International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.3, pp 1900-1909, July-Sept 2010

Once a Day Tablet of Nicorandil for the treatment of angina: *in-vitro* Study

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Abstract : Objective of present study was to develop hydrophilic polymer (HPMC K200M) and hydrophobic polymer (EC, Eudragit RSPO) based Nicorandil matrix SR tablet which can release drug up to time of 24hrs. Powders and tablets were evaluated for various parameters and it showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. Batch A10 was prepared with HPMC K200M: Eudragit RSPO (1:1) indicates 94.46% of drug release at 22 hrs and it has similarity factor (f2) value 68.07. Hydrophilic and Hydrophobic polymer combination gives good result than alone hydrophilic or hydrophobic polymer is used. The objective of the present study was to develop hydrophilic polymer (HPMC K200M) and hydrophobic polymer (Ethyl cellulose, Eudragit RSPO) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs.
Keywords: Nicorandil, HPMCK200M, Eudragit RSPO, EC, Sustained release, Matrix tablets.

Introduction

Hypertension and angina pectoris, the most common car-diovascular diseases, require constant monitoring. Potas-sium channel openers are presently considered an important class of drugs for hypertension and angina pectoris. The first therapeutic drug shown to possess an ability to hyperpolar-ize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator.[1] Although nicorandil is one of the emerging molecules in the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired.[2,3] Nicorandil has a short half-life, and the usual oral dosage regimen is 5 to 40 mg taken 2 to 4 times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of nicorandil is desirable. The drug is freely soluble in water, and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[4] Hence, in the present work, an attempt has been made to develop once-daily sustained-release matrix tablets of nicorandil using putative hydrophilic matrix materials such as hydroxypropyl methylcellulose (HPMC K200M).The drug re-lease for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Therefore, in this study, the hydrophilic polymer was used as matrix material, and the polymers like ethylcellulose (EC) and Eudragit RSPO were used. The objectives of the study were to develop a sustain release matrix formulation of Nicorandil using

combination of hydrophilic and hydrophobic rate retardant material by direct compression technology that gives desired in-vitro release profile comparable to market sample . The strength to be developed is 20 mg/ tablet.

Materials and Methods

Materials

Nicorandil was gifted from Torrent Pharmaceuticals Ltd. (Ahmedabad, India); HPMC K 200M, Eudragit RSPO Ethyl cellulose,, DCP, Aerosil and Calcium stearate was gifted by Jaxani Pharma, (Ahmedabad, India). All the other chemicals used were of high analytical grade.

Methods

Preparation of Tablets

Nicorandil SR matrix tablets were prepared by direct compression technique .Drug was passed through 40# sieve. HPMC K 200M, Eudragit RSPO and Ethyl cellulose were passed through 30# sieve. All other ingredients were passed through 40# sieve. All ingredients were mixed for 15-20 min. After mixing, Mg. stearate (60# sieve), was added to mixer blend and mix again for 3-5 min. Prepared blend was compressed (10/30 diameter, flat punches) using Hydraulic Pellet Press Machine (Type: KP-587, PCI services, Mumbai). Each tablet contains 20 mg of Nicorandil and other pharmaceuticals ingredients as listed in Table 1.

Evaluation of powder

Angel of Repose

Angel of Repose of powder was determined by the funnel method .Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend .Powder blend was allowed to flow through the funnel freely on to the surface .Diameter of the powder cone was measured and angel of repose was calculated using the following equation. [4, 5]

$\tan \alpha = h/r$

Bulk density

a) Loose Bulk density(BD): Weigh accurately 25 g of drug , which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder .Carefully level the powder without compacting , and read the unsetteled apparent volume (V_0) .calculate the apparent bulk density in gm/ml by the following formula. [4, 5]

Bulk density = Weigh of powder/ Bulk volume

b) Tapped bulk density (TD): Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder .Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units,repeat the tapping an additional 750 times and measure the tap volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2).Calculate the tapped bulk density in gm/ml by the following formula. [4, 5]

Tapped density = Weigh of powder / Tapped volume

Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down [4, 5]. The formula for Carr's index is as below:

Carr's index (%) = [(TD-BD)*100] / TD

Husner's Ratio

Husner's Ratio is a number that is correlated to the flowability of a powder. [4, 5]

Husner's Ratio = TD / BD

Evaluation of powder Blend listed in Table 2.

Evaluation of Tablets

Thickness

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India).[6]

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method.[7]

Drug content uniformity

Drug content was determined by taking an accurately weight amount of powdered Nicorandil with water and solution was filtered through 45µ membrane. The absorbance was measured at 262 nm, using double beam UV visible spectrophotometer.[8]

Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm^2 is considered adequate for mechanical stability.[9]

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India).

Tablets of a known weight (W_0) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again .Percentage friability was calculated from the loss in weight as given in equation as below .The weight loss should not be more than 1% w/w.[10]

%Friability = $(W_0-W)/ W_0 *100$

Evaluation of Tablets listed in Table 3

***In Vitro* Release Studies**

In vitro dissolution studies were carried out using USP apparatus type II (at 75 rpm. Dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 24 hours, maintained at 37°C ± 0.5°C. Drug release at different time intervals was measured by UV-visible spectrophotometer at 262 nm. *In vitro* drug release profile of all batches was compared with market product drug release profile[11]shown in fig.1, 2.

Table 1: Composition of Sustained release tablets of Nicorandil*

INGREDIENTS	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Drug(Nicorandil)	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K 200M	20	30	40	-	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	-	15	20	25	-	-	-	-	-	-
HPMC K 200M : EC	-	-	-	-	-	-	15 :15	10 :20	20 :10	-	-	-
HPMC K 200M : Eudragit RSPO	-	-	-	-	-	-	-	-	-	15 :15	10 :20	20 :10
Dibasic Ca.phospate anhydrous	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Mg.stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
TOTAL	**155 mg**											

*qs indicate quantity sufficient.

Table 2: Evaluation of powder Blend*

Powder Blend	Angel of Repose	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
A1	24.12	0.483	0.584	17.29	1.20
A2	23.33	0.487	0.564	13.65	1.16
A3	25.56	0.475	0.586	18.94	1.23
A4	24.89	0.484	0.579	16.41	1.19
A5	23.14	0.497	0.576	13.72	1.16
A6	24.15	0.482	0.566	14.84	1.17
A7	26.13	0.491	0.587	16.35	1.19
A8	25.64	0.483	0.578	16.43	1.19
A9	25.86	0.489	0.584	16.27	1.19
A10	26.54	0.493	0.575	14.26	1.17
A11	25.47	0.496	0.583	14.92	1.18
A12	25.56	0.499	0.594	15.99	1.19

*all results were average of n=3 observation

Table 3: Evaluation of Tablets*

Batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg.wt (mg)	Assay (%)
A1	5.1±0.1	2.2±0.1	0.062±0.003	155.8±1.2	99.47±0.30
A2	5.4±0.1	2.2±0.1	0.056±0.002	155.2±0.6	98.98±0.51
A3	5.4±0.4	2.4±0.06	0.062±0.005	157.5±1.1	99.54±0.16
A4	5.6±0.2	2.2±0.1	0.062±0.004	156.4±1.7	98.32±0.58
A5	5.2±0.1	2.2±0.2	0.059±0.002	155.7±1.1	98.66±0.96
A6	5.4±0.3	2.5±0.2	0.058±0.004	156.2±1.9	99.70±0.15
A7	6.0±0.3	2.2±0.05	0.063±0.001	156.3±1.5	98.82±0.56
A8	5.5±0.3	2.2±0.1	0.062±0.005	152.3±0.8	99.11±0.64
A9	6.2±0.3	2.3±0.2	0.063±0.005	155.3±0.6	99.39±0.52
A10	5.8±0.4	2.3±0.1	0.058±0.005	157.7±0.4	99.76±0.10
A11	6.1±0.6	2.2±0.1	0.060±0.002	155.0±0.5	98.38±0.46
A12	6.5±0.2	2.2±0.2	0.064±0.002	154.8±1.4	99.49±0.16

*above values shows Mean ± S.D

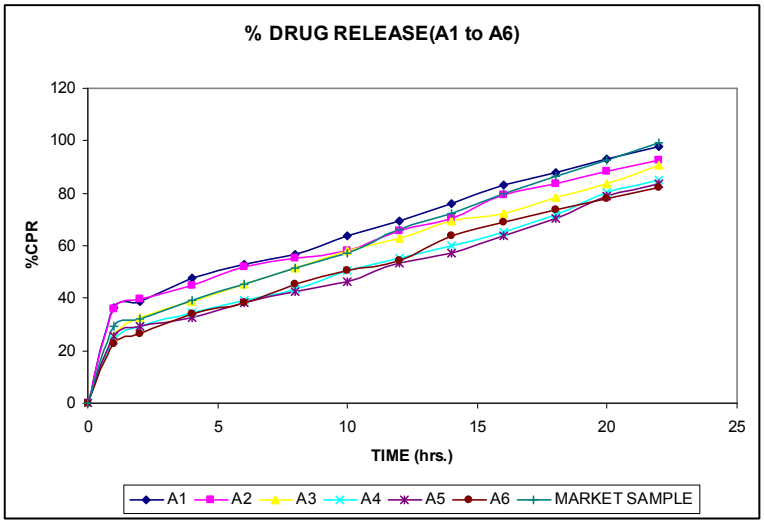

Figure1: Cumulative percentage Drug release from batch A1 to A6

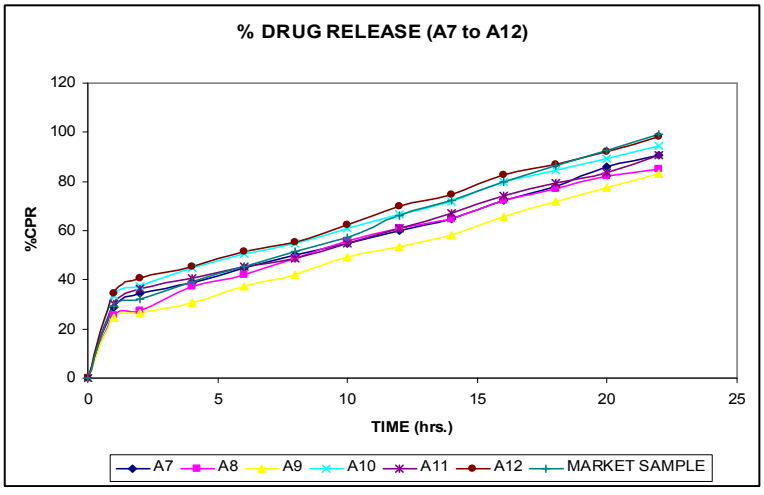

Figure2: Cumulative percentage Drug release from batch A7 to A12

Results and Discussion for Preliminary Batches

Nicorandil is a potent potassium channel opener and coronary vasodilator presently considered an important drug for the treatment of hypertension and angina pectoris. In case of cardiovascular diseases, successful treatment can be achieved only by maintaining blood pressure at a normal physiological level, and for this a constant and uniform supply of drug is desired. Multiple dose administration at intervals of 6 to 8 hours is difficult for a hypertensive patient or a patient with angina, which can lead to patient noncompliance. Nicorandil with all evident advantages proved to be a suitable candidate for development of a controlled-release dosage form. In present study, HPMC K200M, which was used in hydrophilic matrix drug delivery systems, have been employed to formulate sustained-release tablets of nicorandil but alone it was not gives a good result so it was used in combination with hydrophobic polymer like Eudragit RSPO and Ethyl cellulose.

Batches of Nicorandil were prepared with HPMC K200 M, Ethyl Cellulose, and HPMC K 200M-Ethyl cellulose combination, and HPMC K200M- Eudragit RSPO combination. Prepared powder blend of different batches were evaluated. Result showed that powder blend have, Angle of repose range from 23 to 27, Carr's index range from 13 to19 and Husner's ratio range form 1.16 to 1.23, which indicate good flow property. Hardness, Thickness and Friabillity was found to be in range of 5.1 to 6.5, 2.2 to 2.5 and 0.056 to 0.064 respectively, which is in acceptable criteria in tablet formulation.

Rresults of angle of repose (<30) indicate good flow properties of the powder.[12,13] This was further supported by lower Carr's index values . Generally, compressibility index values up to 15-21% result in good to excellent flow properties.[12] Powder density and hardness are often interrelated properties. In addition, powder density may influence compressibility, tablet porosity, dissolution, and other properties. Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and drug content. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution. All formulations showed uniform thickness. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablets of more than 155 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements.[14] Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%.Tablet hardness is not an absolute indicator of strength.[15] Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In present study, percentage friability for all formulations was below 1%, indicating that friability was within the prescribed limits.[15]All tablet formulations showed acceptable Pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

All Batches were evaluated for the cumulative drug release and similarity factor (f2) value. Nicorandil tablets were prepared using plain Hydrophilic and plain Hydrophobic as well as blend of Hydrophilic-Hydrophobic combination. From *in vitro* dissolution profile, the batch (A1) and batch (A2) prepared with 15% and 20% concentration of hydrophilic polymer (HPMC K200M), indicates initially release was not superimposed to market sample. These two batches shows similarity value 60.73 and 62.81. Batch (A3) prepared with 25% concentration of HPMC K200M showed 90.88 % release at 22 hrs and similarity value is 61.59.Increase in concentration of HPMC may result in increase in the tortuosity or gel strength of the polymer.[12-15]

From *in–vitro* dissolution profile of batches (A4 to A6) prepared with three different concentration of ethyl cellulose, the drug release was nearer to 85% in all batches at end of 22 hrs. All batches have f_2 values less than 50. Because of hydrophobicity of Ethyl-cellulose, it retards release for longer period.[16-18]

Batches A7, A8, A9 were prepared with the blend of HPMC K200M and Ethylcellulose respectively in the ratio of 1:1, 1:2 and 2:1. Batches 7 and 8 showed drug release of 85 to 90% at the end of 22 hrs and have similarity factor values more than 50. While in batch 9 releases was about 83 % and have similarity factor value less than 50 showed insignificant batch.

Batch A10, A11 and A12 was prepared with blend of HPMC K200M and Eudragit RSPO in the ratio of 1:1, 1:2 and 2:1 respectively, where drug release was about 94-98%. Batch A10 showed highest similarity factor values (f_2 = 68.07).

Formulation of factorial design batches

Formulation of factorial design batches was listed in Table 4

Evaluation of powder blend of trial batches of Factorial design

Evaluation of powder blend of trial batches of Factorial design was listed in table 5

Evaluation of tablets of trial batches of Factorial design

Evaluation of tablets of trial batches of Factorial design was listed in Table 6

Cumulative percentage Drug release from batch F1 to F9

Cumulative percentage Drug release from batch F1 to F9 was listed in Figure 3

Table 4: Formulation of factorial design batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil	20	20	20	20	20	20	20	20	20
HPMC K 200M	10	10	10	15	15	15	20	20	20
Eudragit RSPO	10	15	20	10	15	20	10	15	20
Dibasic Calcium Phosphate	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Aerosil	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
Mg. Stearate	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
Total	**155.0**								

Note: All weights are in mg.

Table 5: Evaluation of powder blend of trial batches of Factorial design

Powder blend	Angle of Repose (^{0})	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Carr's Index (%)	Hausner's Ratio
F1	24.15	0.484	0.569	14.93	1.17
F2	25.64	0.485	0.577	15.94	1.18
F3	23.14	0.498	0.579	13.98	1.16
F4	26.54	0.491	0.573	14.31	1.16
F5	23.33	0.485	0.568	14.61	1.17
F6	26.13	0.494	0.589	16.12	1.19
F7	25.47	0.498	0.587	15.16	1.17
F8	24.89	0.487	0.583	16.46	1.19
F9	24.15	0.487	0.571	14.71	1.17

*all results were average of n=3 observation

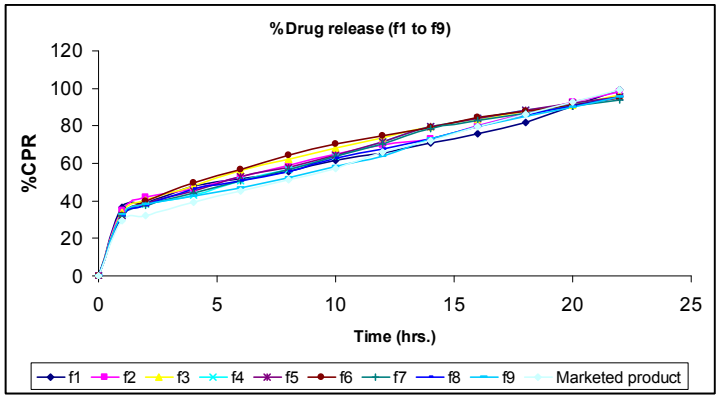

Figure 3: Cumulative percentage Drug release from batch F1 to F9

Table 6 Evaluation of tablets of trial batches of Factorial design

Factorial Batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Wt. (mg)	Assay (%)
F1	5.1±0.05	2.3±0.05	0.061±0.003	154.5±1.11	99.36±0.53
F2	5.3±0.05	2.3±0.15	0.056±0.002	157.7±0.42	99.78±0.09
F3	5.4±0.15	2.3±0.10	0.062±0.004	155.0±0.51	98.39±0.45
F4	5.8±0.40	2.3±0.10	0.058±0.005	156.1±1.51	99.62±0.12
F5	6.1±0.55	2.2±0.10	0.060±0.002	155.7±1.10	99.67±0.09
F6	6.5±0.20	2.2±015	0.063±0.002	155.5±0.86	99.63±0.10
F7	6.1±0.10	2.2±0.05	0.063±0.001	154.7±1.39	99.02±0.57
F8	5.5±0.10	2.3±0.20	0.061±0.003	153.0±0.67	99.53±0.53
F9	6.3±0.05	2.4±0.10	0.062±0.004	155.7±0.15	99.57±0.57

*above values shows Mean ± S.D

Optimization of Effect of Independent variable on dependent variable by 3^2 full factorial designs

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. concentration of HPMC K 200M (X_1) and concentration of Eudragit RSPO (X_2) on dependent variables like %drug release Q_1, Q_{22} & $T_{80\%}$. The results clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F_1 to F_9). The fitted equations (full models) relating the responses (i.e. Q_1, Q_{22} & $T_{80\%}$) to the transformed factor were shown in below tables. (8,9,10) The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative.

Effect of Independent variable on dependent variable by 3^2 full factorial design of Nicorandil Sustained release matrix tablet

Effect of Independent variable on dependent variable by 3^2 full factorial design of Nicorandil Sustained release matrix tablet was listed in Table 7.

Summary output of regression analysis for effect of X_1 & X_2 on Q_1

Summary output of regression analysis for effect of X1 & X2 on Q1 was listed in Table 8

Summary output of regression analysis for effect of X_1 & X_2 on Q_{22}

Summary output of regression analysis for effect of X_1 & X_2 on Q_{22} was listed in Table 9

Summary output of Regression analysis for effect of X_1 & X_2 on $T_{80\%}$

Summary output of Regression analysis for effect of X_1 & X_2 on $T_{80\%}$was listed in Table10

Result and Discussion for Factorial Batches

Concerning Q_1, the results of multiple linear regression analysis showed that both the coefficients b_1 and b_2 bear a negative sign. The fitted equation relating the response Q_1 to the transformed factor is shown in following equation,

$$Q_1 = 58.59 - 2.69867(X_1) - 0.42967(X_2) + 0.038(X_1X_2) + 0.0608(X_1^2) - 0.007(X_2^2) \quad \text{.....(10)}$$

The Q1 for all batches F1 to F9 shows good correlation co-efficient of 0.9857.

From table 8, Variable X1 has p value 0.002942 ($p<0.05$), but variable X2 has p value 0.24932. Variables which have p value less than 0.05, significantly affect the release profile.[27] X1 means the concentration of HPMC K 200M is the dominant variable for the initial release (Q_1) profile. The negative sign of the co-efficient for variable X1 indicates that as the concentration of HPMC K 200M increases, the release of drug is retarded due to entrapment of Nicorandil molecules in the close proximity of HPMC K 200M. It is possible that at higher polymers concentration, Nicorandil is trapped in smaller polymer cells and it is structured by its close proximity to the polymer molecules. So, on increasing the amount of the polymer in the formulations, polymer barrier layer increases thus drug will take longer time to diffuse out to the media and thus release of drug is retarded.[27]

The amount of drug released at the end of 22 hrs is also important parameter for prominent drug release from sustained release matrix formulation. Concerning Q_{22}, the results of multiple linear regression analysis showed that the coefficients b_1 and b_2, as well as interaction term b_{12} bear a negative sign. The fitted equation relating the response Q_{22} to the transformed factor is shown in following equation,

$$Q_{22} = 118.80 - 2.553(X_1) - 0.22967(X_2) + 0.0436(X_1X_2) + 0.054(X_1^2) - 0.016(X_2^2) \quad \text{.....(11)}$$

The Q_{22} for all batches F1 to F9 shows good correlation co-efficient of 0.9903.

From table 9, Variable X1 has p value 0.001806 ($p>0.05$), variable X2 has p value 0.41157 ($p>0.05$), but the interaction term b12 has p value 0.003848 ($p<0.05$). Variables which have p value less than 0.05, significantly affect the release profile.[27] From regression analysis, the p value for Factor X1 and Factor X2, is greater than 0.05, but the interaction term of both factor has p value less than 0.05. So the term X1X2 significant and affect the release profile at 22 hrs. After completely swelling of HPMC K 200M within 8-10 hrs, its erosion will start. So for the remaining end point the release profile is controlled by both HPMC K 200M and Eudragit RSPO. From the equation, the co-efficient value for X2 is higher than X1, so at the ended time point both factors affecting release profile but the more prominent factor is Eudragit RSPO.

The time required for 80% of the drug release was an important parameter for prominent drug release from sustained release matrix formulation.

$$T_{80\%} = 37.15 - 2.61(X_1) - 0.3653(X_2) + 0.0488(X_1X_2) + 0.062(X_1^2) - 0.014(X_2^2) \quad \text{.....(12)}$$

In the case of $T_{80\%}$, Variable X1was found to be significant based on its P-value ($p<0.05$) (see Table 10). From regression analysis, p value for factor X1 is less than 0.05, but p value for factor X2 is not less than 0.05. So the factor X1 means the concentration of HPMC K 200M is the dominant variable for the $T_{80\%}$ release profile. The positive sign of the co-efficient for variable X1 indicates that as the concentration of HPMC K 200M increases, the time period for 80% of drug release increases.

Summary

For water soluble drugs like nicorandil, hydrophobic polymers like Eudragit RSPO and Ethylcellulose in combination with swellable polymer like HPMC K 200M can be succefully utilized for preparation of SR matrix tablet.

Table 7 Effect of Independent variable on dependent variable by 3^2 full factorial

Formulation codes	Independent variable		Dependent variable		
	X_1	X_2	Q_1	Q_{22}	T_{80}
F1	-1	-1	36.73	99.31	17.24
F2	-1	0	35.16	98.05	16.06
F3	-1	+1	33.85	96.46	14.12
F4	0	-1	32.16	95.03	14.12
F5	0	0	32.42	95.38	14.06
F6	0	+1	32.03	95	14.24
F7	+1	-1	31.63	94.04	14.42
F8	+1	0	32.42	95.44	16.06
F9	+1	+1	32.55	95.55	16.18

Translation of coded levels in actual units			
Independent Variables	**Real Value**		
	Low (-1)	**Medium (0)**	**High (+1)**
HPMC K 200 M (X_1)	10 mg	15 mg	20 mg
Eudragit RSPO (X_2)	10 mg	15 mg	20 mg

Table 8 Summary output of Regression analysis of CLR for effect of X_1 & X_2

Regression statistics for Q_1		
Multiple R	0.992803	
R Square	0.985657	
Adjusted R square	0.961752	
Standard error	0.3336	
Observations	9	
Coefficients:		
Coefficient	Coefficient value	P-value
b_0	58.59	0.00036
b_1	-2.69867	0.002942
b_2	-0.42967	0.24932
b_{12}	0.038	0.010732
Equation:		
$Q_1 = 58.59 - 2.69867 (X_1) - 0.42967 (X_2) + 0.038 (X_1X_2) + 0.0608(X_1^2) - 0.007(X_2^2)$		

Table 9 Summary output of Regression analysis for effect of X_1 & X_2 on Q_{22}

Regression statistics for Q_{22}		
Multiple R	0.995134	
R Square	0.990291	
Adjusted R square	0.974109	
Standard error	0.267111	
Observations	9	
Coefficients:		
Coefficient	Coefficient value	P-value
b_0	118.8078	2.24E-05
b_1	-2.553	0.001806
b_2	-0.22967	0.41157
b_{12}	0.0436	0.003848
Equation:		
$Q_{22} = 118.80 - 2.553(X_1) - 0.22967(X_2) + 0.0436 (X_1X_2) + 0.054(X_1^2) - 0.016(X_2^2)$		

Table 10 Summary output of Regression analysis for effect of X_1 & X_2 on $T_{80\%}$

Regression statistics for $T_{80\%}$		
Multiple R	0.979669	
R Square	0.959751	
Adjusted R square	0.89267	
Standard error	0.397101	
Observations	9	
Coefficients:		
Coefficient	Coefficient value	P-value
b_0	37.14667	0.00232
b_1	-2.60533	0.005392
b_2	-0.36533	0.383608
b_{12}	0.0488	0.008671
Equation:		
$T_{80\%} = 37.15 - 2.61(X_1) - 0.3653(X_2) + 0.0488(X_1X_2) + 0.062(X_1^2) - 0.014(X_2^2)$		

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