique and study the various formulation variables. **Materials and Methods:** Hydrophilic polymeric and hydrophobic wax granules were prepared separately, and various formulations were designed with different proportion of these granules. **Results:** As the proportion of hydrophobic granules in formulation increased from 0% to 100%, the mean dissolution time, time for 50% and 80% drug release extended from 4.88-8.95 h; 3.11-9.11 h and 10.51-20.72 h, respectively. All the formulations were following first-order release kinetic. Results of formulation variables indicated that viscosity of the polymer, hardness of tablets and agitation speed can significantly influence the drug release from formulations and no significant effect observed for pH of dissolution media. *In vitro* human plasma concentrations were predicted from *in vitro* release data using convolution method. **Conclusion:** Novel multi granule-based CR tablet formulations of milnacipran hydrochloride were designed and evaluated for its *in vitro* release.

Key words: Controlled release, convolution, milnacipran, multi granules, simplex lattice

INTRODUCTION

Milnacipran hydrochloride (MIL) is well used drug and a selective serotonin and norepinephrine reuptake inhibitor. MIL has been approved since 1997 for treatment of depression and also approved in January 2009 for treatment of fibromyalgia. MIL is a candidate of biopharmaceutical classification system Class I, having high solubility and high permeability.[1] MIL is commercially available as immediate release (IR) formulations in the form of tablets and capsules with dose of 25-100 mg. Its short elimination half-life (6-8 h), frequent dosing requirement (2-4 times) and the number of associated side-effects such as nausea, vomiting cause lack of patient compliance, which led to discontinuation problem.[2,3]

Thus, there is an opportunity to formulate a controlled release (CR) tablet of MIL which will reduce the frequency

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of dosing and lower the incidence and intensity of side effects to get patient compliance with improved therapeutic level for the treatment of depression and fibromyalgia.

Very few publications are reported on CR formulation of MIL. Parejiya *et al.*, worked on "Tab in Tab" type CR formulation and also formulated a CR osmotic pump tablets of MIL.[1] Above reported approaches for CR formulation of MIL are tedious, costly and various critical process parameters are involved. Singhvi *et al.*, worked on design and characterization of cost effective hydrophilic matrix tablets of MIL using hydroxypropyl methylcellulose (HPMC).[4] Some literature revealed that multi granules CR formulations are better in release control than conventional matrix of single granules.[5] It is also reported that a combination of hydrophilic and hydrophobic polymers in a matrix can better control the drug release than alone hydrophilic polymer for prolong time.[6] Hydrophilic polymers have the advantage of rapid hydration and formation of viscous gel layer to restrict the drug percolation,[7,8] whereas hydrophobic polymers not only act as water repellent surface, but also provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications.[9] Thus, to combine the advantages of both hydrophilic and hydrophobic retardant in single dosage form, combination of both types of granules in a compact mass can be excellent to extend the drug release for sufficient time period at low concentration of polymers.[10]

Therefore, in the present work, a novel, simple, economic and reproducible multi granules based CR tablet formulation was designed using a combination of hydrophilic and hydrophobic granules. Simplex lattice design of optimization technique was applied for formulation design to minimize the formulation trials. The effect of formulation variables like polymer proportion, viscosity of hydrophilic polymer, compression force, agitation speed and pH of dissolution medium on *in vitro* release characteristics were also studied with various dissolution parameters. Moreover, pharmacokinetic (PK) properties including plasma profiles of selected formulation were predicted using numerical convolution method to evaluate the suitability of the designed drug delivery system for its practical application in humans.

MATERIALS AND METHODS

Materials

MIL was obtained as gift sample from Torrent Pharmaceutical Limited, Ahmadabad, India. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Analytical method

An in-house developed and validated ultraviolet (UV) spectrophotometric method on UV-VIS-NIR Spectrophotometer (V-570, Jasco, Tokyo, Japan), was used for the estimation of MIL in formulations, *in vitro* release samples and for quality control testing.[11]

Drug excipients compatibility studies

Stability of MIL in presence of excipients like HPMC, di-calcium phosphate (DCP), paraffin wax, stearic acid, polyvinyl pyrrolidone (PVP) K-30, talc and magnesium stearate was studied with differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopic (Shimadzu, Japan). All samples were stored at accelerated (40 ± 2°C/75 ± 5% relative humanity [RH]) and ambient (25 ± 2°C and 60 ± 5% RH) conditions protected from light up to 6 months and DSC and FTIR studies were repeated.

Preparation of controlled-release tablets

CR tablets of MIL were formulated with various proportions of hydrophilic polymer granules and hydrophobic wax granules. Both the granules were prepared separately as given below with composition as given in Table 1.

Preparation of hydrophilic polymer granules

Hydrophilic granules were prepared by wet granulation method. Drug, HPMC 100K and DCP were granulated with PVP K-30 using isopropyl alcohol as granulating agent. The mass was dried and sieved through 16 mesh.

Table 1: Formulation component of multi granules based controlled release tablets of milnacipran

Ingredients (mg)	Hydrophilic granules part Part A (mg)	Hydrophobic granules part Part B (mg)
Drug	100	100
HPMC 100K	100	
DCP	100	100
Stearic acid		60
Paraffin wax		60
Batch no.	**Fraction of part A**	**Fraction of part B**
F-1	100	0
F-2	70	30
F-3	50	50
F-4	30	70
F-5	0	100

HPMC: Hydroxy propyl methylcellulose, DCP: Dibasic calcium phosphate

Preparation of hydrophobic wax granules

Hydrophobic wax granules were prepared by melting stearic acid and paraffin wax at 80-85°C in a water bath. Uniform mixture of drug and DCP was added to molten wax with continuous agitation. The molten mass was allowed to cool at room temperature. The congealed solid mass was then sieved through 16 mesh.

The above hydrophilic polymer granules and hydrophobic wax granules were mixed in different proportions as per study design. The final granules were blended with talc (3% w/w) and lubricated with magnesium stearate (3% w/w). These lubricated granules were compressed on 16-station rotary tableting machine (CMB3-16, Cad Mach, Ahmadabad, India).

Formulation design with simplex lattice optimization technique

In order to design the best formulation, use a trial and error approach is not an effective way. The simplex lattice or mixture designs technique was applied for designing the various formulations. In simplex lattice, given equation is used for design the formulations and predict the responses.[12]

$$Y = \beta_1 (A) + \beta_2 (B) + \beta_{12} (A) (B)$$

In the proposed work "A" is hydrophilic granules part and "B" is hydrophobic granules part. Response "Y" is dissolution parameters like T50%, T80% and mean dissolution time (MDT).

β_1 = response at proportion of "A" is 100%, β_2 = response at proportion of "B" is 100% and β_{12} = 4 (response at proportion of "A" and "B" is 50-50%) − 2 (sum of response of "A" and "B" at 100%).

For experimental design, three formulations (i) tablets with 100% hydrophilic granules (F-1), (ii) tablets with 50% hydrophilic + 50% hydrophobic granules (F-3) and (iii) tablets with 100% hydrophobic granules (F-5) were formulated. Then simplex lattice equation was derived for each response using the experimental values of above formulations. Two check point formulations F-2 (A 70% and B 30%) and F-4 (A 30% and B 70%) were formulated and characterize for all *in vitro* dissolution parameters. Formulation F-2 and F-4 were formulated and characterized for all *in vitro* dissolution parameters and responses were also predicted using simplex lattice equations. Differences between predicted and observed values were tested statistically using one-way analysis of variance (ANOVA).[12] Formulation nomenclature was given on the basis of their composition after complete study as given in Table 1.

Physical characterization of the designed tablets

The weight variation, crushing strength, friability and content uniformity of developed formulations were determined as per standard procedure given in United States Pharmacopeia (USP)[13] using electronic balance (Type ER182A, Afcoset, Mumbai, India), Monsanto hardness tester (MHT20, Campbell Electronics, Mumbai, India), friability tester (FTA-20, Campbell Electronics, Mumbai, India) and UV-spectroscopic respectively.

Dissolution methodology

Dissolution study of all the tablets were performed with USP dissolution testing apparatus Type II Paddle (TDT-08 L, Electro Lab., Mumbai, India) in 900 mL of 0.1 N HCl (pH 1.2) dissolution medium, at 50 rpm and 37 ± 0.5°C. At predetermined time point 10 mL of the sample was withdrawn and analyzed with developed UV-visible method. Percentage cumulative drug release was calculated for data analysis.

In vitro drug release kinetic and mechanism

Various *in vitro* release kinetic models like zero order, first order, Higuchi and Korsmeyer–Peppas model[14,15] were applied in present study. The drug release from all the formulation were also compared with model independent dissolution parameters like MDT, time of 50% (T50%) and 80% (T80%) drug release.[14,15] The similarities between two *in vitro* dissolution profiles were also assessed by other pair wise model independent procedures such as difference factor (f_1) and similarity factor (f_2).[15]

Study of formulation variables

Formulation with equal proportion of hydrophilic and hydrophobic granules (F-3) was selected for study the effect of formulation variables like polymer proportion, viscosity of polymer, compression force, agitation speed and pH of dissolution medium on *in vitro* release.

Prediction of human *in vitro* profile of selected formulation

In vitro plasma profile and various PK parameters of selected multi granules CR tablets and IR formulation of

MIL were predicted with numerical convolution method using *in vitro* release data. Reported PK parameters like elimination rate constant, volume of distribution and oral bioavailability of MIL were used to for convolution method to get the predicted plasma drug levels at various time points. This predicted *in vitro* parameters will help in screening of desire formulation for *in vitro* studies in animal and human. This PK prediction will help to decide the optimized formulation prior to animal study. Thus, this prediction is not only minimize the number of *in vitro* studies but also reduces the time and cost of formulation design.[16] Peak plasma concentration (C_{max}) and time of its occurrence (T_{max}), biological half-life, mean residence time (MRT) and area under the curve (AUC) of both IR and CR tablets were determined using WinNonLin-Professional 2.1 (Pharsight Corporation, USA). Predicted PK parameters of IR formulation were also compared with reported clinical *in vitro* parameters of commercial IR formulations for validation of convolution method.

Statistical analysis

One-way ANOVA was used to determine statistically significant differences between observed and predicted response of formulations designed with simplex lattice. ANOVA was also used between PK parameters of IR and CR tablets. Results with $P < 0.05$ were considered as statistically significant ($\alpha = 0.05$).[12]

RESULTS AND DISCUSSION

Drug excipients compatibility studies

Presence of all the peaks of MIL in all spectrums indicates the stable nature of MIL in the solid admixtures. The DSC thermo grams of pure MIL showed a sharp melting endoderm at 178°C with a normalized energy of 47.55 J/g. The thermo grams of solid admixtures of MIL with various excipients, characterized after 6 months of storage, also had shown similar peak at 178°C with almost the same normalized energy, indicating that MIL is unaffected in the presence of various excipients used in the preparation of CR tablets formulations.

Physical characterization of the designed tablets

The prepared tablets were subjected to all the quality control tests as shown in Table 2. The physical appearance, weight variation, tablet hardness, friability and content uniformity of all tablet formulations were found to be satisfactory and within the official pharmacopoeial limits.

Formulations designs with optimization technique

Simplex lattice equation was derived for each response using experimental values of F-1, F-3 and F-5. Simplex lattice equations for dissolution parameters are given below:

$$T50\% = Y_1 = 3.58\ (A) + 8.79\ (B) - 3.3\ (A)\ (B)$$

$$T80\% = Y_2 = 8.32\ (A) + 20.42\ (B) - 7.72\ (A)\ (B)$$

$$MDT = Y_3 = 4.88\ (A) + 8.95\ (B) + 0.42\ (A)\ (B)$$

Predicted and observed responses of intermediate formulations (F-2 and F-4) are shown in Table 3. One-way ANOVA was applied on predicted and observed values. The calculated *F* value was found lesser than critical *F* value at $P < 0.05$, indicating that predicted and observed values are not significantly different. Results of simplex lattice design in present study indicated that such optimization study can be used for formulation design to get the desire results and process optimization with minimum number of trials.

In vitro drug release study

Various mathematical models were used to study the release kinetic and mechanism of drug release from multi granules CR tablets. Korsmeyer–Peppas model was found to best fit ($r^2 > 0.9869$) for all the formulations F-1 to F-5.

Various formulation variables were studied as follows:

Effect of polymer proportion on drug release

In vitro release profiles of all the formulations as shown in Figure 1 indicated that initial release for first 2 h varied between 22% and 38% depending on hydrophilic-wax granules proportion. The release rate constant of Korsmeyer–Peppas model were found to be 32.20 $h^{-0.386}$, 26.66 $h^{-0.441}$, 21.80 $h^{-0.496}$, 17.64 $h^{-0.545}$ and 14.14 $h^{-0.572}$ for F-1 to F-5 respectively. The release exponent "*n*" values of Korsmeyer–Peppas model for formulations F-1 and F-2 was found to be 0.39 and 0.44 indicating that the release mechanism was Fickian diffusion. This may be due to proportion of hydrophilic polymeric granules (70-100%) is more in these formulations. The release exponent "*n*" values for formulations F-3 to F-5 indicated non-Fickian or anomalous release ($0.45 < n < 0.89$) which indicated that drug release from these CR tablets was dependent on both drug diffusion as well as polymer relaxation. The values of *n* increased (0.39-0.57) as the proportion of hydrophobic wax granules was increased in tablet (F-1 to F-5). Hence, it can be inferred that the influence of polymer relaxation/

Table 2: Physical characterizations of multi granules based controlled release tablets of milnacipran

Formulations	Weight variation (%)	Thickness (mm)	Hardness (kg/cm²)	Friability (% w/w)	Assay (%)
F-1	±0.85	5.05±0.02	7.10±0.24	<0.40	99.85±2.50
F-2	±0.92	5.10±0.02	7.00±0.30	<0.50	100.25±1.82
F-3	±1.25	5.20±0.03	7.00±0.30	<0.50	101.02±1.57
F-3/H4K	±0.85	5.20±0.04	7.10±0.30	<0.60	99.72±0.90
F-3/H15K	±2.00	5.20±0.03	7.00±0.40	<0.50	100.95±1.30
F-3/4	±0.85	5.30±0.03	4.20±0.20	<0.60	100.45±0.70
F-3/10	±1.35	5.10±0.04	10.10±0.30	<0.40	100.83±1.47
F-4	±1.65	5.30±0.03	7.10±0.30	<0.50	98.95±0.93
F-5	±1.74	5.30±0.04	7.00±0.40	<0.60	99.82±2.05

Table 3: *In vitro* release characterizations of multi granules based controlled release tablets

Formulations	Korsmeyer-Peppas model			MDT (h)	T50% (h)	T80% (h)
	R^2	K (% h^{-n})	n			
F-1	0.9869	32.25	0.39	4.88	3.11	10.51
F-2	0.9937	26.66	0.44	5.94	4.31	11.56
F-2 (predicted)	-	-	-	4.45	11.33	11.33
F-3	0.9957	21.80	0.49	7.02	5.33	13.73
F-3/H4K	0.9999	58.68	0.30	1.55	0.58	2.83
F-3/H15K	0.9854	36.83	0.39	3.68	2.21	7.46
F-3/4.0	0.9990	27.35	0.53	4.10	3.14	7.67
F-3/10.0	0.9838	16.06	0.56	7.26	7.59	17.56
F-3/pH 6.8	0.9902	22.78	0.48	6.84	5.09	13.46
F-3/rpm 100	0.9922	29.51	0.42	5.26	3.47	10.50
F-3/rpm 150	0.9985	35.34	0.42	3.54	2.27	6.86
F-4	0.9988	17.64	0.54	8.31	6.77	16.03
F-4 (predicted)	-	-	-	7.80	6.54	15.96
F-5	0.9990	14.14	0.57	8.95	9.11	20.72

MDT: Mean dissolution time, T50%: Time of 50%, T80%: Time of 80%

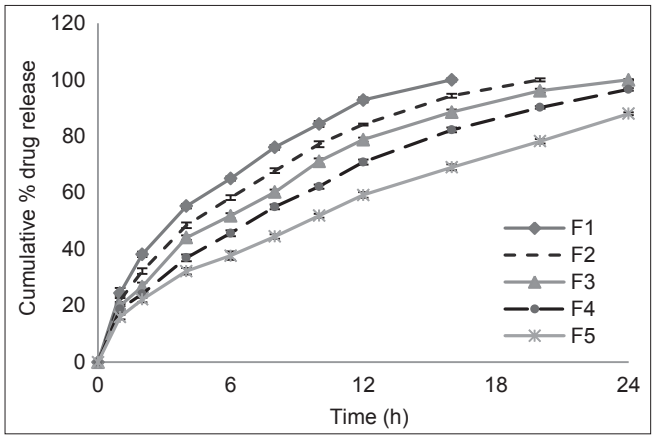

Figure 1: Comparative *in vitro* release profile of milnacipran from multi granules based controlled release tablets containing varying proportions of hydrophilic polymeric and hydrophobic wax granules. Each data point represents the mean of 6 tablets from three batches with standard deviation

erosion on the mechanism of drug release increased with increase in hydrophobic wax proportion.[9] The MDT, T50% and T80% increased from 4.88-8.95 h; 3.11-9.11 h and 10.51-20.72 h respectively as hydrophobic content increased from 0 to 100% in formulations (Table 3).

All the dissolution parameters indicated that hydrophobic wax proportion is playing a major role in controlling the drug release. The release of MIL from the combinations get more retarded than that of alone hydrophilic content, it may be due to higher lipophilicity offered by combination of waxes.[10] This may be due to the slower penetration of dissolution medium in matrices due to increased liophilicity of matrix.[17] Further, penetration of solvent molecule was hindered due to formation of gel layer of hydrophilic part leading to the slow percolation of drug for a prolonged period.[18]

Effect of viscosity of hydrophilic granules

The effect of polymer viscosity on drug release was studied with formulation F-3 containing 50% proportion of HPMC hydrophilic granules and 50% of hydrophobic wax granules. Three formulations containing constant portion of HPMC, but different viscosity grades 4K, 15K and 100K were evaluated for *in vitro* release behavior. Plot of per cent cumulative release versus time for various grade of HPMC are shown in Figure 2.

As the viscosity of HPMC was increased from 4K to 100K the release rate extended from 6 h to 24 h as shown in Figure 2. The release rate constant of Korsmeyer–Peppas model was found to be 58.68 $h^{-0.30}$, 36.83 $h^{-0.39}$ and 21.80 $h^{-0.49}$ for formulations containing 4K, 15K and 100K respectively. The release rate decreased as viscosity of polymer increased. The MDT, T50% and T80% also extended from 1.55-7.02 h; 0.58-5.33 h and 2.83-13.73 h respectively as shown in Table 3. The f_2 (similarity factor) were found to be 18.10 (for HPMC 4K vs. 100K) and 34.30 (for HPMC 15K vs. 100K) also indicated the viscosity of polymer significantly influence the drug release from designed formulations.

The release rate was faster with lower viscosity grades of HPMC. The possible explanation can be as follows. It has been reported that at the same polymer concentration, a polymer of higher viscosity (high molecular weight) induces greater chain entanglement than a polymer of low viscosity.

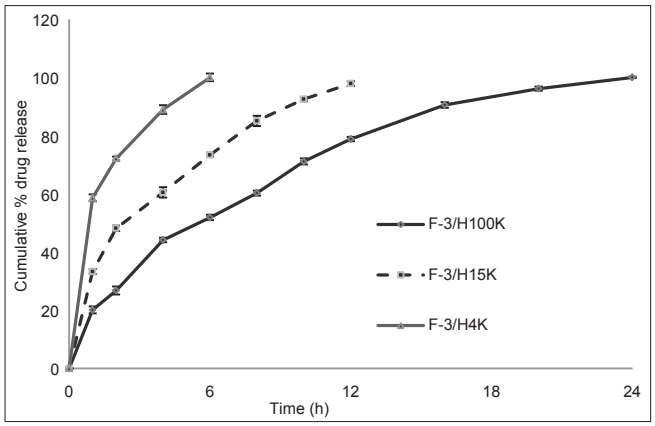

Figure 2: Effect of viscosity of HPMC polymer on milnacipran release from multi-granules based controlled release tablets. Each data point represents the mean of 6 tablets from three batches with standard deviation

Therefore, it is harder for longer chains to dissolve because of the high energy required for pulling them off the matrix. Thus, higher viscosity polymers induce the formation of a thicker gel layer after hydration lead to more retarded drug release than lower viscosity grade polymers.[19]

Effect of compression force

The effect of compression force on the drug release was studied with F-3 formulation compressed at different compression forces to get tablets with different hardness levels, 4, 7 and 10 kg/cm^2. The release of the drug from formulations compressed at low compression force (4 kg/cm^2) was found to be significantly much faster with K value 27.35 h$^{-0.527}$ than formulation compressed at higher compression force with K value 21.80 h$^{-0.496}$ (for 7-7.5 kg/cm^2) and 16.06 h$^{-0.560}$ (for 10-10.50 kg/cm^2). The MDT, T50% and T80% values increased from 4.10-7.26 h; 3.14-7.59 h and 7.67-17.56 h respectively as compression force increased from 4 to 10 kg/cm^2 (Table 3). The f_2 (similarity factor) were found to be 40.82 for release profiles 4 versus 7 kg/cm^2 and 49.43 for 7 versus 10 kg/cm^2 indicated the compression force significantly influence the drug release from formulations.

The drug release was found to be faster at lower compression forces than at higher ones because of the relatively larger matrix porosity of the tablet, which allowed greater penetration of dissolution fluid into the matrix, thus enhancing polymer disentanglement and drug dissolution.[18,20]

Effect of pH of dissolution medium

The effect of pH of dissolution media on the drug release was performed with F-3 formulation in pH 1.2 and 6.8 disso medium at 50 rpm. Drug release pattern indicated that there was no significant difference observed in release profile at pH 1.2 and 6.8 buffer. The release rate constants were found to be 21.80 h$^{-0.496}$ in pH 1.2 and 22.78 h$^{-0.483}$ for pH 6.8 dissolution media (Table 3). The f_2 (similarity factor) value was found to be 86.65 indicated the similarity of release profile in different dissolution medium.

This is because MIL is highly soluble at pH range 1.2-12, which shows its pH independent solubility. The hydrophobic waxes are water insoluble and having pH independent dissolution. The hydrophilic part consists of HPMC, a cellulose derivative with methoxyl and hydroxypropyl substituents on a β-o-glucopyranosyl ring backbone, is very resistant to changes in pH or ionic content of the medium. At pH values from 2 to 13, HPMC is relatively stable.[19,20]

Effect of agitation speed

For study the effect of agitation speed, dissolution of F-3 formulation was performed at three different stirring speed 50, 100 and 150 paddle rpm. As the rpm increased from 50 to 150 the release rate decreased as shown in Figure 3. The release rate constant increased from 32.38 h$^{-0.35}$ to 41.25 h$^{-0.34}$ as stirring speed increased from 50 to 150 rpm. When agitation speed or paddle rpm increased 50-150, the MDT, T50% and T80% decreased from 7.02-3.54 h; 5.33-2.27 and 13.74-6.86 h respectively (Table 3). The f_2 (similarity factor) were found to be 49.73 and 33.38 for release profiles between 50 versus 100 rpm and 50 versus 150 rpm indicated the significant difference at different rotation speed. The observed variation in release change with rpm might be due to the difference in the hydrodynamic stress around the surface of tablets undergoing dissolution. At lower rpm (50 rpm), there is slow fluid motion and formation of stable stagnant layer surrounding the tablets. This prevents the quick entry into fluid and also the release of drug out of the tablet. However as rpm increased (100 and 150 rpm) there was greater fluid flow that resulted in increased attrition of the tablet matrix with fluid and disturbs the stagnant layer around the tablets. This caused in higher drug release.[18,20]

Prediction of *in vitro* profile of developed formulation

The predicted plasma profiles obtained from *in vitro* release data of F-4 CR formulation and IR formulation of equal dose using simple numerical convolution method are shown in Figure 4. These predicted plasma drug concentrations were used to determine various PK parameters from WinNonlin software using non-compartment modeling as shown in Table 4. The C_{max} and $AUC_{(0-t)}$ values calculated from the predicted plasma profiles of the IR tablets and CR tablets were found to be 210.86; 1 h and 93.46 ng/mL; 12 h respectively. The differences between the two formulations for C_{max} and T_{max} were statistically significant ($P < 0.05$),

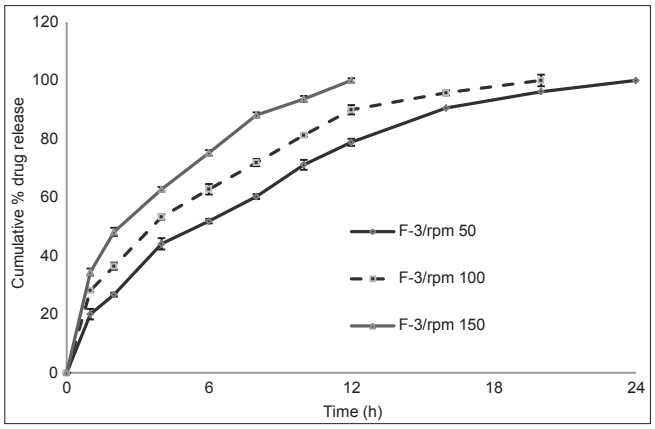

Figure 3: Effect of agitation speed on milnacipran release from multi-granules based controlled release tablets. Each data point represents the mean of 6 tablets from three batches with standard deviation

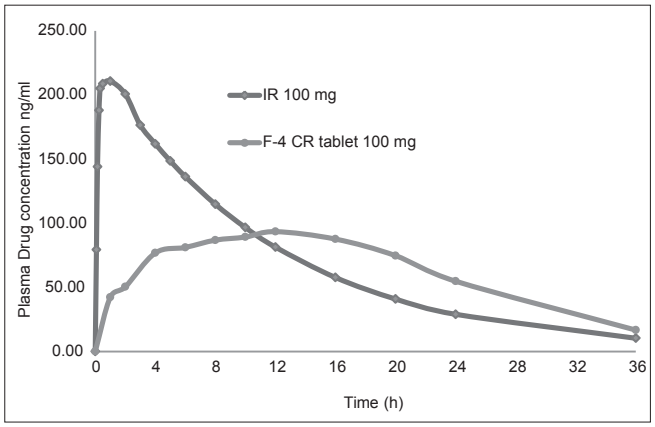

Figure 4: Predicted *in vitro* plasma drug concentration - time profile of immediate release (IR 100 mg) and controlled release (F-4 CR 100 mg) formulations of milnacipran

Table 4: Predicted pharmacokinetic parameters of immediate release and controlled release formulations of milnacipran using *in vitro* dissolution data

Pharmacokinetic parameters	Immediate release formulations		Controlled release formulation (F-4)
	Reported	Predicted*	Predicted*
Dose	100 mg	100 mg	100 mg
C_{max} (ng/mL)	209.80	210.86	93.46
T_{max} (h)	1.00	1.00	12.00
$T_{1/2}$ (h)	8.20	8.15	18.00
AUC $_{(0-24)}$ (ng/mL/h)	2280.61	2492.73	2254.54
AUC $_{(0-\infty)}$ (ng/mL/h)	2627.84	2624.04	2903.18
MRT (h)	8.26	8.10	15.09

*Parameters were predicted from *in-vitro* dissolution data using convolution method, C_{max}: Maximum plasma concentration, T_{max}: Time taken to reach maximum concentration, $T_{1/2}$: Elimination half-life, $AUC_{(0-24)}$: Area under the plasma drug concentration versus time curve from 0 time to 24 h, $AUC_{(0-\infty)}$: AUC from 0 time to infinite time, MRT: Mean residence time

clearly demonstrate that the designed CR formulation has capability to sustain the plasma level for sufficient time and developed tablet would be suitable to deliver highly water soluble drugs like MIL for once daily dose regimen following oral administration. Predicted PK parameters of IR formulation were compared with reported PK parameters of marketed formulation of MIL[2] as shown in Table 4. No significant difference was found between predicted and reported PK data. In fact, this demonstrated the reliability of convolution analyses in predicting plasma profiles by comparing the predicted profiles with *in vitro* data obtained from studies in humans as well as give a reasonable degree of confidence on reliability of the designed drug delivery system.

CONCLUSION

Novel multi granule based CR tablet formulations of MIL were designed and evaluated for its *in vitro* release. Simplex lattice technique was applied to formulation design and selection of desire formulation with minimum trials. It was concluded that multi granules based formulation were greatly influenced by proportion of hydrophobic granules, viscosity of HPMC, agitation speed and hardness of tablets. It was also observed that the designed formulations were not influenced by pH of dissolution media. *In vitro* plasma drug level and various PK parameters were predicted from *in vitro* release data using convolution method confirms the sustained action of designed formulations.

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