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RESEARCH ARTICLE

DEVELOPMENT OF ISOSORBIDE-5-MONONITRATE SUSTAINED RELEASE MATRIX TABLET BY STATISTICAL OPTIMIZATION TECHNIQUE

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Abstract:
The aim of the project is to prepare and optimize the sustained release matrix tablets of Isosorbide-5-mononitrate (ISMN). Elimination half-life of ISMN is 4-5 h and has to be administered 2-3 times a day. In order to reduce the dosage frequency and to increase patient compliance sustain release preparation was made. The tablets were formulated by wet granulation technique using HPMCK4M, Eudragit NE30D, and Ethylcellulose polymers. The constrained mixture experimental design was used to prepare systematic model formulations, which were composed of thee formulation variables: the content of HPMCK4M, Eudragit NE30D, and Ethylcellulose. Prepared tablets were evaluated for hardness, friability, % drug content. Drug release was evaluated in phosphate buffer pH-6.8 and the drug release responses were evaluated at 1 h, 2 h, 4 h, and 6 h. The result shows that the HPMC is a major release-retarding polymer. Result of optimized formula coincided well with the predicted value, indicating it was quite useful for optimizing pharmaceutical formulation. The analysis of the release profiles in the light of distinct kinetic models (zero-order, first-order, Higuchi, Peppas) shows that the value of release exponent n for all formulation ranging from 0.4633-0.7184, which indicate that the mechanism of release is anomalous diffusion. This is due to the coupling of diffusion and relaxation.

Keywords: Sustained Release, Isosorbide-5-mononitrate, Higuchi, Peppas, Anamolous diffusion

Introduction

Isosorbide-5-mononitrate (ISMN) is an active metabolite of the vasodilator isosorbide-5-dinitrate and is used in the long-term management of the angina pectoris and heart failure. An elimination half-life of about 4-5 hours has been reported. The usual oral dose is 20 mg 2-3 times daily, although dose ranging from 20-120 mg daily have been given.[1] Sustained release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects.[2] Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view.[3] It has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form.[4] The use of mixtures of polymers represents a potential way of achieving required release properties.[5]

In the development of extended release dosage form, an important issue was to design an optimized pharmaceutical formulation with appropriate dissolution rate in a short time period and minimum trials. For this purpose, a computer optimization technique, based on response surface methodology utilizing polynomial equation.[6, 7, 8]

The optimization procedure involved systematic formulations design to minimize the number of trials, and analyze the response surfaces in order to realize the effect of causal factors and to obtain the appropriate formulations with target goals as well as the acceptable component region as process control conditions in practical preparation.

2. Materials and Methods

2.1. Materials

ISMN was received as gift sample from M/S. Zydus Cadila limited, Ahmedabad, India. HPMC K4M, Eudragit NE30D, Ethylcellulose were obtained from M/S. Bangalore Pharmaceutical Research Laboratory, Bangalore, India. Potassium di-hydrogen orthophosphate, NaOH were of analytical grade and supplied by M/S. Qualigens Limited, India. Methanol and Water used were of HPLC grade and supplied by M/S Merck Limited, India. All other chemicals were purchased from commercial sources and were of analytical grade.

2.2. Experimental design

Here simplex design was utilized to optimize the formula. The formulation variables and their ranges were chosen from the knowledge obtained from the preliminary studies.[9] HPMC K4M (X_1), Eudragit NE30D (X_2), Ethylcellulose (X_3) were chosen as formulation variables and the drug release percent at 1 h, 2 h, 4 h, 6 h were selected as response variables. The levels of excipients were set at HPMC (X_1): 30-60 mg; Eudragit NE 30D (X_2): 30-60 mg; Ethylcellulose (X_3): 10-40mg. (Table No 1)

2.3. Preparation of ISMN matrix tablet

Dissolve ethylcellulose in isopropyl alcohol and put aside for sometime to dissolve. Then add Eudragit NE 30D to the above solution and dissolve. Mix Isosorbide-5-mononitrate, lactose and hydroxypropylemethylcellulose in polythene bag and then granulate it with above solution in mortar and pestle. Then the wet component was passed through a 24-mesh sieve. Dry at 40^0C for 3 h in hot air oven (Model DTC, PROTROL, and India) and kept it for air-drying for 30 min. Then blended with magnesium stearate and talc and compressed using 9.5 mm diameter flat-faced punch (Cadmach, Zydus Cadila, India) under the 4-5 kg compression force.

2.4. In-vitro dissolution studies

The USP paddle method (Electrolab TDT-08L, India) was used for all the in-vitro dissolution studies. The in-vitro release studies were carried were carried out at 37 ± 0.5 ^{0}C for 8 h. The stirring rate was 100 RPM. The dissolution medium was a pH-6.8 Phosphate buffer (900 ml). The samples (10 ml) were withdrawn at predetermined time and replaced with an equivalent amount of fresh medium. The samples were filtered through a 0.45µm nylon membrane filter and analyzed by HPLC method. Dissolution studies were performed two times for each batch of tablets and the results were registered as an average.

2.5. HPLC analysis

The samples were analyzed using High Performance Liquid Chomatography (LC-10AT *VP*, Shimadzu, Japan) using RP-18 Column (250 × 4.6 mm and 5 µm particle size- Phenomanex). A mobile phase consisting of water: methanol (80:20). A flow rate of 1 ml/min was employed and wavelength of UV detector was set at 220 nm. 20 µl samples were injected every time.

2.6. Curve fitting

The kinetics of ISMN release from matrix tablet was determined by finding the best fit of the dissolution data to distinct models: zero-order (eq. 1), Higuchi (eq. 2), first-order (eq. 3), Korsmeyer-Peppas (eq. 4) [10, 11]

$M_t = M_0 + K_0 t$ _____(1)

M_t is the amount of drug released at time‘t’, M_0 is the concentration of drug in the solution at t = 0, K_0 is the zero-order release constant.

$M_t = k_H t^{1/2}$ _____eq. (2)

Mt is the amount of drug release at time √t and k_H is the Higuchi release constant.

$M_t = M_\infty(1-e^{-k1t})$ _____eq. (3)

M_t is the amount of drug released at time‘t’, M_∞ being the total amount of drug in the matrix and k_1 the first-order kinetic constant.

$M_t/M_\infty = k_{KP} t^n$ _____eq. (4)

M_t/M_∞ is fraction of drug released at time‘t’, k_{KP} the release rate constant comprising the structural geometric characteristics of the tablets and n the release exponent. For the case of cylindrical tablets, $n \leq 0.45$ corresponds to a Fickian diffusion release (case I diffusional), $0.45 < n \leq 0.89$ to an anomalous (non-Fickian) transport, n = 0.89 to a zero order (case II) release kinetics, and n > 0.89 to a super case II transport.

2.7. Regression analysis[12]

The effect of formulation variables on the response variable were statistically evaluated by applying one-way ANOVA using a commercially available software package DESIGN-EXPERT® version 6.05 (stat-ease Inc.). To describe the response surface curvature, the design was evaluated by linear model, which bears the form of equation,

$Y = b_1X_1 + b_2X_2 + b_3X_3$

Where, Y is the response variable, b_1, b_2, b_3 are the regression coefficients X_1, $X2$, X_3 are the formulation variables.

2.8. Scanning electron microscopy [13]

Scanning electron microscopy studies were performed using the JSM-840A scanning microscope, (Jeol-Japan)

Fig.1 Contourgraph for release 1h

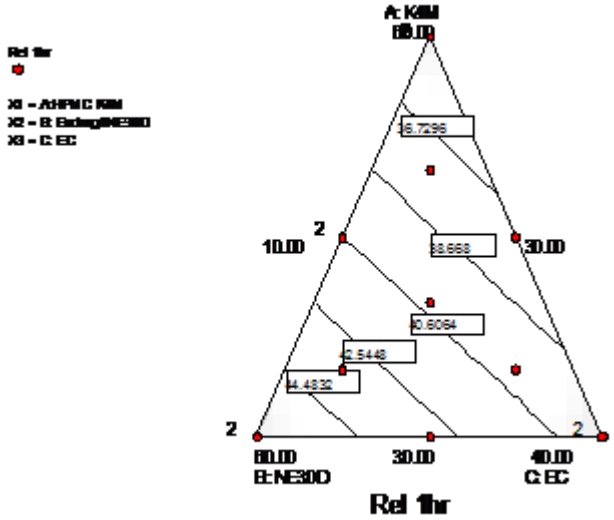


Fig.2 Contourgraph for release 2h

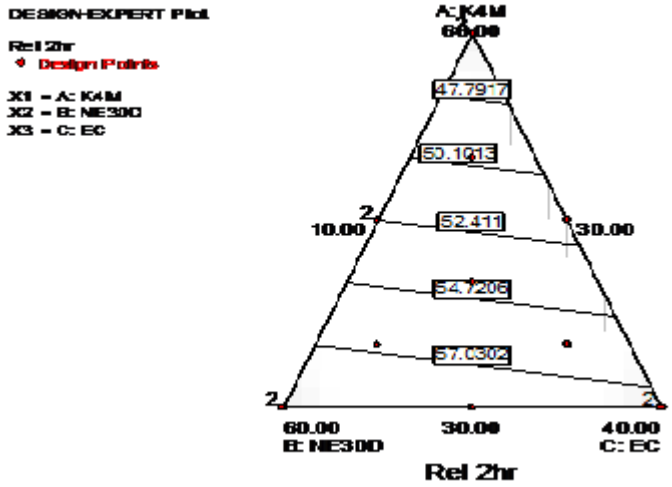


Fig.3 Contourgraph for release 3h

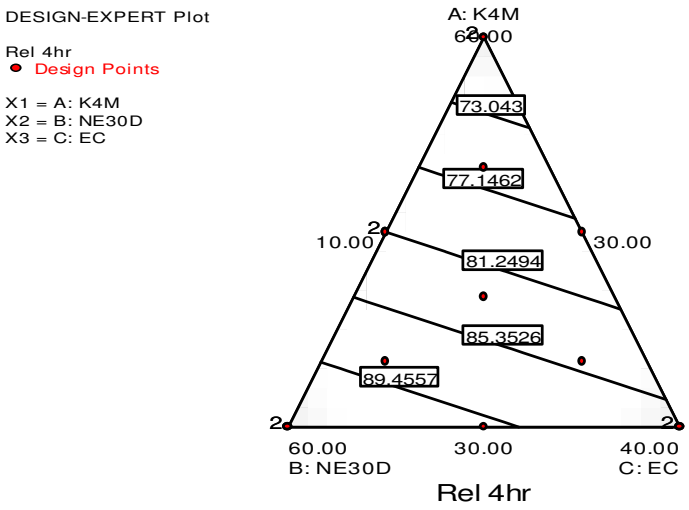


Fig.4 Contourgraph for release 4h

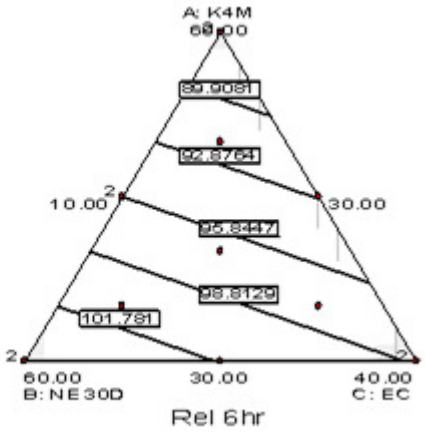


Fig.5 Contourgraph for release 5h

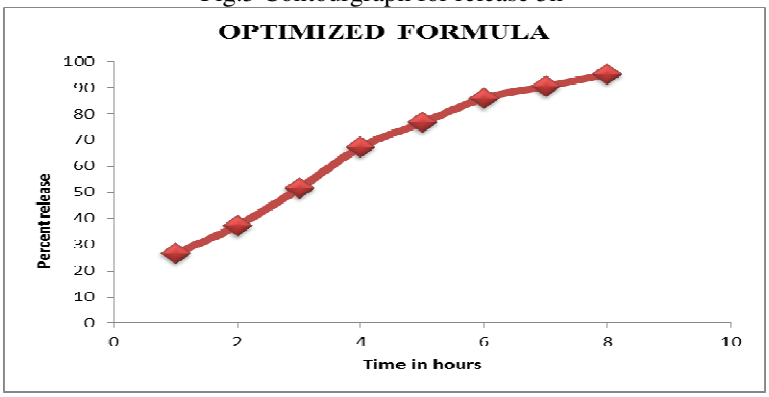
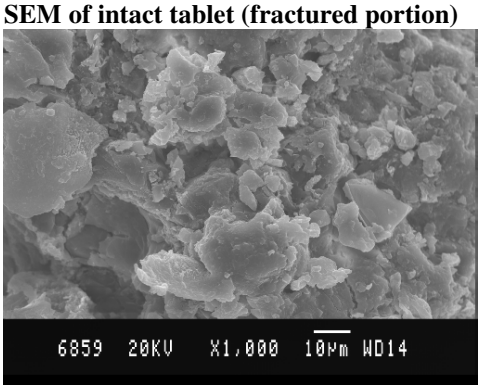
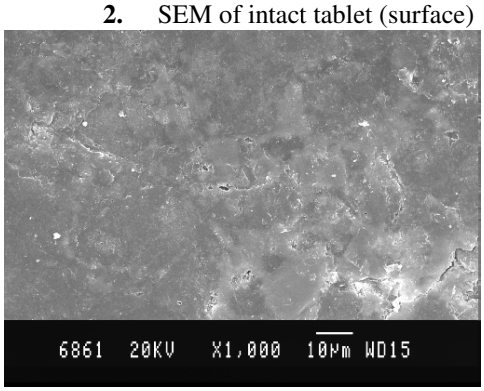


Fig No. 6 SEM study of intact and dry tablet

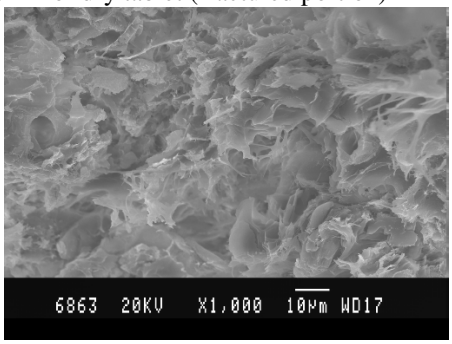
1. SEM of intact tablet (fractured portion)



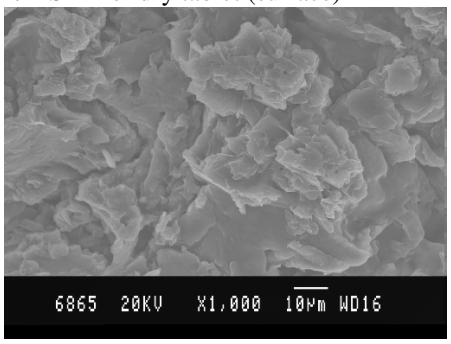
2. SEM of intact tablet (surface)



3. SEM of dry tablet (fractured portion)



4. SEM of dry tablet (surface)



with JFC-1100E Ion sputtering device. The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. All the samples were examined with a SEM at an accelerating voltage of 20 kV. SEM was performed on intact and dry tablet (for that tablet was allowed to hydrate overnight in dissolution medium and then dried at 40 ^{0}C for 7-8 h in hot air oven (Model DTC, PROTROL, India) to observe the changes in surface topography due to some degree of swelling and erosion.

Results and Discussions

Effect of formulation variables on percentage ISMN release at different h

In order to evaluate the effect of formulation ingredients on the dissolution pattern, the causal factor and response variables were related using linear model with statistical analysis. The values of the coefficients X_1, X_2, X_3 are related to the effect of these variables on the response. The contour plots illustrating the simultaneous effect of the causal factors on individual response variables. A positive sign of co-efficient indicates a synergistic effect upon the response. The larger co-efficient means the causal factor has more potent influence on the response.
The factors affecting the release were X_1= K4M, X_2= NE30D, X_3= EC. In case of release from formulation within one hour the Linear equation is

$Y_{1h} = 0.21511\ X_1 + 0.60279\ X_2 + 0.38012\ X_3$
The ANOVA of the mixture linear model for Y_{1h} holds significant with probability value of 0.0401 with R^2 value 0.4428 and R-adjusted is 0.3414 in the model. The coefficients of factors are positive in which NE30D have the major effect, which indicates that NE30D is contributing for the release. In the other two factors, EC had more effect than K4M.

In case of release of drug from formulations within 2 h the Linear equation is
$Y_{2h} = 0.27555\ X_1 + 0.73747\ X_2 + 0.68250\ X_3$
The ANOVA of the mixture linear model for Y_{2h} holds significant with probability value of 0.0204 with R^2 value 0.5074 and R-adjusted is 0.4178 in the model. The major contributing factors are NE30D and EC because of swelling property and the least contributing factor is K4M, which indicates that K4M is controlling the release by forming matrix.

In case release of drug from formulations within 4 hours, the equation is
$Y_{4h} = 0.38430\ X_1 + 1.205\ X_2 + 0.97281\ X_3$
The ANOVA of the mixture linear model for Y_{4h} holds significant with probability value of 0.0053 with R^2 value 0.6148 and R-adjusted is 0.5447 in the model. In case of release with in 4 hours the releasing factors are similar to release in the 2 hours. Overall the controlling factor for achieving the sustained dosage form is HPMC K4M, which is forming matrix. Similar results are observed in case of release within 6 hours. For release of drug from formulation within 6 h, the equation is,

$Y_{6h} = 0.65\ X_1 + 1.25\ X_2 + 1.04\ X_3$ The ANOVA of the mixture linear model for Y_{6h} holds significant with probability value of 0.0024 with R^2 value 0.6655 and R-adjusted is 0.6047 in the model.

The range of these responses was restricted to $26 \le Y_1 \le 35$, $45 \le Y_2 \le 55$, $65 \le Y_3 \le 85$, $85 \le Y_4 \le 107$ (Table-1). Under these conditions, these four responses were then combined to determine an all over optimum region. An optimum response was found with Y_1, Y_2, Y_3, Y_4 of 34.81%, 45.51%, 68.98%, 86.97% at X_1, X_2, X_3 values of 59.94, 30.04, and 10.02 respectively. To verify these values the optimum formulation was prepared according to the above values of the factor and subjected to the dissolution test. The dissolution profiles of the optimum formulation and the predicted profile are shown in table.

Conclusions: HPMC is the major release controlling polymer and each polymer has synergistic effect on release rate. The matrix tablet of isosorbide 5 mono nitrate can be prepared successfully. The mechanism of release kinetics (n value is nearly 0.5) is non-Fickian or nearly diffusion controlled. The hardness is 5 kg/cm^2 which can withstand mechanical stress. FTIR studies revealed that there is no chemical interaction with other excipients. SEM studies revealed that gel is formed. The simplex model is significant with linearity.

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Table 1
Variables in the mixture design

Formulation variables	Levels	
	Low	High
X_1 = Amount of HPMC K4M	30	60
X_2 = Amount of Eudragit NE 30D	30	60
X_3 = Amount of Ethylcellulose	10	40
Response variables	**Constraints**	
Y_1 = Percent release in 1 h	$26\ \% \leq Y_1 \leq 35\ \%$	
Y_2 = Percent release in 2 h	$45\ \% \leq Y_2 \leq 55\ \%$	
Y_3 = Percent release in 4 h	$65\ \% \leq Y_3 \leq 85\ \%$	
Y_4 = Percent release in 6 h	$85\ \% \leq Y_4 \leq 107\ \%$	

$X_1 + X_2 + X_3 = 100$ mg

Table . 2

Formulations

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
1.	ISMN	30	30	30	30	30	30	30	30	30	30	30	30	30	30
2.	Lactose	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8	170.8
3.	Methocel K4M	60	45	45	30	30	30	50	35	35	40	60	30	30	45
4.	Eudragit NE 30 D	30	45	30	60	45	30	35	50	35	40	30	30	60	45
5.	Ethocel	10	10	25	10	25	40	15	15	30	20	10	40	10	10
6.	Carbomer 934P	4	4	4	4	4	4	4	4	4	4	4	4	4	4
7.	Talc	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8.	Mag. Stearate	18	18	18	18	18	18	18	18	18	18	18	18	18	18
	Total Weight	**320**	**309.5**	**320**	**299**	**309.5**									

Table No 3
The composition and responses of formulations ISMN matrix tablets

Run	X_1	X_2	X_3	Y_{1h}	Y_{2h}	Y_{4h}	Y_{6h}
1	60	30	10	26.62	37.24	67.25	85.93
2	45	45	10	30.61	45.42	68.53	90.72
3	45	30	25	36.61	53.27	78.67	90.52
4	30	60	10	43.35	58.38	87.36	98.94
5	30	45	25	39.08	53.62	97.21	-
6	30	30	40	39.15	55.15	82.39	97.57
7	50	35	15	42.22	48.05	68.37	87.53
8	35	50	15	39.19	56.73	92.53	102.66
9	35	35	30	39.33	59.00	84.21	97.85
10	40	40	20	41.46	58.04	83.18	102.69
11	60	30	10	37.67	54.24	75.89	88.06
12	30	30	40	42.66	58.79	87.68	100.78
13	30	60	10	50.28	63.23	95.99	107.27
14	45	45	10	47.51	55.46	91.36	104.16

Table no 4
Fitting result of the experimental ISMN release data to different kinetic equations

Formulation	Zero-order		First-order		Higuchi		Korsmeyer-Peppas	
	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2
1	15.07	0.8925	0.2894	0.9492	33.77	0.9260	0.7018	0.9867
2	16.33	0.8905	0.3370	0.8892	36.31	0.9272	0.6980	0.9854
3	16.59	0.5289	0.3882	0.9640	37.77	0.9902	0.5126	0.9907
4	19.49	0.2753	0.4835	0.9668	41.49	0.9831	0.4633	0.9878
5	24.76	0.8650	0.4613	0.8653	42.92	0.8815	0.7184	0.9521
6	19.14	0.5631	0.4420	0.9637	40.51	0.9899	0.5276	0.9920
7	16.55	0.3721	0.3242	0.8269	35.10	0.9385	0.4829	0.9393
8	19.87	0.5795	0.4786	0.9366	42.02	0.9666	0.5370	0.9701
9	19.33	0.4604	0.4621	0.9761	41.02	0.9921	0.5007	0.9921
10	19.65	0.4947	0.4759	0.9555	41.66	0.9993	0.5074	0.9995
11	14.65	0.0738	0.3725	0.9772	35.85	0.9603	0.4229	0.9839
12	22.70	0.6041	0.5171	0.9495	44.09	0.9898	0.5456	0.9952
13	21.56	0.2691	0.6160	0.8812	45.89	0.9727	0.4627	0.9775
14	18.64	0.2726	0.5364	0.8984	42.67	0.9649	0.4588	0.9707

Table no 5

Optimized Formula

S. No	Ingredients	Quantity in mg
1	**ISMN**	**30**
2	**Lactose**	**170.75**
3	**HPMC K4M**	**59.94**
4	**Eudragit NE30D**	**30.04**
5	**Ethylcellulose**	**10.02**
6	**Carbomer 934 P**	**4**
7	**Talc**	**10**
8	**Magnesium Stearate**	**18**
	Total	**320**

Optimized release formula

Time (h)	Percent release
1	26.62
2	37.24
3	51.46
4	67.25
5	76.59
6	85.93
7	90.46
8	95.1