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Research Article

FORMULATION AND OPTIMIZATION OF THE EXTENDED RELEASE TABLETS OF DALFAMPRIDINE BY 2^3 FACTORIAL DESIGN

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ABSTRACT

The purpose of the present study was to develop and optimize the pH independent Dalfampridine extended release tablets by employing 3 factors 2 level (2^3) factorial design. Combination of hydrophilic polymer and methacrylates as matrix formers and MCC PH 102 as direct compressible diluents were used. The independent variables were the concentration of the matrix formers Eudragit RSPO (X_1), Eudragit RLPO (X_2), HPMC K100M (X_3) whereas the dependent variables were the cumulative % drug release at 1 hr (Y_1), 6 hrs (Y_2), 12 hrs (Y_3) and the time for the 50 % of the drug release (Y_4), which were restricted to 10-30 %, 40-70 %, NLT 80 % and NLT 3 hrs respectively. Statistical elucidations of the polynomials were established for all the responses. The formulations were evaluated for the pre-compression and post-compression parameters. The *in vitro* results revealed that formulations with high concentration of HPMC and RLPO were unable to control the drug release whereas formulations with high concentration of RSPO with other two met the extended release criteria. From the kinetic and mathematical results, the drug release follows the first order and Higuchi's Fickian diffusion kinetics.

Keywords: Dalfampridine, factorial design, optimization, levels, eudragit RSPO and RLPO.

INTRODUCTION

Dalfampridine popularly known as fampridine (USA) / pyridin-4-amine (chemically) is the first drug used in the treatment of Multiple Sclerosis. It is a broad spectrum voltage dependent potassium channel blocker, it restores conduction in demyelinated axons i.e., patients with multiple sclerosis[1]. Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipient in order to achieve release by a continuous leaching of the drug from the inert matrix core[2].

Hydrophilic matrix tablets are among the most widely used controlled release dosage forms for oral delivery due to their low cost and ease of fabrication. Drug release from hydrophilic matrix tablets upon contact with dissolution media or physiological fluids involves hydration of tablet surface and formation of the gel layer that swells imbibing additional amount of water. The dissolved drug diffuses through the gel layer and hydration and swelling progress into tablet core. These processes are dependent on the type and proportion of polymer used as a controlled release agent[3]. The use of mixtures of polymers represents a potential way of achieving required release properties[4]. Mixtures of different proportions of polymers with different permeation characteristics can provide a wide range of release rates of a drug by changing the diffusivity of the drug through a polymer barrier[5]. Swellable matrices may modify their dissolution pattern and dissolution rate on addition of a second polymer to the matrix. The change in dissolution is due to the second polymer solubility and the physicochemical interactions between the polymers in an aqueous medium[6].

It is well known that traditional experimentation involves a good amount of effort and time when complex formulations are to be developed. In order to readily reach our goal, a statistical optimization technique, based on a full factorial design utilizing polynomial equation was used to search for optimal dalfampridine extended release formulation and efficiently quantify the influences of formulation variables on the drug release[7].

The present study was aimed to evaluate the feasibility of using Eudragit RSPO, Eudragit RLPO and HPMC K100M as matrix materials for extended release of dalfampridine. The influence of varying the concentration of Eudragit RSPO, Eudragit RLPO and HPMC K100M on drug release was investigated. The various pre and post-compression properties of the tablets obtained with different formulations were also examined.

MATERIALS AND METHODS

The following materials were used as received: Dalfampridine (Manus Aktteva Biopharma LLP, Gujarat), Eudragit RSPO, Eudragit RLPO USF/NF (Evonik industries, Germany), HPMC K100M (Dow chemicals, Germany), Avicel PH-102 (FMC Biopolymer, New York), PVP K90 (BASF, India), Magnesium stearate (SD Fine chemicals, Mumbai). All other reagents were at least of analytical reagent grade and were used without further purification.

Identification of variables and fixing the levels of variables

The critical variables which will affect the final output i.e., drug release at various time points were identified by extensive literature survey as concentration of Eudragit RSPO (X_1), Eudragit RLPO (X_2) and HPMC K100M (X_3).

Experimental design[8-10]

A two level factorial design was employed using Design Expert to determine the effect of the three factors: amount of Eudragit RSPO, amount of Eudragit RLPO and amount of HPMC K100M on drug release characteristics. Each factor was tested at two levels designated as -1 and +1 as follows: amount of

Eudragit RSPO – 37.5 mg (-1) and 62.5 mg (+1), amount of Eudragit RLPO – 37.5 mg (-1) and 62.5 mg (+1) and amount of HPMC K100M – 29 mg (-1) and 60 mg (+1) for each tablet weighing 250 mg. Based on Design of Experiments (DOE), 8 types of tablets (F1 to F8) were prepared as shown table 1. A randomized table (table 2) was generated using Design Expert software. For each formulation, response variables studied were the cumulative % drug release at 1 hr, 6 hrs, 12 hrs and $t_{50\%}$ (time for the 50 % of the drug to release). After performing the experiments, multiple linear regression was applied to evaluate the regression coefficients of the mathematical model that included the linear terms of three factors investigated, as well as the interaction factors:

$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_1b_2X_1X_2 + b_1b_3X_1X_3 + b_2b_3X_2X_3 + b_1b_2b_3X_1X_2X_3$

ANOVA test was applied to each term of the linear model to evaluate their significance. Only terms that were significant were included in the final model. An experimental matrix after the estimation of regression coefficients was used to characterize the results by factorial design. Response surface and contour plots were drawn to visualize the effect of investigated factors. The value and sign of regression coefficient indicates the magnitude of influence of the particular factor on the response. The regression coefficient give the average change in a response when the particular factor is changed by a unit, when all the other terms remain constant, a positive sign on the regression coefficient indicates the factor has a positive effect on the response and the negative sign indicates a negative effect.

Drug - Excipient Interaction studies

Differential Scanning Calorimetry

The possibility of drug excipient interaction was investigated by differential scanning calorimetry. The DSC thermograms of pure drug, individual excipients and drug excipient mixtures were recorded. The samples were separately sealed in aluminium cells and set in Mettler TA 4000 thermal analyzer. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 °C / min over a temperature range of 30-300 °C. Alumina was employed as the reference standard.

Infrared Spectroscopy

The IR absorption spectra of the pure drug, formulation and placebo were taken in the range of 4000-400 cm^{-1} using ATR. The Infrared spectrum of API was recorded by using ATR spectroscopy and observed for characteristic peaks of drug. These functional groups should be retained when formulated with excipients and charged in a stability chamber. Tablet blend was thoroughly passed through the sieve no. #40 and finally Placebo (without API) was subjected for ATR studies. The blend was filled in glass vials and closed with gray rubber stoppers and sealed with aluminium seal and charged at 60ºC for 30 days in a stability chamber. ATR spectra was compared with the initial spectra and reported for any variations.

Formulation of Matrix Tablets[11]

Matrix tablets were prepared with a total weight of 250 mg of varying polymer composition and a fixed quantity of Dalfampridine of 10 mg. Dalfampridine matrix tablets were prepared employing Eudragit RSPO, Eudragit RLPO, HPMC K100M as matrix former polymers by direct compression technique using microcrystalline cellulose (avicel pH 102) as diluents. All the ingredients were passed through the sieve no 40 separately and shifted in plastic bag to attain uniformity. The powder blend was lubricated with 1% w/w magnesium stearate which was previously passed through the sieve no 60. Lubricated blend was then compressed into tablets of weigh 250 mg using B tooling in a rotary tablet press.

EVALUATION OF FORMULATIONS

Evaluation Parameters for Pre Compression Blend

Angle of repose

Angle of repose (θ) is the measure of a frictional force in a loose powder. It is nothing but the maximum angle between the surface of the pile of powder and the horizontal plane. It is a characteristic property related to interparticulate friction or resistant to movement between the particles.

A funnel with a stem of inner diameter of 10 mm was fixed at a height of 3 cm over a platform. About 10 g of sample was slowly passed along the walls of the funnel, till the tip of the pile was formed and touched the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose (θ) was carried out thrice and average is determined using the following formula,

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

Where, θ = Angle of repose, h = height of the pile, r = radius of the pile.

Bulk density and tapped density

Bulk density is of great importance when one considers the size of a high dose drug product or homogeneity of low-dose formulations. Bulk density is often referred to the density of the powder as poured or as passively filled into a measuring vessel.

The tapped density is a limiting density attained after 'tapping down' usually in a device that lifts and drops a volumetric measuring cylinder containing powder at a fixed distance. The bulk density and trapped density are reported as g/ml values.

Apparent bulk density was determined by pouring the blend of 25 g gently through a glass funnel into a 100 ml graduated cylinder. After pouring, the powder bed was made uniform without disturbing. The volume was then measured directly from the graduated marks of the cylinder. The volume measure was called bulk volume and the bulk density was calculated by the following formula,

Bulk density = Weight of the powder (g) / bulk volume (ml)

Tapped density of the drug was determined by pouring the blend of 25g gently through a glass funnel into a 100ml graduated cylinder. Using the USP Tap Density Tester, the cylinder was tapped from the height of 2 inches until a constant volume was obtained. The tapped density was measured for 500 tappings and 750 tappings giving densities (V_a), and (V_b) with a drop time of 299 to 302 tappings per minute.

If the percentage difference between the 'V_a' and 'V_b' exceed about 2% then 'V_c' is measured by 1250 tappings. Either 'V_b' or 'V_c' is taken as the final tapped density. The volume occupied by the sample after tappings were recorded and the tapped density was calculated by the formula below,

Tapped density = Weight of the powder (g) / tapped volume (ml)

Compressibility index and Hausner's ratio

Carr's Compressibility is the ability of the powder to decrease in volume under pressure. Compressibility is a measure that is obtained from the density determinations. It is also one of the simple method to evaluate flow property of a powder by taking the difference between the bulk density and tapped density.

Hausner's ratio provides an indication of the density of densification resulting from the feed hopper vibrations. A lower value indicates better flow.

The Carr's Compressibility index (%) is calculated by taking the percentage difference between the bulk density and the tapped density using the formula

Carr's compressibility Index = [(Tapped density – Bulk density) / tapped density] X 100

Hausner's ratio was calculated as the simple difference between the Tapped density and the bulk density using the formula

Hausner's ratio = Tapped density / bulk density

Evaluation Tests for Post Compression Parameters

Weight variation test

Twenty tablets were taken randomly selected and weighed accurately. The average weight is calculated by:

Average weight = Weight of 20 tablets /20

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits.

In the drug : excipients ratio, if the drug concentration is less than 90-95% then we have to conduct assay of the particular drug which is official in respected pharmacopeia to know the content uniformity, if the drug ratio is more than 90 % in a unit dosage form then weight variation test suffices the necessity of content uniformity test.

Hardness

This is the force required to break a tablet in a diametric compression. Hardness of the tablet was determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 5-6 kg was considered as suitable for handling the tablet.

Tablet size and thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet was measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability

This test was performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these were placed in the friabilator, rotating at 25 rpm for 4min. The difference in the weight was noted and expressed as percentage. It should be preferably between 0.5 to 1.0 %.

$$\% \text{ Friability} = [(W_1-W_2)/W_1] \text{ X } 100$$

Where, W_1 = weight of tablets before test,

W_2 = weight of tablets after test

***In vitro* dissolution study**

The dissolution behaviour of Dalfampridine was measured using an Electrolab dissolution tester and a model UV1800 double beam spectrophotometer (Shimadzu) at 262 nm. The USP type II apparatus was used, at 50 rpm, in 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. At appropriate intervals, 5 ml of the samples were taken and filtered through a 0.45 µm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The mean of six determinations was used to calculate the drug release for each of the formulations.

Drug release kinetic studies[12, 13]

The data obtained from *in vitro* drug release studies were plotted according to various kinetic models to assess the kinetics and mechanism of drug release as follows:

1. Zero order: Cumulative % of drug released versus time ($Q_t = Q_0 – K_0t$)
2. First order: Log cumulative % of drug remaining to be released versus time ($\ln Q = \ln Q_0 – K_1t$)
3. Higuchi: Cumulative % of drug released versus square root of time ($Q = K_ht^{1/2}$)
4. Korsmeyer – Peppas: Log cumulative % of drug released versus log time ($M_t/M_\alpha = Kt^n$)

Where

Q_i and K_i stand for the amount of drug release and kinetic release constant, respectively. M_t/M_α indicates the fractional drug release and 'n' is the diffusional exponent which gives the mechanism of drug release. When $n < 0.5$, the drug diffuses through polymeric matrix by Fickian diffusion (case I) mechanism. For $0.5 < n < 1$, an anomalous (non-Fickian) mechanism occurs; $n = 1$ indicates a zero order (case II) and $n > 1$ indicates non-Fickian super case II release mechanism.

The plots were drawn using Microsoft excel 2007 and the regression equations were obtained for each plot. The linearity of the plots was obtained from the value of regression coefficient (r^2). The model with highest linearity was chosen as the best fit kinetic model.

Stability study

Formulations were selected for stability on the basis of the *in vitro* drug release profile and the values of coefficient of regression for zero order, first order and Higuchi model. The optimized formulation was strip packed (Al–Al strip) and subjected to accelerated stability studies as per ICH guidelines i.e. room temperature, 30 °C/60% RH and 40 °C/75% RH. Sampling was done at predetermined time intervals of 0, 15, 30, 60, 90 and 180 days. Tablets were evaluated for the different physico-chemical parameters viz. appearance, weight variation, thickness, hardness, friability, drug content and *in vitro* release.

RESULTS AND DISCUSSION

Compatibility Studies

DSC analyses were performed in order to evaluate possible solid-state interactions between the components and to assess the actual drug-excipient compatibility in all the examined formulations. The DSC thermogram for the drug gave a sharp melting endotherm at 177.36 °C. The individual excipients did not show any characteristic peaks. There was no shift in the endotherm of Dalfampridine in the drug–excipient mixtures indicating compatibility of the drug with all the excipients. The comparative DSC thermograms of the drug, individual excipients and drug–excipient mixtures are depicted in Figure 1. The ATR spectra revealed that there is no addition or deletion of peaks except the peak elongation showed that there is no significant interaction between the drug and excipients which shows that the drug and excipients are compatible with each other. (Figure 2-4, Table 3-5).

Pre Compression Data

The pre compression results were shown in table 6. The bulk density was in range of 0.786-0.82 g/ml. The tapped density was found to be in range of 0.923-0.941 g/ml. The compressibility index and hausner's ratio were found to be between 12.24 % - 15.93 % & 1.13-1.16 respectively. The angle of repose was in range of 22°.5' - 26°.9'. From the above results it was found that the powder blend has good to excellent flow properties.

Post Compression Data

Post compression results were shown in table 7. Weight variation results were found to be within specifications $\pm$ 7.5 % as per I.P. Hardness of all the formulations lies between 7.84 – 8.14 kg/ cm^2 & the for the best formulation (F2) was found to be 7.84. Thicknesses of the entire tablets were found to be 4.234 mm - 4.438 mm. Friability of all the formulations were found to be < 0.10 % and were within specifications and for optimized formulation the friability was found to be 0.56 %.

Drug Release Studies

In vitro drug release data was shown in Table 8, Figure 5. From the *in vitro* data it was concluded that all the formulations were able to extend the drug release for duration of 12 hours. But the formulations with high concentration of HPMC (F5, F6 & F7) were not able to control the burst release (> 30% release in 1 hour), whereas the formulations with high concentration of eudragit RLPO were also not able to meet the extended release criteria in 1st hour & 6th hour (F3, F4). Formulations with high concentration of eudragit RSPO, low concentration of RLPO & HPMC met the extended release criteria i.e., NMT 30% release in 1st hour, 30-70% release within 6 hours & NLT 80% release in 12 hours. The above criteria were met by F2 formulation were selected as best formulation. The regression coefficient values (Table 9) obtained from the various release kinetic models reveled that all the formulations follow the first order release with Higuchi diffusion (r^2 near to 0.99) & follows Fickian diffusion (n value $\leq$ 0.5) and the plots were shown in Figure 6-13.

Multiple Regression Analysis

Multiple regression analysis technique was used to generate the best fit models for the analyzed responses. The final equations of reduced model contain only the significant factor terms corresponding to the response analyzed.

Reduced model equations for responses are as follows:

1. Drug release at 1st hr (Y_1) = $35.25 + 1.75\ X_1 + 1.75\ X_3 - 2.50 X_2X_3 - 2.0\ X_1X_2X_3$
2. Drug release at 6th hr (Y_2) = $74.13 + 2.012 X_2 + 2.63 X_1X_3$
3. Drug release at 12th hr (Y_3) = $89.88 + 3.62 X_2 + 2.38 X_1X_3 - 1.62\ X_2X_3$
4. Time to release 50 % of the drug, $T_{50\%}$ (Y_4) = $2.32 - 0.19 X_2 - 0.20\ X_1X_3 + 0.24\ X_2X_3 + 0.20\ X_1X_2X_3$

From the ANOVA results (Table 10), it was found that the major factors affecting the drug release at 1st hour was factor X_1, X_3, X_2X_3 & $X_1X_2X_3$. The first two had the positive effect whereas the latter ones had negative effect. By increasing the concentration of RSPO, HPMC the drug release increases at the 1st hour due to the burst release whereas interaction between at the factors will retard the drug release. Contour plots (Figure 14) and 3D surface plots (Figure 15) showed the effect of factor X_2 and factor X_3 on the response 1 (Drug release at 1 hr). From the picture it was observed that in order to control the initial drug release i.e., < 30%, the concentration of factor X2 and factor X3 were kept at low level.

From the ANOVA results (Table 11), it was found that the major factors affecting the drug release at 6th hour was factor X_2 & X_1X_3 interaction both showed positive effect. On increasing the concentration of RLPO the drug release increases as it is high permeable polymer. Contour plot (Figure 16) and 3D surface plot (Figure 17) showed the effect of factor X_2 and factor X_1X_3 on the response 2 (Drug release at 6 hr) the required criteria is to maintain the drug release in between 40-70%. From the picture it was observed that in order to attain the drug release criteria at 6 hr the concentration of factor X_2 and factor X_3 were kept at low level.

From the ANOVA results (Table 12), it was found that the major factors affecting the drug release at 12th hour were factor X_2, X_1X_3 & X_2X_3 interaction. The first two factors had the positive effect whereas the latter one has the negative effect. Contour plot (Figure 18) and 3D surface plot (Figure 19) showed the effect of factor X_2 and factor X_3 on the response 3 (Drug release at 12 hr) the required criteria is the drug release from the dosage form is not less than 80%, but in this scenario we will select the design space with more drug release and from the picture it was observed that by increasing the concentration of factor X_2 and factor X_3 the drug release also enhanced but it may alters the drug release criteria at 1st hour and 6th hour. But at the same time by maintaining those factors at low level all the criteria will meet.

From the ANOVA results (Table 13), it was found that the major factors affecting $T_{50\ \%}$ were X_2, X_1X_3, X_2X_3 & $X_1X_2X_3$ interactions. Contour plot (Figure 20) and 3D surface plot (Figure 21) showed the effect of factor X_2 and factor X_3 on the response 4 ($T_{50\%}$).

Accelerated Stability Study

Accelerated stability study data shown in table 14 revealed that the formulation has not undergone any physical or chemical degradation during the period. There were no significant differences in the *in vitro* drug release and drug content of the optimized formulation.

Table 1: Composition of Dalfampridine matrix tablet batches F1 – F8

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	10	10	10	10	10	10	10	10
Eudragit RSPO	37.5	62.5	37.5	62.5	37.5	62.5	37.5	62.5
Eudragit RLPO	37.5	37.5	62.5	62.5	37.5	37.5	62.5	62.5
HPMC K 100M	29	29	29	29	60	60	60	60
MCC pH 102	121	96	96	71	90	65	65	40
PVP K 90	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	250	250	250	250	250	250	250	250

Table 2: Experimental Design plan generated by software

Runs	X_1	X_2	X_3
I	-1	-1	-1
X_1	+1	-1	-1
X_2	-1	+1	-1
X_1X_2	+1	+1	-1
X_3	-1	-1	+1
X_1X_3	+1	-1	+1
X_2X_3	-1	+1	+1
$X_1X_2X_3$	+1	+1	+1

Table 3: Characteristic functional groups of Dalfampridine

Functional Group	Wave number (cm^{-1})
N-H (Stretching)	3294.97
C-H (Stretching, Aromatic)	3031.90
C=N	1643.45
C=C	1499.18
C-H (Bending)	1428.56
N-H (Bending)	1209.77

Table 4: Characteristic functional groups of Placebo

Functional Group	Wave number (cm^{-1})
O-H	3588.73
C-H (Stretching, Aliphatic)	2916.83
C-H (Stretching, Aldehyde)	2849.50
C=O	1721.94
C=C	1459.43
C-Cl	1056.05

Table 5: Characteristic functional groups of best formulation

Functional Group	Wave number (cm^{-1})
O-H	3588.73
N-H	3342.32
C-H (Stretching, Aromatic)	3070.031
C-H (Stretching, Aliphatic)	2916.83
C-H (Stretching, Aldehyde)	2849.50
C=O	1721.94
C=N	1642.35
C=C	1459.43
N-H (Bending)	1266.31
O-H (Bending)	1056.05

Table 6: Pre-compression parameters of final batches F1-F8

Code	Bulk Density (gm/mL) ± SD*	Tapped Density (gm/mL) ± SD*	Compressibility Index (%) ± SD*	Hausner' s Ratio ± SD*	Angle of Repose (θ) ± SD*
F1	0.82±1.1	0.941±0.2	13.05±0.2	1.13±0.9	25.51±0.35
F2	0.80±1.4	0.936±0.8	14.525±0.4	1.16±0.4	25.83±0.78
F3	0.78±1	0.935±0.3	15.936±0.8	1.14±0.3	26.12±0.91
F4	0.81±0.7	0.923±0.1	12.24±0.3	1.13±1.9	26.96±0.78
F5	0.80±0.2	0.925±0.5	13.40±0.7	1.15±0.7	25.25±0.23
F6	0.81±0.7	0.928±0.9	12.60±0.4	1.14±0.5	26.22±0.59
F7	0.81±0.9	0.932±0.1	13.19±0.6	1.15±0.3	26.55±0.99
F8	0.81±0.3	0.929±0.2	13.24±0.8	1.13±0.9	25.23±0.43

*represents mean ± SD (n = 3)

Table 7: Post-compression parameters of final batches F1-F8

Formulation Code	Parameters			
	Average Weight of Tablet in (mg) ± SD*	Hardness in (Kg/cm^2)± SD**	Thickness (in mm) ± SD**	Friability (%)± SD***
F1	250.30±0.0033	7.94±0.219	4.232±0.0130	0.406±0.406
F2	250.19±0.0032	7.84±0.114	4.244±0.0167	0.56±0.421
F3	250.26±0.0028	8.08±0.130	4.234±0.0114	0.06±0.007
F4	250.01±0.0027	8.08±0.164	4.248±0.013	0.108±0.013
F5	250.24±0.0025	7.98±0.148	4.234±0.011	0.108±0.013
F6	250.17±0.0027	8.02±0.836	4.256±0.013	0.06±0.007
F7	250.22±0.0025	8±0.1	4.244±0.013	0.56±0.421
F8	250.34±0.0025	8.14±0.054	4.246±0.011	0.048±0.008

*represents mean ± standard deviation (n = 20), **represents mean ± standard deviation (n = 5), ***represents mean ± standard deviation (n = 3)

Table 8: Dissolution Profiles of formulations F1-F8

Time (in hours)	Cumulative % Drug Release ± SD*							
	F1	F2	F3	F4	F5	F6	F7	F8
0.5	22±1.21	19±0.75	20±0.40	31±1.47	24±1.16	32±0.4	28±0.54	23±0.63
1	31±0.81	30±4.14	33±0.83	40±0.54	35±0.89	43±0.63	35±0.81	31±0.81
2	46±1.21	43±2	51±0.54	51±1.21	47±1.09	53±0.98	48±1.83	50±1.03
4	61±1.50	56±0.83	67±0.51	65±0.83	55±0.51	60±0.98	60±1.72	65±1.03
6	74±1.47	70±1.22	79±1.51	76±0.75	69±1.37	75±0.75	71±1.16	74±0.98
8	78±1.37	75±3.38	84±0.51	81±1.50	74±0.54	80±0.40	87±0.81	77±0.81
10	82±1.97	79±0.54	90±0.40	88±0.89	79±1.16	86±0.81	91±1.21	82±1.81
12	87±1.86	81±1.78	96±1.63	93±1.04	85±0.81	92±0.51	93±0.51	87±1.41

Table 9: Kinetic & mathematical treatment of the dissolution data

Formulation Code	Zero Order R^2 value	First order R^2 value	Higuchi R^2 value	Korsemeyer Peppas	
				R^2	n value
F1	0.9719	0.9901	1	0.9992	0.5048
F2	0.9884	0.9946	0.9982	0.9977	0.5442
F3	0.992	0.9978	0.9959	0.9992	0.5011
F4	0.9531	0.9917	0.9976	0.9999	0.4
F5	0.9778	0.9877	0.9996	0.9975	0.476
F6	0.9625	0.9871	0.9993	0.9954	0.385
F7	0.9449	0.9911	0.996	0.9985	0.444
F8	0.971	0.990	0.9994	0.9938	0.4877

Table 10: ANOVA table for the first response (Drug release at 1st hr)

Source	Sum of Squares	Df	Mean n square	F value	p- value Prob> F	Significant
Model	131.00	4	32.75	39.30	0.0063	
A – Eudragit RSPO	24.50	1	24.50	29.40	0.0123	
C – HPMC	24.50	1	24.50	29.40	0.0123	
BC	50.00	1	50.00	60.00	0.0045	
ABC	32.00	1	32.00	38.40	0.0085	
Residual	2.50	3	0.83	-	-	
Cor Total	133.50	7	7	-	-	

Table 11: ANOVA table for the second response (Drug release at 6th hr)

Source	Sum of Squares f	Df	Mean n square	F value	p- value Prob> F	Significant
Model	91.25	2	45.63	16.74	0.0061	
B – Eudragit RLPO	36.12	1	36.12	13.26	0.0149	
AC	55.13	1	55.13	20.23	0.0064	
Residual	2.50	5	0.83	-	-	
Cor Total	104.88	7	7	-	-	

Table 12: ANOVA table for the third response 3 (Drug release at 12th hr)

Source	Sum of Squares f	df	Mean n square	F value	p- value Prob> F	Significant
Model	171.38	3	57.13	24.05	0.0051	
B – Eudragit RLPO	105.12	1	105.12	44.26	0.0027	
AC	45.13	1	45.13	19.00	0.012	
BC	21.12	1	21.12	8.89	0.0406	
Residual	9.50	4	2.38	-	-	
Cor Total	180.88	7	7	-	-	

Table 13: ANOVA table for the third response 3 (Time for 50% drug release)

Source	Sum of Squares	df	Mean n square	F value	p- value Prob> F	Significant
Model	1.40	4	0.35	12.09	0.0311	
B – Eudragit RLPO	0.30	1	0.30	11.06	0.0449	
AC	0.31	1	0.47	17.32	0.0252	
BC	0.47	1	0.32	11.90	0.0409	
ABC	0.32	1	0.32	11.90	0.0409	
Residual	0.082	3	0.027	-	-	
Cor Total	1.49	7	-	-	-	

Table 14: Stability data of the best formulation (F2) for 6 months

S. No	Parameter	Test (F2)			
		0 month	1st month	2nd month	3rd month
1	Strength	10 mg	10 mg	10 mg	10 mg
2	Description	White colored circular and flattened	White colored circular and flattened	White colored circular and flattened	White colored circular and flattened
3	Weight (mg)	250.19±0.0032	251.56±0.012	252.02±0.09	252.15±0.32
4	Hardness (kg/cm^2)	7.84±0.114	7.78±0.56	7.56±0.016	7.54±0.078
5	Thickness (mm)	4.244±0.0167	4.25±0.15	4.55±0.09	4.58±0.13
6	Friability (%)	0.56±0.421	0.57±0.12	0.576±0.26	0.58±0.14
7	Dissolution (%)	92±1.78	92±1.64	91±1.36	91±0.89

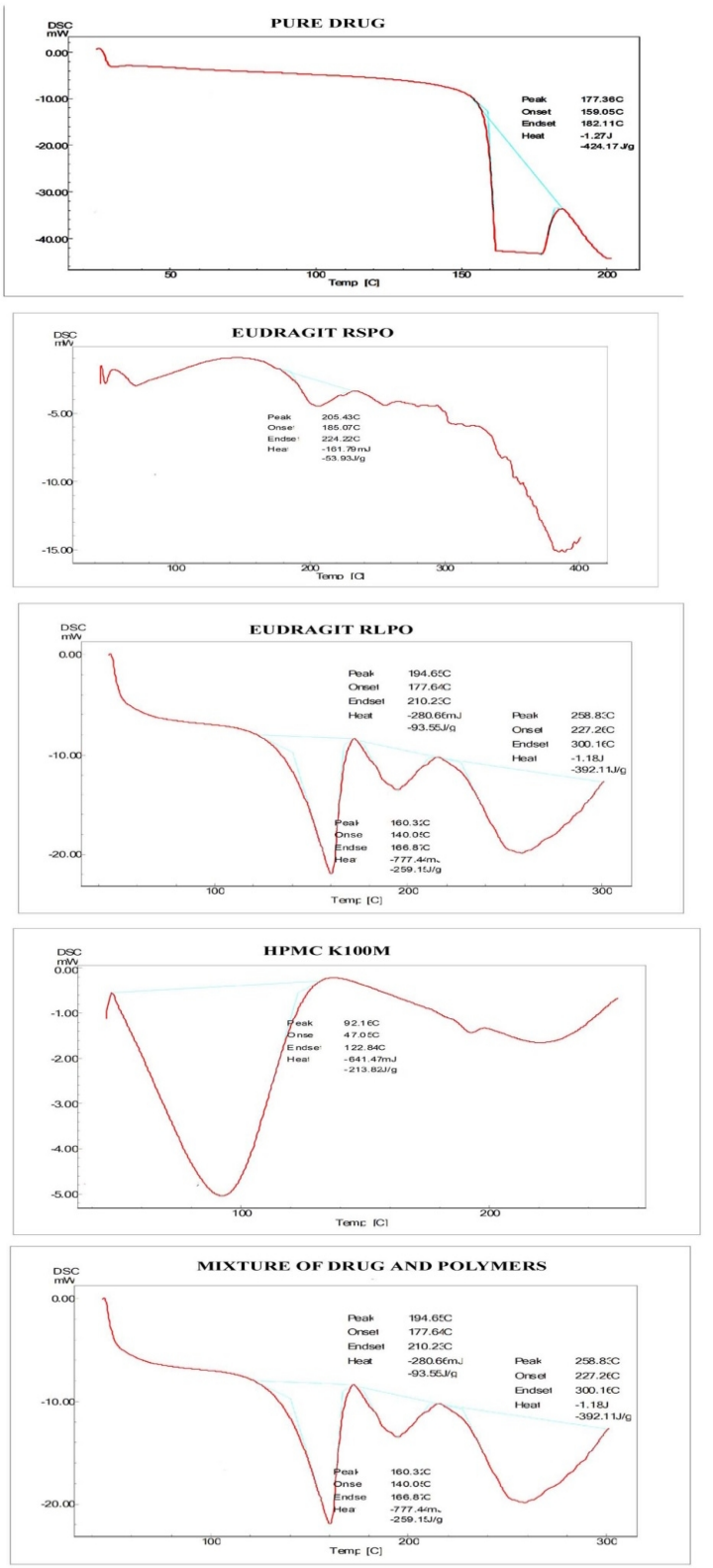

Figure 1: DSC thermograms of pure drug, Eudragit RSPO, Eudragit RLPO and polymeric mixture with drug

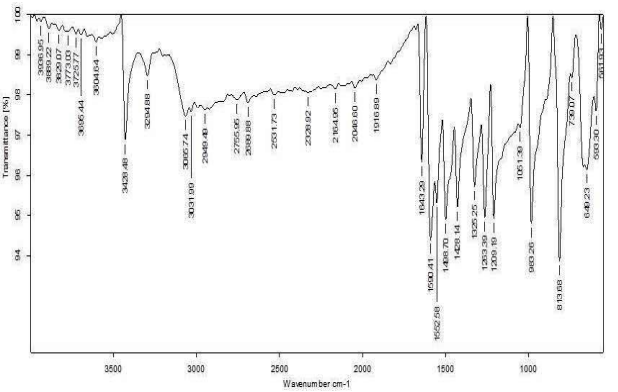

Figure 2: ATR Spectrum of Pure Drug

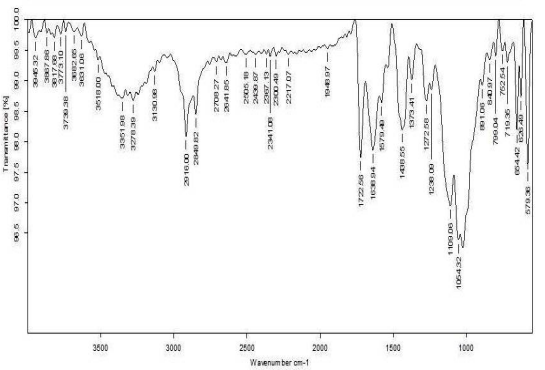

Figure 3: ATR Spectrum of Placebo

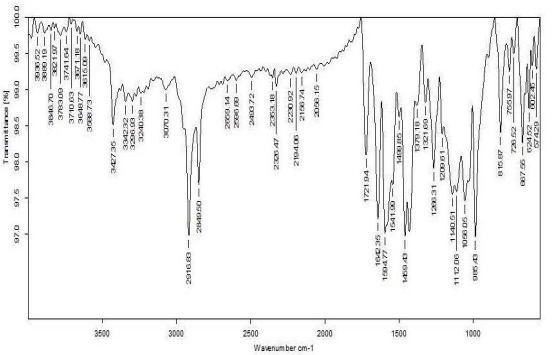

Figure 4: ATR Spectrum of stable formulation

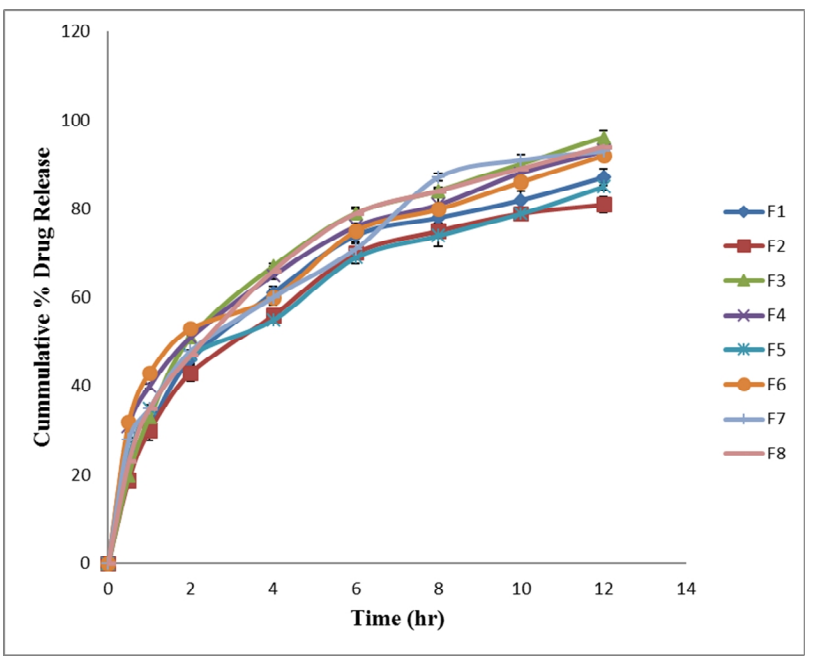

Figure 5: *In vitro* dissolution profiles of the all formulations

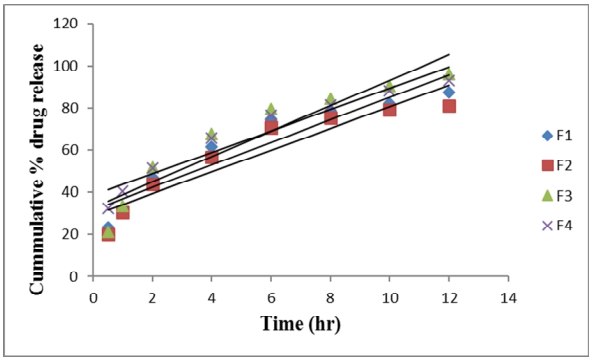

Figure 6: Zero Order plots for the formulation F1-F4

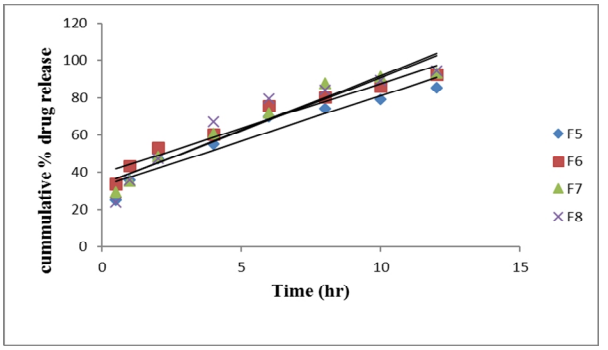

Figure 7: Zero Order plots for the formulation F5-F8

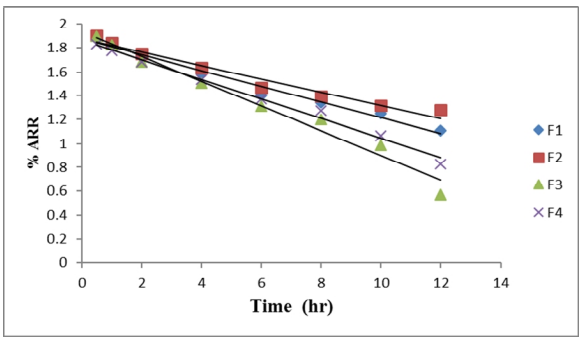

Figure 8: First Order plots for the formulation F1-F4

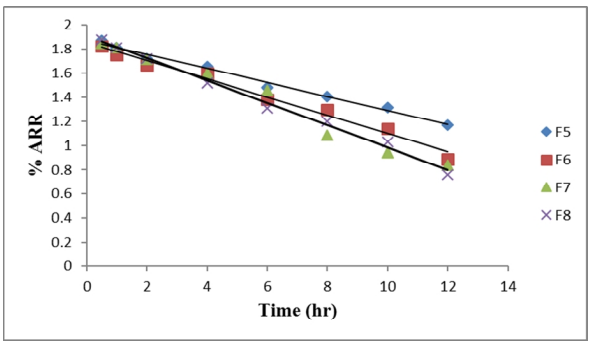

Figure 9: First Order plots for the formulation F5-F8

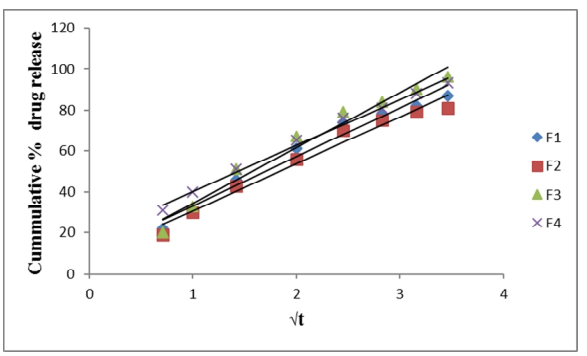

Figure 10: Higuchi plots for the formulation F1-F4

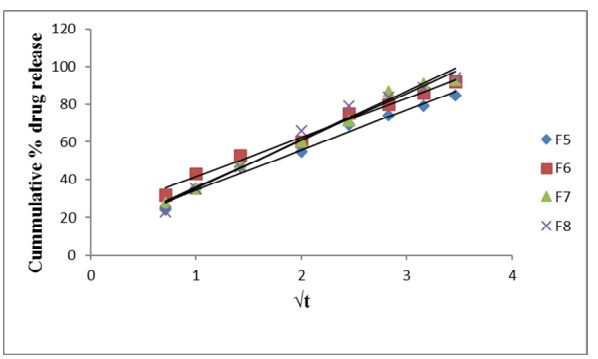

Figure 11: Higuchi plots for the formulation F5-F8

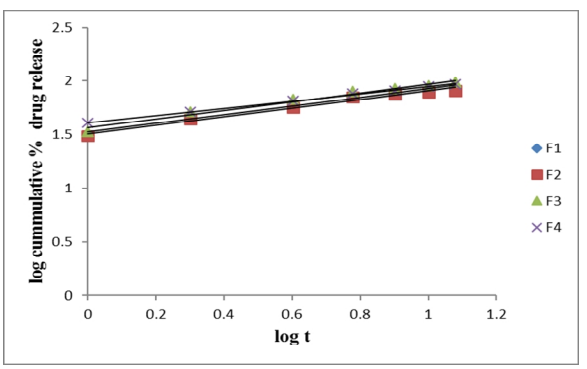

Figure 12: Korsmeyer - Peppas plots for the formulation F1-F4

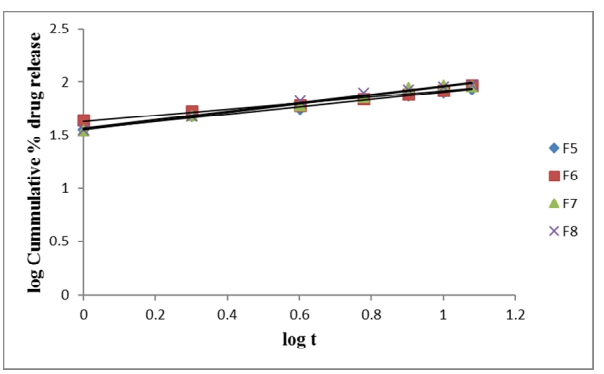

Figure 13: Korsmeyer - Peppas plots for the formulation F5-F8

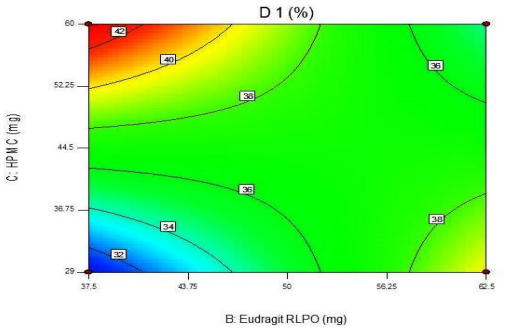

Figure 14: Contour plot showing the effect of Eudragit RLPO and HPMC on Drug release at 1st hour

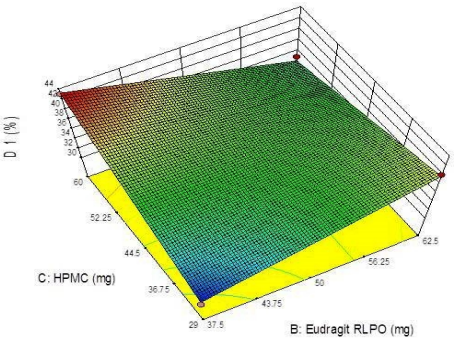

Figure 15: 3D response plot showing the effect of Eudragit RLPO and HPMC on Drug release at 1st hour

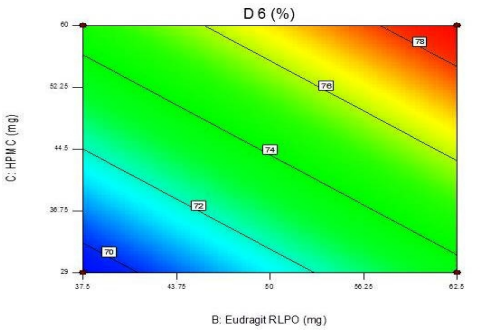

Figure 16: Contour Plot showing the effect of Eudragit RLPO and HPMC on Drug release at 6th hour

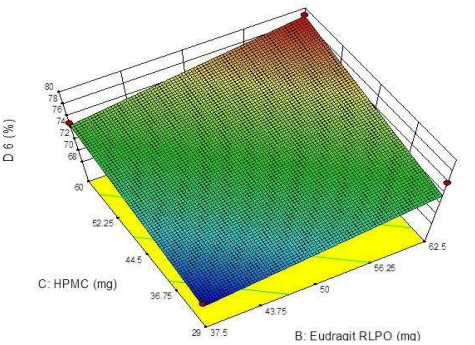

Figure 17: 3D response plot showing the effect of Eudragit RLPO and HPMC on Drug release at 6th hour

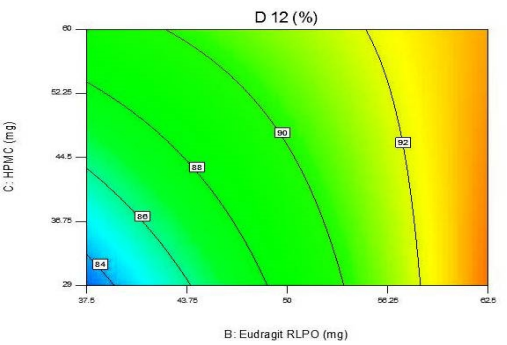

Figure 18: Contour plot showing the effect of Eudragit RLPO and HPMC on Drug release at 12th hour

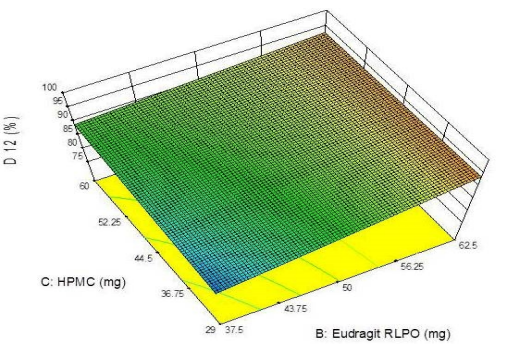

Figure 19: 3D response plot showing the effect of Eudragit RLPO and HPMC on Drug release at 12th hour

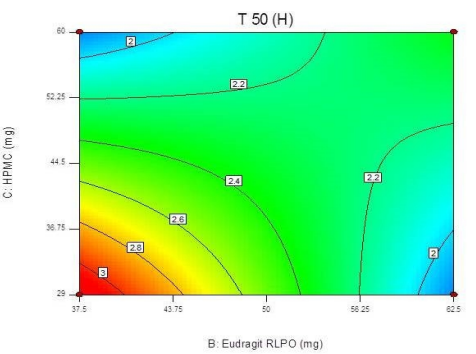

Figure 20: Contour plot showing the effect of Eudragit RLPO and HPMC on T_{50} (Hours)

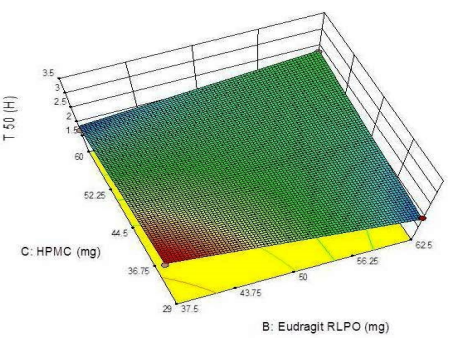

Figure 21: 3D response plot showing the effect of Eudragit RLPO and HPMC on T_{50} (Hours)

CONCLUSION

The present study was focused at the formulation and optimization of the Dalfampridine extended release tablets to improve the versatility and patient compliance. The ER tablets were formulated by direct compression and were optimized using the Design Expert Software (9.0.3). Results demonstrated that high concentration of Eudragit RLPO, HPMC K100M were unable to control the initial burst release because of their high permeability and hydrophilicity respectively. Whereas the Eudragit RSPO a low permeability polymer at high concentrations in combination with the Eudragit RLPO, HPMC K100M at low concentrations were able to retard the drug release for a period of 12 hr. The formulations F2 with Eudragit RSPO at high Concentration and Eudragit RLPO, HPMC K100M at low concentration were able to meet the extended release criteria. Finally, from the results it was concluded that for the drugs with high solubility and high permeability (BCS Class I) single polymer can't extend the drug release for longer times, so combination of high viscosity polymers viz HPMC K100M with the methacrylates viz Eudragit RSPO & RLPO can extend the drug release up to 12 hours.

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