Biological Forum – An International Journal **15(1): 439-447(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Development and Characterization of Coated Matrix Multiparticulate System for Milnacipran HCl Sustained Release Imbibing Design of Experiments

Shekhar V. Kokate* and Punit R. Rachh
Department of Pharmacy,
Bhagwant University, Sikar Road, Ajmer (Rajasthan) India.

(Corresponding author: Shekhar V. Kokate)*
(Received: 02 December 2022; Revised: 09 January 2023; Accepted: 14 January, 2023; Published: 19 January, 2023)
(Published by Research Trend)

ABSTRACT: Oral drug delivery systems are very well accepted by patients due to self-medication and its stability over other dosage forms. The formulation of sustained release product is always a challenging task and when it is employed from highly water-soluble drugs; its complexity is greatly increased. Nowadays, multi-unit particulate systems (MUPS) are gaining an interest for delivering water soluble drugs at a controlled rate. So, in the present study, coated pellets were designed for water soluble model drug Milnacipran HCl (MIL). The drug was quantified by UV spectrophotometer at 223 $\lambda_{max.}$ The core matrixpellets were prepared by Extrusion Spheronization techniques using MCC and HPMC K100M. The core pellets were further coated by Eudragit®NE based coating solution using pan coater. The coating was optimized by Box Behenken Design keeping concentration of matrix polymer (HPMCK100M) (X_1), concentration of coating solution (Eudragit®NE) (X_2) and %weight gain (X_3) was selected as independent variables while, Q2 (Y_1), Q12 (Y_2), Q20 (Y_3), and Aspect ratio (Y_4) were taken as dependent variables. The developed pellets were characterized for various physicochemical parameters. The drug release from formulation was fitted for various drug release kinetics models. The optimized formulation was subjected for accelerated stability study as per stability guidelines by ICH. The results indicated that selected independent variables had strong impact on response which was confirmed by contour and response surface plot. SEM analysis indicated proximal spherical shape of pellets. Drug release from optimized pellets was fitting to first order release kinetics. Accelerated stability study indicated stable characteristics of optimized formulation. Developed Eudragit®NE coated pellets can be promising technology for delivering highly water-soluble drugs at a controlled rate.

Keywords: Milnacipran HCl, Eudragit NE, Coated matrix pellets, Box-behenken Design, Multi-unit particulate systems (MUPS).

INTRODUCTION

Among all drug delivery system, oral route of drug administration is the most convenient option as it provides maximum surface area. When administered in terms of oral delivery systems like tablet and capsules the attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs (Ratnaparkhi and Gupta Jyoti 2013).

A sustained release dosage form is developed with a goal to reduce the dosing frequency, dose and uniform drug delivery for a suitable period of time. So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. By this was the sustained release dosage forms provide better control over plasma concentration of drugs leading to reduced dosage frequency, dose, side effect with improved efficiency and patient compliance due to constant drug delivery.

MUPS also known as multi-unit particulate system is a multiple unit sustained release dosage form. MUPS like pellets are having many therapeutic advantages compared to single unit dosage form. MUPS like pellets can distribute homogeneously in the GIT (gastro intestinal tract), maximizing absorption and minimizing peak plasma fluctuations. Minimization of peak plasma fluctuation results in minimal risk of local GI tract irritation and dose dumping, which may result in decreasing dosing frequency and increasing patient compliance, improving the safety and efficacy of the active ingredient (Hu *et al.*, 2006).

The development of sustained release formulation of a highly water-soluble drug required keen attention for its sustained release and prevention of dose dumping. The formulation of sustained release dosage form majorly depends on drug solubility, dose and various other biopharmaceutical parameters.

Milnacipran hydrochloride (MIL), [101152-94-7], $C_{15}H_{22}N_2O{\cdot}HCl$, molecular weight 282.81 g/mol, is a racemic mixture with the chemical name (±)-

[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride, and its solubility in water is 19 mg/mL (Chen *et al.,* 2008; Dias *et al.,* 2011). MIL is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated as an antidepressant and for the management of fibromyalgia. It shows preferential blockade of norepinephrine reuptake over serotonin and minimal activity at other receptors or transporters (Vaishnavi *et al.,* 2004; Rao *et al*., 2007). MIL is well absorbed after oral administration without any effect of presence of food, and the maximum concentration reaches within 2-4h.the absolute bioavailability of MIL was reported to be approximately 85–90%. The biopharmaceutical classification system (BCS) considers MIL to be a class I drug showing higher aqueous solubility and permeation across biological membranes resulting in higher absolute bioavailability. If the drug is well absorbed throughout the GIT, it is an ideal candidate for immediate release formulation but its effect is heavily dependent on gastric emptying rate and some correlation with dissolution rate is expected only if the dissolution is slower than gastric emptying (Amidon *et al.,* 1995).

The faster (quick) release of MIL from the immediate release tablets is often linked with unwanted effects such as GI irritation which may result in diarrhoea and nausea. The higher drug release may also result in tachycardia, palpitations, hypertension, extremes of elevated mood or feelings of happiness which may then pass to a depressed or sad mood, unsteadiness or falling, and swelling of the mouth or throat (English *et al.*, 2010; Kyle *et al*., 2010). This results in poor compliance with formulation so, there is a requirement of a sustained release formulation which may minimise all the problems associated with higher drug concentration so that the problem of therapeutic efficiency and patient compliance can be achieved for approximately 24 h when administered orally.

Various scientists have contributed in development of different sustained release formulations of Milnacipran HCl. Parejiya *et al*. (2012) have developed various controlled release systems including Tab in Tab (Parejiya *et al*., 2013), Osmotic pump (Parejiya *et al*., 2013) and solid dispersion based compressed unit (Parejiya *et al.,* 2014) for MIL. They also evaluated the *In vivo* performance. Establishment of IVIVC for osmotic pump based extended-release formulation of milnacipran HCl proved the sustained release of MIL through osmotic pump using rabbit model (Parejiya *et al.,* 2013). Kothari *et al*. (2018) have developed herbal product using wax material.

Hussain *et al.* (2020) have developed a gastro-retentive mucoadhesive sustained release matrix formulation for MIL by modified solvent-based wet granulation through mixing of MIL, chitosan low molecular weight, chitosan medium molecular weight and polycaprolactone (Hussain *et al.*, 2020).

So, in the present study attempts were made to develop sustained release coated pellets for highly water-soluble drug, Milnacipran HCL (MIL). The pellets were optimized by application of DoE concept. The developed pellets were fully characterized by various physicochemical and performance characterization.

MATERIALS AND METHODS

Milnacipran HCl (MIL) was generously gifted by Intas pharmaceuticals, Selaqui, Dehradun, India. Eudragit® NE was gifted by Evonik Healthcare, Mumbai, India. Avicel® pH 101 was given as a gift sample by Research Lab-Fine Chem industries, Mumbai, India. Talc, magnesium stearate, and other chemicals were obtained from Loba Chemicals Pvt. Ltd. Mumbai, India and were of analytical grade.

Quantification of Milnacipran HCl. A double beam UV spectrophotometer (UV-1800, Shimadzu, Japan) was used to measure MIL in bulk samples and all *in vitro* studies. A known amount of MIL(1mg/mL) was dissolved in suitable solvents, followed by filtration and was kept in quarts' cell for analysis against solvents as blank reading. Suitable dilutions were prepared (2-40µg/ml) and linearity was observed. Samples were prepared and checked for 3 days for inter and intraday variability. The λ_{max} for MIL was measured for measurement of drug content in bulk and *in vitro* studies was analyzed at this wavelength. A standard curve was prepared and linearity function was applied.

Preparation of Matrix Pellets by Extrusion Spheronization Technique. Pellets contained MIL, microcrystalline cellulose (Avicel® PH-101) and HPMCK100M. HPMC K100M was selected as a matrix forming agent. The dry substances were blended in a high shear mixer for 1 min. PVA(Poly vinyl alcohol)was used as dry binder and ethanol: water (9:1) was used as a solvent to prepare dough mass. The mass was extruded immediately. The extrudate was spheronized using a speed of 900 rpm in a spheronizer. The pellets were dried on trays as a monolayer at room temperature.

Coating of Matrix pellets by Pan Coating. Preparation of coating solution. The coating formulation was prepared using Eudragit®NE as a coating polymer and PEG6000 as the plasticizer and solubilized in ethanol. The coating solution was stirred for at least 15 min before use, and agitation was maintained until satisfactory weight gain was obtained.

Pellet Coating. Pellet coating was carried out using the pan coater. Process conditions for pan coating are gun to bed distance 12cm, pan speed 10rpm, inlet air temperature 60-65°C while inlet air velocity was 165-175 m^3/h with a spray rate of 6mL/min, atomization pressure was kept to 2bar and air flow rate was adjusted to 26.1m^3/h. Pellets were coated to 4, 6, 8 % w/w theoretical weight gain. Theoretical weight gain was defined as the theoretical increase in dry weight of pellets after coating. Pellet coating was carried out immediately after drying in to hot air oven.

Optimization of Formulation using Box Behenken Design (Bodea and Leucuta 1998; **Wang *et al.*, 2015).** A Box Behenken design with 3 factors and 3 levels was selected for optimization of coated matrix pellets. Concentration of matrix polymer (HPMCK100M)(X_1), concentration of coating solution (Eudragit®NE) (X_2) and % weight gain (X_3) was

selected as independent variables while, Q2 (Y_1), Q12 (Y_2), Q20 (Y_3), and Aspect ratio (Y_4) were taken as dependent variables. Design Expert Software [Version 12.0.1, Stat ease Inc., Minneapolis, MN) was used to evaluate the effect of significant factors on dependent variables. The effect of independent variable one each dependent variable can be studied using following polynomial equation.

$Y= \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_1X_2 + \beta_5X_1X_3 + \beta_6X_2X_3 + \beta_7X_1^2 + \beta_8X_2^2 + \beta_9X_3^2 + ...\beta nXn.$ [II]

Here, Y is the response, β_0 is intercept and β_1 to β_n are coefficients for independent variables. In equation, positive sign of the coefficientsuggests a symbiotic effect on the response while the negative sign suggests an inimical effect on the response. ANOVA studies were performed on each response to identify the significant parameters affecting the response as described by Meena *et al.* (2021); Singh *et al.* (2021); Singh and Rajpoot (2021).

The response may be linear; two factor interaction, quadratic or cubic. Polynomial equations were generated for each response and optimization was done by graphical method. From design space, three check point batch were selected and formulated to validate the methodology. Observed and predicted response was compared and % predicted error values were calculated. Composition of batch according to design is depicted in Table 1.

Table 1: Composition of factorial batches as per Design of Experiment.

Composition of Matrix pellets													
Batch	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
MIL (g)	5	5	5	5	5	5	5	5	5	5	5	5	5
HPMCK100 M (g)	1.5	1.5	1.5	1.5	1	1	1	2	1	2	2	1.5	2
Avicel pH 101 (g)	3.5	3.5	3.5	3.5	4	4	4	3	4	3	3	3.5	3
PVA (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Alcohol+water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1
Composition of coating solution													
Matrix Pellets	Equivalent to 12.5 mg MIL												
Eudragit NE (g)	9	8	7	9	8	9	7	8	8	7	9	7	8
PEG 6000 (g)	1	2	3	1	2	1	3	2	2	3	1	3	2
Ethanol (ml)	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10	q.s. to 10
Total	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

Characterization of pellets

Entrapment efficiency. Entrapment efficiency of pellets determines the amount of drug incorporated in to pellets.

100 mg of pellets were suspended in 100ml phosphate buffer pH 6.8 with constant agitation at room temperature for 24h. Solution was then filtered through Whatman filter, and drug content was determined UV spectrophotometrically (Shimadzu 1800), at the λ_{max} using 6.8 pH phosphate buffer as blank. The entrapment efficiency was calculated by using the given equation.

$$\% \text{ Entrapment Ef1iciency} = AQ/TQ * 100$$

AQ = the actual quantity of drug present in pellets

TQ = the theoretical quantity of drug present in the pellets

Aspect ratio (AR). It was investigated by optical microscopy by randomly selected pellets. The microscope was fitted with ocular and stage micrometers. Aspect ratio of formulation was calculated from following equation

$$\text{Aspect Ratio} = d_{max}/d_{min}$$

d_{max} and d_{min} are Feret diameter measured by image analysis software.

Particle Characterization. In order to determine the particle size of pellets optical microscopy was used. Around 100 pellets were taken for measurement of particle size and average particle size was calculated.

Scanning Electron Microscopy. The surface morphology of matrix pellets before coating and after coating was observed under Scanning Electron Microscope (Leo 440i, Cambridge, UK). The complex was captured at different pixels with pellets mounted on metal stub using double-sided adhesive tape.

Flow Properties. The flow properties of the pellets was determined by measuring Carr's Compressibility Index and Hausner's Ratio. They were calculated using the formula.

$$\text{Compressibility Index} = 100* [(Vo – Vt)/ Vo]$$

$$\text{Hausner Ratio} = Vo / Vt$$

Angle of Repose. Angle of repose for the pellets was measured using fix funnel height method. On a horizontal surface a funnel was paced with its tip 2com above a blank sheet of paper; secured with the help of a stand. Pellets were added in the funnel until the tip of cone was formed. After that, measurements were taken for the radius and the equation was used to calculate angle of repose.

$$\theta = \tan^{-1} (h/r)$$

h = height of the powder cone r = radius of the cone's base.

Friability. Friability of pellets was measured using Roche friability testing apparatus. Around 10g of pellets were taken and rotated in the friabilator for 4

min at the speed of 25rpm and the friability was calculated using following equation.

%Friability = (Initial Weight of pellets -Final Weight of pellets)/Initial Weight of pellets × 100

***In vitro* Drug Release Studies.** MIL release studies were performed on USP Type I apparatus rotating at the speed of 100 rpm and maintained at 37°C in 900 ml of 0.1N HCl for initial 2 hours followed by phosphate buffer (pH 6.8) for the rest of period. Samples were withdrawn at the time interval of 0, 1, 2, 4, 8, 12, 16, 18, 20, 24 h and fresh media was replenished to maintain sink condition. Each sample was filtered through a membrane filter with a pore size of not more than 0.45mm. The samples were analysed after appropriate dilution by UV spectrophotometer at λ_{max} of 223nm against a blank reagent.

Kinetic Analysis of Dissolution drug release Data (Dash *et al.*, 2010). In order to understand the drug release mechanism from the coated matrix pellets the dissolution data of optimized formulation was fitted to different kinetic models. The drug release data was fitted to zero order, first order, Korsmeyer-Peppas and Higuchi equations. Zero order, first order, Higuchi's and Korsmeyer-Peppas are given as follows.

$$Q_t = Q_0 + K_0 t$$

$$\text{Log } Q_t = \log Q_0 - K_t t$$

$$Q = KHt^{1/2}$$

$$F = Mt/M = Kmt_n$$

Where, Q_t is the amount of drug released at time t, Q_0 is the initial amount of the drug in the formulation. K_0, K_t, KH and Km are the release rate constants for zero order, first order, Higuchi model and Korsmeyer-Peppas model, respectively. Mt/M is the amount of drug released in time t and n is the diffusion coefficient. The criteria for the selection of most suitable model were the value of regression coefficient (R^2) nearer to 1, SSR(sum of squared residuals) values and F value.

Stability Studies (Aashigari *et al.*, 2018). To determine the stability of formulation and to understand the effect of additives on the stability of formulation during the storage, stability studies were carried out as per the ICH guidelines. The formulations were stored in an aluminium foil and subjected to elevated temperature and humidity conditions of 40±2 °C/75±5 % RH for a time period of three months as per ICH guidelines. The formulations were evaluated for their entrapment efficiency, aspect ratio, and drug content.

RESULT AND DISCUSSION

Quantification of Milnacipran HCl. MIL showed maximum absorbance wavelength at 223nm. Linearity range was observed in 2-40µg/ml and intraday and interday linearity was observed.

Optimization using Box Behenken Design. Factorial batches for pellets were prepared using the experimental matrix as given by Design Expert® software and the results of all factorial batches are shown in Table 2 and 3. Results of factorial batches were evaluated by the Design Expert®(V 12.0.1, Stat ease, Philadelphia, USA) software and the relationship between independent and dependent variables were established.

Table 2: Results of prepared factorial batches.

	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
Run	A: Matrix Agent	B: Coating Agent	C: %Weight gain	Q2	Q12	Q20	Aspect Ratio
1	30	90	8	20.15±1.25	52.12±0.89	92.18±1.02	0.94
2	30	80	6	22.26±1.08	52.01±0.97	91.69±1.56	0.88
3	30	70	8	21.87±1.13	54.23±1.08	94.31±1.25	0.75
4	30	90	4	25.63±0.98	55.23±1.25	95.21±1.36	0.93
5	20	80	4	22.36±1.94	53.68±1.38	93.99±1.02	0.85
6	20	90	6	20.51±0.89	49.88±0.974	90.2±1.36	0.92
7	20	70	6	24.56±1.23	53.28±1.23	94.15±1.98	0.79
8	40	80	8	18.56±1.44	49.21±1.08	89.11±1.64	0.87
9	20	80	8	20.18±1.52	50.22±1.6	90.12±1.38	0.88
10	40	70	6	21.56±1.02	51.22±1.32	91.36±1.36	0.81
11	40	90	6	16.96±1.18	48.63±1.02	88.36±1.41	0.93
12	30	70	4	28.63±1.23	58.23±1.20	98.56±1.02	0.78
13	40	80	4	21.6±0.878	52.64±1.56	92.68±1.6	0.85

Table 3: Results of factorial batches.

Batch	1	2	3	4	5	6	7	8	9	10	11	12	13
%Entrapment Efficiency	93.36 ±0.96	94.56 ±1.02	97.23 ±1.12	98.23 ±1.25	91.23 ±1.09	93.36 ±1.22	94.12 ±1.65	95.01± 0.998	94.03 ±1.44	93.06 ±1.23	91.66 ±1.63	92.23 ±1.55	93.01 ±1.23
Aspect Ratio	0.94	0.88	0.75	0.93	0.85	0.92	0.79	0.87	0.88	0.81	0.93	0.78	0.85
Angle of Repose	23.56	24.12	23.69	23.56 5	24.56	24.12	25	24.13	24.16	23.65	23.98	24.01	24.12
Compressibility Index	9.98	10.02	10.11	10.15	9.98	9.56	9.69	10	10.26	10.35	9.65	9.46	9.23
Hausner's Ratio	1	1.01	1.02	1.05	1.03	1.06	1.01	1.02	1.03	1.05	1.02	1	1.03
Friability	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Effect of independent variables on Q2 (% drug release at 2h). The drug release from developed pellets at 2 h followed linear model (Table 4). It can be observed from the ANOVA table that P-values less than 0.0500 indicate model terms are significant (Meena *et al*., 2021). In present scenario coating composition and % weight gain are considered significant. The graphical representation of relationship between independent variable and dependent variable is shown in the form of contour plot and response surface plot (Fig. 1). It can be observed from the contour plot and response surface plot that the response followed linear model.

Table 4: ANOVA table for response Q2.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	70.42	3	23.47	5.29	0.0224	significant
A-Matrix Agent	9.97	1	9.97	2.25	0.1681	
B-Coating Agent	22.34	1	22.34	5.04	0.0515	
C-%Weight gain	38.11	1	38.11	8.59	0.0167	
Residual	39.92	9	4.44			
Cor Total	110.34	12				

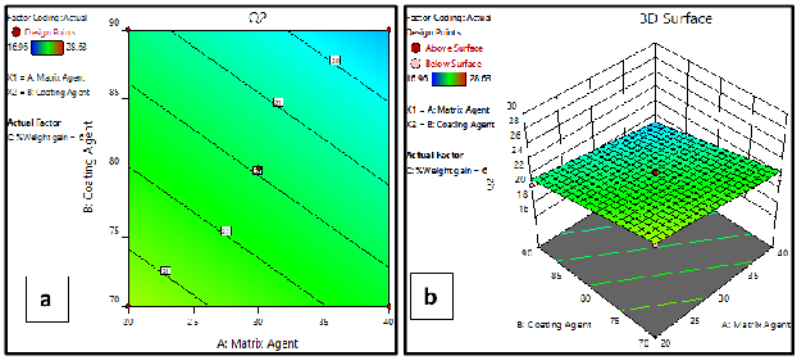

Fig. 1 (a) Contour plot and (b)3-D Response surface graph showing the relationship of independent variables on Q2.

Effect of independent variables on Q12(% drug release at 12h). Response values for % drug release at 12h followed quadratic model (Fig. 2) *i.e.*, it shows nonlinear correlation between independent variables and response values. A wide variation in the response values confirms selection of suitable independent variables and their levels. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, A^2, B^2, C^2 are significant model terms (Table 5). Values greater than 0.05 indicate the model terms are not significant (Singh and Rajpoot 2021).

Table 5: ANOVA table for response Q12.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**84.60**	**9**	**9.40**	**93.60**	**0.0016**	**significant**
A-Matrix Agent	3.59	1	3.59	35.76	0.0094	
B-Coating Agent	15.40	1	15.40	153.35	0.0011	
C-%Weight gain	24.50	1	24.50	243.94	0.0006	
AB	0.1640	1	0.1640	1.63	0.2912	
AC	0.0002	1	0.0002	0.0022	0.9652	
BC	0.1980	1	0.1980	1.97	0.2549	
A^2	13.02	1	13.02	129.59	0.0015	
B^2	2.91	1	2.91	29.00	0.0125	
C^2	7.52	1	7.52	74.87	0.0032	
Residual	0.3013	3	0.1004			
Cor Total	84.90	12				

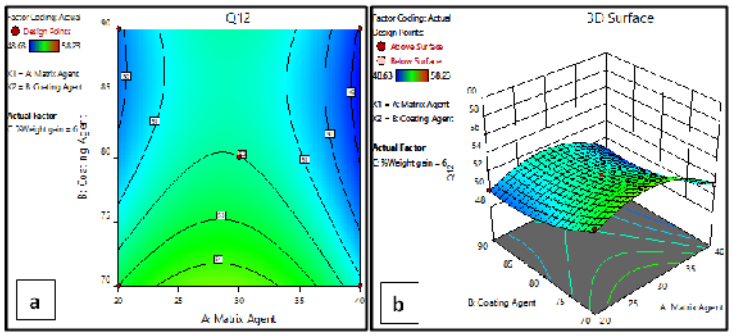

Fig. 2 (a) Contour plot and (b) 3-D Response surface graph showing the relationship of independent variables on Q12.

Effect of independent variables on Q20 (% drug release at 20h). Response values for % drug release at 20 h followed quadratic model (Fig. 3) *i.e.*, it shows nonlinear correlation between independent variables and response values. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, A^2, B^2, C^2 are significant model terms (Table 6). Values greater than 0.05 indicate the model terms are not significant (Singh and Rajpoot 2021). Wide variation in the response values confirm the suitability of selected variables and their levels.

Effect of independent variables on Aspect Ratio. Aspect ratio followed linear model as observed from Fig. 4. P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term (Table 7).

Table 6: ANOVA table for response Q20.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**93.00**	**9**	**10.33**	**32.97**	**0.0076**	**significant**
A-Matrix Agent	6.04	1	6.04	19.26	0.0219	
B-Coating Agent	19.31	1	19.31	61.62	0.0043	
C-%Weight gain	27.08	1	27.08	86.41	0.0026	
AB	0.2256	1	0.2256	0.7198	0.4585	
AC	0.0225	1	0.0225	0.0718	0.8061	
BC	0.3721	1	0.3721	1.19	0.3556	
A^2	10.38	1	10.38	33.12	0.0104	
B^2	4.86	1	4.86	15.52	0.0292	
C^2	8.39	1	8.39	26.78	0.0140	
Residual	0.9403	3	0.3134			
Cor Total	93.94	12				

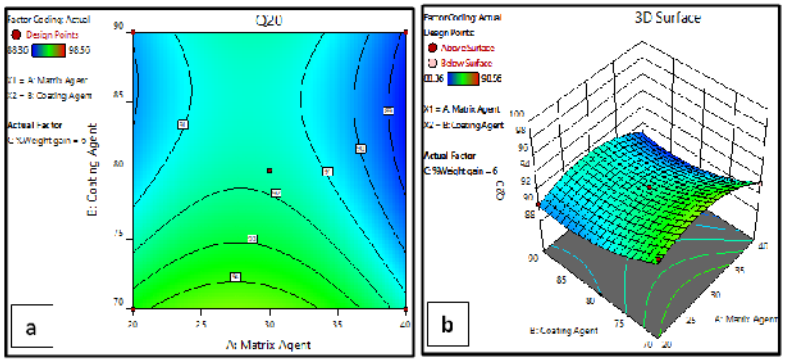

Fig. 3 (a) Contour plot and (b) 3-D Response surface graph showing the relationship of independent variables on Q20.

Table 7: ANOVA table for response Aspect Ratio.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**0.0437**	**3**	**0.0146**	**41.93**	**< 0.0001**	**significant**
A-Matrix Agent	0.0000	1	0.0000	0.1440	0.7131	
B-Coating Agent	0.0435	1	0.0435	125.32	< 0.0001	
C-%Weight gain	0.0001	1	0.0001	0.3240	0.5831	
Residual	0.0031	9	0.0003			
Cor Total	0.0468	12				

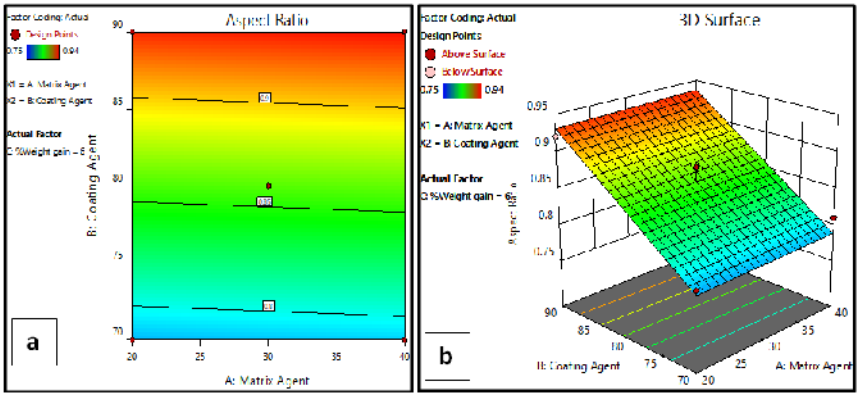

Fig. 4 (a) Contour plot and (b) 3-D Response surface graph showing the relationship of independent variables on Aspect Ratio.

Optimization of coated matrix pellets. The overlay plot of responses, generates an optimized area as per desired criteria as shown in Fig. 5. After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria that the said formulation released around 20-25 % of the drug in 2 h and 50-55 % in 12 h, however, the drug completely got released, *i.e.*>90 % in 20 h, and aspect ratio was 0.9 (near to 1). Yellow region in the overlay plot shows optimization region (Fig. 5).

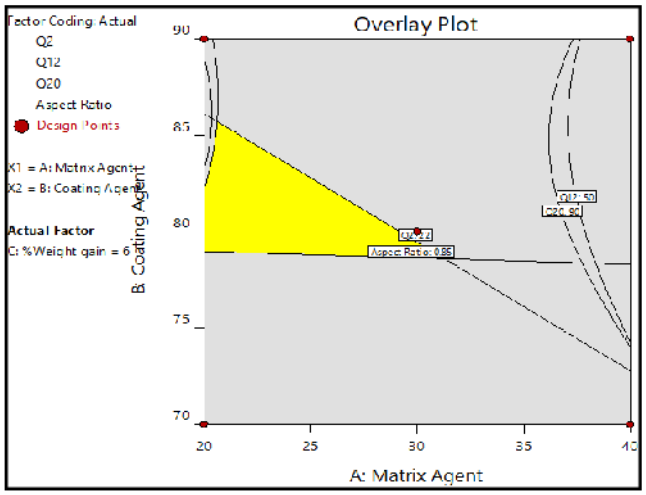

Fig. 5. Overlay Plot for optimization of pellets

Checkpoint Analysis. Three checkpoint batches were prepared and evaluated for % CDR at 2 hr, % CDR at 12 hr, % CDR at 20 h and aspect ratio. When measured values were compared with predicted values, the differences were found to be insignificant (Table 8). Thus, it can be concluded that the obtained mathematical equations are valid for predicted values.

Characterization of Pellets

Scanning Electron Microscopy. As observed from (Fig. 6), pellets were of nearly spherical shape. The Aspect ratio of pellets increased significantly after coating with Eudragit®NE and PEG6000.

Table 8: Checkpoint batches composition with predicted and measured value.

Check Point Batch	Predicted value				Actual value				%Predicted Error			
	Q2	Q12	Q20	Aspect Ratio	Q2	Q12	Q20	Aspect Ratio	Q2	Q12	Q20	Aspect Ratio
1	21.569	50.277	90.313	0.908	21.6	50.18	90.56	0.905	0.14352	-0.1933	0.272747	-0.33149
2	21.399	54.367	94.474	0.79	21.65	54.39	94.23	0.79	1.15935	0.042287	-0.25894	0
3	18.056	52.038	91.976	0.938	18.56	52.36	91.28	0.94	2.71552	0.614973	-0.76249	0.212766

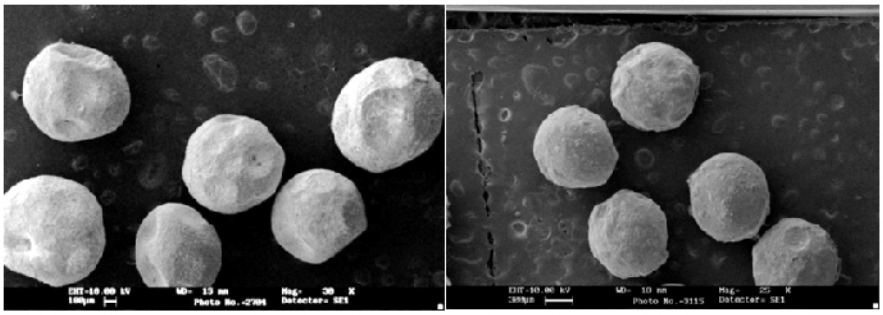

Fig. 6. SEM images (a) Pellets before coating (b) Pellets after coating.

***In vitro* Drug Release Studies.** The studies of the formulation Batches were carried out to know the *in-vitro* drug release pattern. It was observed that the drug release decreased with the increase in the concentration of the polymers. The % CDR was found to be in the range of 88.23% to 99% at the end of 24h. The value of release after 2h varied between 16.96% and 28.63%; release after 12 h found between 48.54% and 58.78 % and release after 20h found between 88.19% and 98.76%. HPMCK100M was used as a matrix polymer because it is hydrophilic in nature and could be useful in controlling the release in delivery system by formation of matrix and gel. Further rate of drug delivery depended on coating solution and % weight gain. During the initial period of drug release, it majorly dependent on coating composition and % weight gain. Afterwards it is dependent on matrix agent, coating composition and % weight gain and interaction effects of thereof.

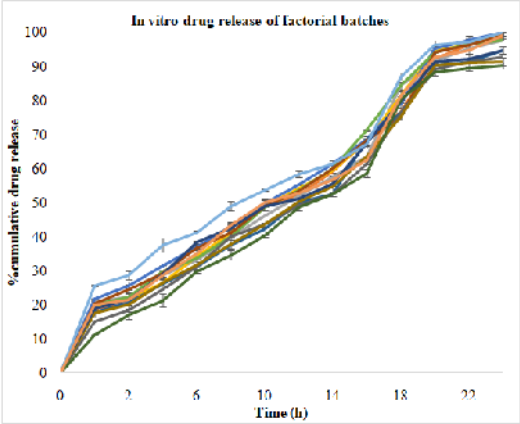

Fig. 7. Drug release profile of factorial batches**.**

Kinetic release of dissolution data with different models. Mathematical modelling of drug release plays vital role in the interpretation of mechanism of drug release from the formulation. Mathematical modelling adds value to complete understanding of the drug release mechanism from the optimized formulation resulting in complete product understandings. The drug release data of optimized batch of pellets was fitted to different models and it was found that the drug release followed First order releae mechanism. The R^2 value, F value and SSR values of all models were derived. It was observed (Table 9) that drug release has maximum R^2 value (0.9974), lowest F value (226.89) and lowest SSR value (2098.36), entailing the drug release followed first order release kinetics.

Table 9: Results of curve fitting with various matematical model for optimized batch of coated matrix pellets.

Drug release kinetics	Coated matrix pellets (Optimized batch)		
	r^2	SSR	F
Zero order	0.9256	3058.94	334.08
First Order	**0.9974**	**2098.36**	**226.89**
Higuchi Model	0.9725	2405.2	325.35
Korsmeyer Peppas	0.9254	2987.36	348.81
Hixon Crowell Model	0.9782	2369.87	321.59

Accelerated Stability Study. The entrapment efficiency, drug content and aspect ratio before and after storage were found to be nearly similar. The dissolution profiles before and after storage were nearly overlapped (Fig. 8). The stability studies of the optimized formulation showed no significant changes in the physical parameters, entrapment efficiency, drug content and aspect ratio. The results of stability study are mentioned in Table 10.

Table 10: Results of Stability study for optimized batch of coated matrix pellets.

Sr. No.	Month	Entrapment efficiency	Drug content	Aspect Ratio
1.	0	91.23±1.12	99.87±2.01	0.91
2.	1	90.98±1.29	99.59±1.26	0.90
3.	2	91.12±1.56	99.28±1.14	0.89
4.	3	91.08±1.89	99.56±1.26	0.90

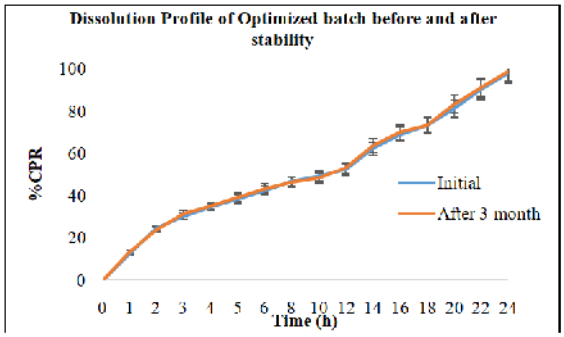

Fig. 8. Dissolution profile of optimized batch before and after stability.

CONCLUSION

From the results, it can be concluded that applied box Behnken design had assisted in development of coated pellets. The role of Eudragit®NE as a coating agent and HPMCK100M as matrixing agent was found to be critical in achieving desired drug release pattern. The process parameters were optimized successfully to yield pellets in near to spherical shape. The concept of use of matrixing hydrophilic polymer in core and additional coating of hydrophobic polymer over core pellet for highly water-soluble drug can be a promising approach to deliver drug in a controlled manner.

FUTURE SCOPE

This study entails development of multiparticulate system for sustained release of hydrophilic drug. Developed formulation can be used as a platform technology for highly soluble drugs. Further, *in vivo* studies in animals and human can be used to predict the performance of the formulation better.

Author Contributions. Mr. Shekhar Kokate has Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper. While Dr. Punit Rachhhas given significant insights in data analysis and paper writing.

Acknowledgement. The authors are grateful to Shri Panchvati Education Society Institute of Pharmacy, Nasik, Maharashtra, India and Department of Pharmacy, Bhagwant University, Sikar Road, Ajmer, Rajasthan, India., for their support during this research work.

Conflict of Interest. None.

REFERENCES

Aashigari, S., Goud, R., Sneha, S., Vykuntam, U. and Potnuri, N. R. (2018). Stability studies of pharmaceutical products. *World J. Pharm Res, 8*, 479-492.

Amidon, G. L., Lennernäs, H., Shah, V. P. and Crison, J. R. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical research, 12*(3), 413-420.

Parejiya, B. P., S. Barot, B., K. Patel, H., K. Shelat, P. and K. Shukla, A. (2012). Development of platform technology for oral controlled delivery of highly water soluble drugs using milnacipran HCl as a model drug. *Drug Delivery Letters, 2*(1), 35-45.

Bodea, A. and Leucuta, S. (1998). Optimization of propranolol hydrochloride sustained-release pellets using box-behnken design and desirability function. *Drug Development and Industrial Pharmacy, 24*(2), 145-155.

Chen, C., Dyck, B., Fleck, B. A., Foster, A. C., Grey, J., Jovic, F. and Vickers, T. (2008). Studies on the SAR and pharmacophore of milnacipran derivatives as monoamine transporter inhibitors. *Bioorganic & medicinal chemistry letters, 18*(4), 1346-1349.

Dash, S., Murthy, P. N., Nath, L. and Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm, 67*(3), 217-223.

Dias, C. L., Rossi, R. C., Bajerski, L. and Froehlich, P. (2011). Dissolution method for milnacipran hydrochloride capsules: Development, validation, and study of changes in dissolution rate after storage. *Diss. Tech, 18*(3), 47-53.

English, C., Rey, J. A. and Rufin, C. (2010). Milnacipran (Savella), a treatment option for fibromyalgia. *Pharmacy and Therapeutics, 35*(5), 261.

Hu, L.-D., Liu, Y., Tang, X. and Zhang, Q. (2006). Preparation and in vitro/in vivo evaluation of sustained-release metformin hydrochloride pellets. *European journal of pharmaceutics and biopharmaceutics, 64*(2), 185-192.

Hussain, T., Ijaz, M., Shamim, R., Hussain, K., Abbas, N., Hussain, A. and Bukhari, N. I. (2020). In vivo evaluation of a novel chitosan-polycaprolactone based mucoadhesive gastro-retentive sustained release drug delivery system for milnacipran HCl. *AAPS Pharm Sci Tech, 21*(2), 1-11.

Kothari, R., Shukla, B., Gautam, D., Bagaria, M., Sharma, A. J. I. J. o. T. and Sciences, A. (2018). Formulation and evaluation of herbal lipstick from natural edible coloring matter. *10*(1), 17-20.

Kyle, J. A., Dugan, B. D. and Testerman, K. K. (2010). New drug approvals: milnacipran for treatment of fibromyalgia. *Annals of Pharmacotherapy, 44*(9), 1422-1429.

Meena, V. K., Verma, P., Tak, Y. and Meena, D. (2021). Genetic Variability, Correlation and Path coefficient Studies in Chickpea (*Cicer arietinum* L.) Genotypes in South Eastern Rajasthan. Paper presented at the *Biological Forum–An International Journal, 13*(3a), 93-98.

Parejiya, P. B., Barot, B. S., Patel, H. K., Chorawala, M. R., Shelat, P. K. and Shukla, A. (2013). In vivo performance evaluation and establishment of IVIVC for osmotic pump based extended release formulation of milnacipran HCl. *Biopharmaceutics & drug disposition, 34*(4), 227-235.

Parejiya, P. B., Barot, B. S., Patel, H. K., Mehta, D. M., Shelat, P. K. and Shukla, A. (2014). Release modulation of highly water soluble drug using solid dispersion: impact of dispersion and its compressed unit. *Journal of Pharmaceutical Investigation, 44*(3), 163-175.

Parejiya, P. B., Barot, B. S., Patel, H. K., Shelat, P. K. and Shukla, A. (2013). Innovation of novel 'Tab in Tab'system for release modulation of milnacipran HCl: optimization, formulation and in vitro investigations. *Drug Development and Industrial Pharmacy, 39*(11), 1851-1863.

Rao, S. G., Gendreau, J. F. and Kranzler, J. D. (2007). Understanding the fibromyalgia syndrome. *Psychopharmacology Bulletin, 40*(4), 24-67.

Ratnaparkhi, M. and Gupta Jyoti, P. (2013). Sustained release oral drug delivery system-an overview. *Terminology, 3*(4), 10.22270.

Singh, B. and Rajpoot, V. (2021). Assessment of Genetic Variability for Different Parameters in Fenugreek under Moisture Regime. *Biological Forum–An International Journal, 13*(3a), 232-237.

Singh, S. K., Manoj Kumar, S., Korada, M., Khaire, A., Majhi, P. K., Singh, D. and Jayasudha, S. (2021). Genetic Variability and Divergence Studies for Yield and its related traits in Rice (*Oryza sativa* L.). Paper presented at the *Biological Forum–An International Journal, 13*(4), 687-695.

Vaishnavi, S. N., Nemeroff, C. B., Plott, S. J., Rao, S. G., Kranzler, J. and Owens, M. J. (2004). Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. *Biological psychiatry, 55*(3), 320-322.

Wang, J., Kan, S., Chen, T. and Liu, J. (2015). Application of quality by design (QbD) to formulation and processing of naproxen pellets by extrusion–spheronization. *Pharmaceutical development and technology, 20*(2), 246-256

.

How to cite this article: Shekhar V. Kokate and Punit R. Rachh (2023). Development and Characterization of Coated Matrix Multiparticulate System for Milnacipran HCl Sustained Release Imbibing Design of Experiments. *Biological Forum – An International Journal, 15*(1): 439-447.